4:1 Thiourea-18-Crown-6 Complex (9). 18-Crown-6 (264 mg, 1.0 mmol) and thiourea (304 mg, 4.0 mmol) were refluxed for 30 min in 5 mL of methanol and then evaporated to dryness. The crystalline residue was recrystallized from acetone or methanol/ethyl acetate (1:1): yield 186 mg (32.7%); mp 168-174 °C. Anal. Calcd for $C_{16}H_{40}N_8O_6S_4$ (mol wt 568.8): C, 33.78; H, 7.09; N, 19.70. Found: C, 33.88; H, 7.21; N, 19.86.

4:1 Thiourea-1,7,10,16-Tetraoxa-4,13-diazacyclooctadecane Complex (10). An analogous procedure to that above was followed: yield 259 mg (45.7%): mp 148-151 °C. Anal. Calcd for $C_{16}H_{42}N_{10}O_4S_4$ (mol wt 566.8): C, 33.90; H, 7.47; N, 24.71. Found: C, 33.60; H, 7.50; N, 24.74.

Acknowledgment. We thank the Robert A. Welch Foundation (Grant P-074) and the TCU Research Foundation for their financial support. This is FASTBIOS Contribution No. 102.

Registry No. 1, 73961-14-5; 2, 87843-32-1; 3, 80027-36-7; 4, 87843-33-2; 5, 87843-34-3; 6, 87843-35-4; 7, 87843-36-5; 8, 86797-40-2; 9, 87843-37-6; 10, 83654-18-6.

Supplementary Material Available: Tables of atomic parameters and other distances for 18-crown-6 complexes (24 pages). Ordering information is given on any current masthead page.

Enantiomeric Recognition of Organic Ammonium Salts by Chiral Crown Ethers Based on the Pyridino-18-crown-6 Structure[1,2]

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Received September 21, 1983

Enantiomeric recognition by several chiral dimethyl-substituted macrocycles of the pyridino-18-crown-6 type for chiral organic ammonium salts has been studied by titration calorimetry in CH_3OH, temperature-dependent ^1H NMR spectroscopy in CD_2Cl_2, and selective crystallization. Results from the three procedures are consistent in demonstrating either host–guest recognition or nonrecognition in the systems investigated. Furthermore, enantiomeric recognition by one chiral host for a pair of chiral guests is correlated with X-ray crystallographic data for the same system. The chiral dimethyl-substituted ligands used in the study include three dimethyl diester pyridino-18-crown-6 ligands (1–3), dimethyl thiono diester pyridino-18-crown-6 (4), and dimethylpyridino-18-crown-6 (5). All of these ligands exhibited chiral recognition. Dimethylpyridino-18-crown-6 (5) in complexation with (*R*)- and (*S*)-[α-(1-naphthyl)ethyl]ammonium perchlorate exhibited the largest ratio of $\Delta G_c^{\ddagger}$ yet observed by the ^1H NMR technique. A diphenyl-substituted diester pyridino-18-crown-6 (6) where the phenyl substituents are in a less rigid portion of the macrocycle failed to show chiral recognition.

Introduction

There has been considerable interest in the design and synthesis of host chiral macrocyclic ligands that are able to distinguish between guest organic ammonium enantiomers.[3-6] A variety of chiral host macrocycles and chiral guests have been studied by using a number of different techniques. Cram and his co-workers have prepared chiral crown ethers containing the 1,1-binaphthyl moiety and have studied chiral recognition by these compounds using ^1H NMR spectroscopy,[7] solvent extraction,[8] transport through a liquid membrane,[9] and enantiomeric separation on either silica gel or polystyrene containing a chiral crown molecule.[10] A high degree of chiral recognition was observed in these studies. Lehn and his co-workers have prepared a large number of chiral macrocylic ligands of the 18-crown-6 variety from tartaric acid derivatives.[11] Although they did not study chiral recognition per se, they did observe interesting differences in reactivity between chiral host and chiral guest molecules.[5,11-13] Certain carbohydrate molecules have been incorporated into synthetic macrocyclic ligands by Stoddard and his co-workers. Little chiral recognition was observed by a ^1H NMR technique when these chiral host molecules were complexed with chiral alkylammonium salts.[14] Sutherland and his co-workers used the same ^1H NMR

† Contribution No. 313 from the Institute for Thermochemical Studies.

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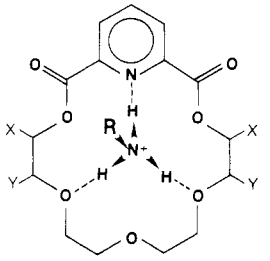
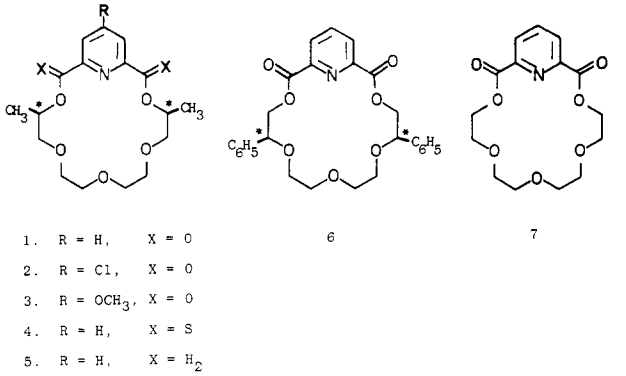


Figure 1. Host–guest interaction.

chiral recognition by host chiral macrocyclic aza compounds with chiral amino acids.[15] Tundo and Fendler[16] have reported K values for chiral recognition reactions in homogeneous solutions. The energetics of aggregation of chiral ions in solution have been measured by Arnett and Zingg[17] by using a thermometric titration procedure. Enantiomeric differentiation by (*R*)- or (*S*)-α-phenethylamine for (*R*)- or (*S*)-mandelic acid was observed in either dioxane or dimethyl sulfoxide but not in water.[17]

Protonated organic amines and macrocycles of the pyridino-substituted cyclic polyether type should provide excellent model systems for evaluating enantiomeric recognition in host–guest interactions. The rationale for this expectation is as follows. In Figure 1, the interaction of an RNH_3^+ guest with a macrocycle host is represented. Log $K(CH_3OH)$ data[18] show that stable complexes are formed between 18-crown-6 and a variety of RNH_3^+ cations and that appropriate choice of R results in marked differences in log K due to steric effects. Structural data for $CH_3NH_3^+$-18-crown-6[19] and *tert*-butyl-NH_3^+-pyridino-18-crown-6[20] show that the host–guest interaction is essentially that illustrated in Figure 1. Proper choice of R groups to include those with benzyl, naphthyl, etc. rings capable of π–π interactions with the pyridine ring should further stabilize this complex. Because of the fixed primary binding site, it should be possible by appropriate choice of R, X, and Y (Figure 1) to identify and evaluate the complementary host–guest structural features that determine enantiomeric selectivity.

Our approach to the investigation of those factors that determine host–guest enantiomeric recognition is to synthesize a series of chiral macrocycles based on the pyridino-18-crown-6 structure in which X and Y (Figure 1) are varied in a systematic manner. The extent of chiral recognition, if any, shown by these macrocycles for chiral protonated amine guests in which R (Figure 1) is varied in a systematic way is then measured quantitatively by using a combined calorimetric and ^1H NMR procedure. Using this approach, we have been successful in measuring differences in equilibrium constants (K) and in free energies of activation ($\Delta G_c^{\ddagger}$) for complex dissociation in several host–guest systems and in relating these differences to host–guest enantiomeric recognition.[2] Finally, the structural basis either for the observed recognition or for the lack of it is sought with use of X-ray crystallographic data for the systems involved. Such a structural basis has been identified for the interaction of two enantiomers of a chiral guest with one enantiomer of a chiral host.[21] In these cases, structural features of these complexes have been identified that correlate well with the relative kinetic and thermodynamic stabilities of the same host–guest systems.



1. R = H, X = O
2. R = Cl, X = O
3. R = OCH_3, X = O
4. R = H, X = S
5. R = H, X = H_2

6

7

Figure 2. Macrocyclic ligands.

In the present paper, we report thermodynamic (log K, ΔH, $T\Delta S$) and kinetic ($\Delta G_c^{\ddagger}$) data for the interaction of several chiral disubstituted macrocycles of the pyridino-18-crown-6 type with several nonchiral and chiral organic ammonium cations. The chiral macrocycles studied are represented in Figure 2 and include dimethyl-substituted diester crowns **1–3**,[22] thiono diester crown **4**,[23] pyridino crown **5**,[23] and diphenyl-substituted diester crown **6**.[24] Enantiomeric recognition in these systems is identified, when present, and thermodyanmic, kinetic, and structural data are correlated in one case where all of these data are available.

Experimental Section

Materials. The preparation of chiral macrocyclic compounds was reported previously: **1–3**,[22] **4** and **5**,[23] and **6**.[24] The HCl salts of (*R*)- and (*S*)-methyl alaninate (AlaOMe) and (*R*)- and (*S*)-methyl tryptophanate (TrpOMe) were used as received from the U.S. Biochemical Corp. The $HClO_4$ salts of benzylamine (Bnz) and of (*R*)- and (*S*)-α-(1-naphthyl)ethylamine (NapEt) (mp 186 °C) were prepared by treating the free amines (Pfaltz and Bauer) with 70% aqueous perchloric acid. The $HClO_4$ salts of (*R*)- and (*S*)-methyl phenylalaninate (PheOMe) were used as received from Dr. J. F. Stoddart, The University, Sheffield, England. Silver nitrate (reagent, Sargent-Welch) and NH_4Cl (reagent, J. T. Baker) were dried prior to use.

Each of the chiral macrocyclic ligands was titrated against standard $AgNO_4$ by using the method of Lamb et al.[25] to establish the purity of the ligand and its concentration in the CH_3OH solvent. Except for **5**, the purities of the macrocycles were determined by this technique to be >99%. The concentration of ligand **5** could not be determined accurately by titration calorimetry due to unknown impurities that interferred with the titration reaction. The ^1H NMR spectrum of compound **5** exhibited extra peaks, indicating a purity of about 90%.

Determination of Log K, ΔH, and $T\Delta S$ Values. Log K, ΔH, and $T\Delta S$ values for the interaction of the several macrocycles with $AgNO_3$, NH_4Cl, and the chiral alkylammonium salts were determined in CH_3OH (Fisher reagent, <0.05% H_2O) at 25 °C

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Table I. Log K, ΔH (kcal/mol), and $T\Delta S$ (kcal/mol) Values[a] in CH_3OH at 25 °C for the Interaction of Several Macrocyclic Ligands with Silver Nitrate, NH_4Cl, and Several Chiral Alkylammonium Salts

ligand	value	(S)-TrpOMe[b]	(R)-TrpOMe[b]	(S)-NapEt[b]	(R)-NapEt[b]	(S)-AlaOMe[b]	(R)-AlaOMe[b]	NH_4Cl	Ag^+
7	log K							3.29 ± 0.01	5.15
	ΔH							−6.21 ± 0.12	−8.20
	$T\Delta S$							−1.72	−1.17
(S,S)-1	log K	1.76 ± 0.04	1.73 ± 0.03	2.06 ± 0.01	2.47 ± 0.01	1.78 ± 0.14	2.02 ± 0.01	2.81 ± 0.06	5.01
	ΔH	−4.58 ± 0.20	−4.12 ± 0.16	−6.32 ± 0.10	−6.59 ± 0.07	−3.48 ± 0.12	−3.53 ± 0.05	−6.25 ± 0.08	−8.97
	$T\Delta S$	−2.19	−1.77	−3.51	−3.22	−1.06	−0.78	−2.42	−2.14
(S,S)-6	log K	2.00 ± 0.03	1.96 ± 0.05			1.84 ± 0.03	1.85 ± 0.03	2.72 ± 0.01	5.01
	ΔH	−3.98 ± 0.15	−3.67 ± 0.24			−3.35 ± 0.15	−3.30 ± 0.09	−5.50 ± 0.07	−8.51
	$T\Delta S$	−1.26	−1.01			−0.85	−0.79	−1.79	−1.68
(S,S)-5	log K	2.29 ± 0.02	2.43 ± 0.03	[c]	[c]				
	ΔH	−3.43 ± 0.03	−3.45 ± 0.10						
	$T\Delta S$	−0.32	−0.15						

[a] The average of three independent measurements. Uncertainties are given as standard deviations. [b] TrpOMe = the hydrogen chloride salt of (R)- or (S)-methyl tryptophanate; NapEt = the hydrogen perchlorate salt of (R)- or (S)-α-(1-naphthyl)ethylamine; AlaOMe = the hydrogen chloride salt of (R)- or (S)-methyl alaninate. [c] The calculated log K values in the case of (S,S)-5 are not considered reliable since the calorimetric titration curve generated using them did not fit the experimental curve well. However, relative values of the equilibrium constants that we infer from the curvature of the thermograms show the same trend as in the TrpOMe-(S,S)-5 cases, i.e., the (S)-NapEt complex was less stable than the (R)-NapEt complex. Also, the log K values were larger than those for the corresponding (S,S)-1-NapEt complexes.

Table II. Free Energies of Activation ($\Delta G_c^{\ddagger}$, kcal/mol) in CD_2Cl_2[a] for the Interaction of Chiral Macrocyclic Ligands with Chiral Alkylammonium Salts

ligand	value	Bnz[b]	(S)-NapEt[b]	(R)-NapEt[b]	(S)-PheOMe[b]	(R)-PheOMe[b]
(S,S)-1	T_c, °C	−25	−19	12	−36	−25
	$\Delta G^{\ddagger}_c$	12.4	12.3	13.4	11.8	12.1
(R,R)-1	T_c, °C	−21	13	−13	−25	−36
	$\Delta G^{\ddagger}_c$	12.6	13.4	12.5	12.1	11.8
(S,S)-2	T_c, °C	−30			−48	−34
	$\Delta G^{\ddagger}_c$	12.2			11.1	11.6
(S,S)-3	T_c, °C	−8			−26	−11
	$\Delta G^{\ddagger}_c$	13.4			12.4	12.7
(S,S)-4	T_c, °C	−33	−30	0	−61	−38
	$\Delta G^{\ddagger}_c$	12.1	11.8	13.0	11.0	11.4
(S,S)-5	T_c, °C	−29	−86	−56	−73	−40
	$\Delta G^{\ddagger}_c$	11.7	8.7	10.3	10.0	11.3
(S,S)-6	T_c, °C	10			−28	−33
	$\Delta G^{\ddagger}_c$	12.9			11.6	11.5
7[c]	T_c, °C	10				
	$\Delta G^{\ddagger}_c$	13.0				

[a] A Varian SC-300 spectrometer was used to record all ^1H NMR spectra. The CH_3 substituents on the macrocycle were used as the ^1H NMR probe for **1–5**. The ester CH_2 was the probe for **6** and **7**. T_c = coalescence temperature. $\Delta G^{\ddagger}_c$ values are ±0.2. [b] Bnz = the hydrogen perchlorate salt of benzylamine; NapEt = the hydrogen perchlorate salt of (R)- or (S)-α-(1-naphthyl)ethylamine; PheOMe = the hydrogen perchlorate salt of (R)- or (S)-methyl phenylalaninate. [c] Reference 29.

by an isoperibol titration calorimetry procedure, which has been described.[25-27] The data were analyzed on a DEC VAX 11/780 computer.

Determination of $\Delta G_c^{\ddagger}$ Values. These values were obtained by using the following experimental sequence. First, the ^1H NMR spectrum of the macrocyclic compounds (about 10 mg) in CD_2Cl_2 was obtained. Then, the solution was mixed with an equimolar amount of the alkylammonium salt and another ^1H NMR spectrum was obtained. Next, the probe temperature was lowered until one or more sets of peaks separated (usually −30 to −70 °C). In this slow-exchange limit, the chemical-shift difference ($\Delta\nu$) was measured. Successive ^1H NMR spectra were taken while the temperature was raised to about 20 °C above the temperature at which the peaks merge, i.e., the coalescence temperature, T_c. The $\Delta G_c^{\ddagger}$ values were calculated from the $\Delta\nu$ and T_c values by the procedure of Sutherland.[28] The $\Delta G_c^{\ddagger}$ values reported here are based on the coalescence of the peaks for the methyl hydrogen atoms for ligands **1–5** and on the methylene hydrogen atoms of the ester groups ($COOCH_2$) for **6** and **7**. Other probes such as either the pyridine ring hydrogen atoms for all ligands or the ester methine hydrogen atom (COOCH) for ligands **1–5**, while having different T_c and $\Delta\nu$ values, result in the same calculated $\Delta G_c^{\ddagger}$ for the dissociation of the complex.[30] For example, the following kinetic parameters were obtained for the (S,S)-1-Bnz complex by using the following ^1H NMR probes: CH_3, $\Delta\nu$ = 30.0 Hz, T_c = −25 °C, $\Delta G_c^{\ddagger}$ = 12.4 kcal/mol; COOCH, $\Delta\nu$ = 213 Hz, T_c = −13 °C, $\Delta G_c^{\ddagger}$ = 12.4; and pyridine ring hydrogens, $\Delta\nu$ = 127 Hz, T_c = −18 °C, $\Delta G_c^{\ddagger}$ = 12.4.[30]

Results and Discussion

The log K, ΔH, and $T\Delta S$ values for macrocycle-protonated amine and $-Ag^+$ interaction in CH_3OH are given in Table I. In Table II, $\Delta G_c^{\ddagger}$ values are given for macrocycle-protonated amine interactions in CD_2Cl_2 to-

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gether with the T_c values at which they were determined.

The affinity of the series of diester pyridino crown ligands (*S,S*)-**1**, (*S,S*)-**6**, and **7** for silver ion was the same within experimental error (Table I). From this result, we conclude that the presence and location of either methyl or phenyl groups has little effect on Ag^+ complexation. On the other hand, the log *K* data in Table I show that NH_4^+ binds much more strongly to the unsubstituted ligand **7** (log *K* = 3.29) than to (*S,S*)-**1** (log *K* = 2.81). The decreased complex stability in this case may reflect conformational effects. The directionality of the N–H···O bonds for the NH_4^+ complex requires conformational reorganization on the part of the host. The difference in log *K* (0.5) for the methyl-substituted and nonsubstituted host probably reflects a greater reorganizational energy for the former. A similar decrease in complex stability is seen, in the case of NH_4^+, between **7** and (*S,S*)-**6** in which substituted phenyl groups are present. Additional effects over that noted for NH_4^+ are found when R in Figure 1 is either TrpOMe, NapEt, or AlaOMe as evidenced by the further decrease in log *K* for the interaction of these cations with either (*S,S*)-**1** or (*S,S*)-**6**. In these cases, steric effects are probably also involved in determining differences in log *K*. The substantial difference in the *K* values for the interaction of (*S,S*)-**1**, with the enantiomer pairs of NapEt (2.6-fold) and AlaOMe (1.7-fold) is taken to be conclusive evidence of chiral recognition by this macrocycle. The absence of significant differences in the log *K* values for the interactions of (*S,S*)-**1** with the TrpOMe enantiomer pair and of (*S,S*)-**6** with the TrpOMe and AlaOMe enantiomeric pairs indicates no enantiomer recognition in these cases. The log *K* data in Table I indicate that there is enantiomeric recognition by (*S,S*)-**5** for the TrpOMe enantiomeric pair. However, in the case of this ligand log *K* values for the reaction of pyridino-18-crown-6 with either NH_4^+ or any of the RNH_3^+ ions used in the study are unavailable for comparison.

The thermodynamic results are corroborated by the kinetic data as is seen by examining the $\Delta G_c^{\ddagger}$ values in Table II. Systems common to the two studies are those involving (*S,S*)-**1**-NapEt and (*S,S*)-**5**-NapEt. Enantiomeric recognition by both of these macrocycles for the NapEt isomers is evident from the data in Table II. The (*S,S*)-**1** enantiomer formed a more kinetically stable complex in CD_2Cl_2 with (*R*)-NapEt than with the (*S*)-form by 1.1 kcal/mol. That enantiomeric recognition is involved in this result is confirmed by the fact that the (*R,R*)-**1** enantiomer formed a more kinetically stable complex with (*S*)-NapEt than with the *R* form by 0.9 kcal/mol. Similar results are found in the formation of complexes of (*S,S*)- and (*R,R*)-**1**, with the *R* and *S* forms of PheOMe although the effect is smaller. Ligand (*S,S*)-**1** formed a more kinetically stable complex with (*R*)-PheOMe by 0.3 kcal/mol and (*R,R*)-**1** with (*S*)-PheOMe by the same amount. Ligands (*S,S*)-**2** and (*S,S*)-**3**, which are the same as (*S,S*)-**1** except with an additional substituent on the pyridine ring, also exhibited enantiomeric recognition for (*R*)-PheOMe. On the other hand, the diphenyl-substituted diketo ligand **6** failed to show chiral recognition for the enantiomers of PheOMe.

The kinetic data indicate that chiral macrocycles (*S,S*)-**4** and (*S,S*)-**5** also exhibit enantiomeric recognition. Ligand (*S,S*)-**4**, which is similar to (*S,S*)-**1** except that the two carbonyl oxygen atoms have been replaced by sulfur atoms, showed chiral recognition for (*R*)-NapEt and (*R*)-PheOMe over the corresponding *S* forms by about the same amount as did (*S,S*)-**1**. No calorimetric data were obtained for the interaction of RNH_3^+ with **4** since this macrocycle decomposes in CH_3OH. The parent chiral dimethylpyridino-18-crown-6 ligand, (*S,S*)-**5**, exhibited the largest enantiomeric recognition effect yet observed by the temperature-dependent ^1H NMR technique. The (*S,S*)-**5** host formed complexes of greater kinetic stability with (*R*)-NapEt and with (*R*)-PheOMe than with the corresponding *S* forms of these guest cations by 1.6 and 1.3 kcal/mol, respectively. It is interesting to note that the complexes with (*S,S*)-**5** are less stable kinetically than those with (*S,S*)-**1** (Table II) and yet (*S,S*)-**5** exhibited greater chiral recognition.

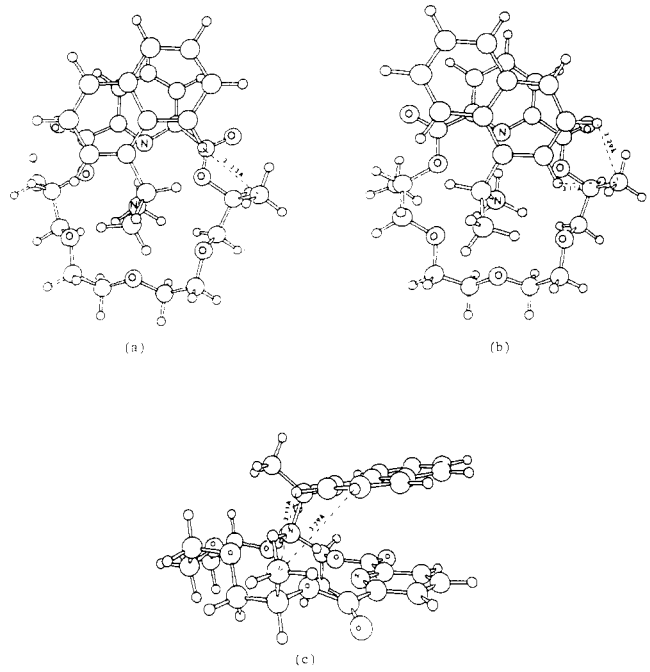

Figure 3. ORTEP[32] drawings of (*S,S*)-**1**–(*R*)-NapEt (a and c) and (*S,S*)-**1**–(*S*)-NapEt (b) complexes taken from X-ray crystallographic data.[21] Oxygen and nitrogen atoms are designated O and N, respectively.

The structures of the (*S,S*)-**1**–(*R*)-NapEt and (*S,S*)-**1**–(*S*)-NapEt complexes have been determined by an X-ray crystallographic procedure.[21] The results of this study that are pertinent to the present investigation are depicted in Figure 3. In this figure, a and b are representations of the (*S,S*)-**1**–(*R*)-NapEt and the (*S,S*)-**1**–(*S*)-NapEt complexes, respectively. Figure 3c shows a side view of the (*S,S*)-**1**–(*R*)-NapEt complex. A significant feature of the structures of both of these host–guest complexes is that the guest naphthyl groups are adjacent to, and nearly parrallel to, the host pyridino group (Figure 3c) with the geometric centers of the moieties separated by 3.52 and 3.64 Å for the (*S,S*)-**1**–(*S*)-NapEt and (*S,S*)-**1**–(*R*)-NapEt complex, respectively. Apparently, π–π interactions are of sufficient strength to stabilize this spatial arrangement in both cases. This interaction together with the primary hydrogen-bonding interactions (Figures 3a and 3b) appears to anchor the guest into a fixed position relative to the host.

An additional important feature of the structures is the near approach of certain guest naphthyl hydrogen atoms to the substituent methyl group at one chiral site on the macrocycle (Figures 3a and 3b). In the case of the (*S,S*)-**1**–(*S*)-NapEt complex (Figure 3b), two hydrogen atoms of the naphthyl moiety are close enough to interact sterically with the host methyl substituent. The distances between the indicated naphthyl hydrogen atoms and the methyl carbon atom are 3.11 and 3.29 Å. In the complex with the opposite enantiomer (Figure 3a), the minimum

approach distance is 3.33 Å. Although the precise locations of the methyl hydrogen atoms are unknown, steric interference is inferred by the assumptions that the van der Waals radius for hydrogen is 1.2 Å,[31] and the C–H bond length is 1.08 Å. With use of these assumptions, a maximum distance for steric interference of 3.48 Å is estimated. Interference resulting in restriction of free rotation of the methyl group at this site is expected to be greater for the (*S,S*)-**1**–(*S*)-NapEt complex than for the (*S,S*)-**1**–(*R*)-NapEt complex. Comparison of these sites in Figures 3a and 3b shows that the indicated differences in the distances result from the placement of the naphthyl group in the two enantiomers. While we recognize that the geometrical configuration is less restricted in solution than in the crystal, the crystallographic results are consistent with less steric interference in the (*S,S*)-**1**–(*R*)-NapEt complex than in the (*S,S*)-**1**–(*S*)-NapEt complex. Thus, the structural data provide a rational explanation for the relative magnitudes of the log K and $\Delta G_c^{\ddagger}$ values in these cases.

Chiral recognition in the complexation of (*S,S*)-**1** with NapEt was also shown by a simple selective crystallization study. The chemical shift in the ^{1}H NMR spectrum for the complex of (*S,S*)-**1** with (*R*)-NapEt is slightly different than that for the complex with (*S*)-NapEt. The complex formed when 1 equiv of (*S,S*)-**1** was mixed with 2 equiv of racemic NapEt was found to contain 68% of the *R* and 32% of the *S* isomer of NapEt. A similar study was not completed for the complexes of (*S,S*)-**1** with AlaOMe and PheOMe since those complexes could not be crystallized.

Detailed explanations of the observed presence and absence of enantiomer recognition in the remaining cases must await additional structural studies. However, the data in Tables I and II provide some insight into the effect of substituent location and type on enantiomeric recognition.

The diphenyl-substituted ligand **6** failed to show enantiomeric recognition for any of the enantiomeric pairs studied by either the calorimetric or kinetic procedure as is seen by the log K and $\Delta G_c^{\ddagger}$ data in Tables I and II. The $\Delta G_c^{\ddagger}$ data show that less steric hindrance is caused in these complexation reactions by the phenyl than by the methyl substituents of **1**–**5**. The $\Delta G_c^{\ddagger}$ values are 13.0 and 12.9 kcal/mol for the complexation of Bnz with unsubstituted **7** and diphenyl-substituted **6**, respectively, and 12.4, 12.6, 12.1, and 11.7 kcal/mol for the complexation of Bnz with dimethyl-substituted (*S,S*)-**1**, (*R,R*)-**1**, and the *S,S* forms of **4** and **5** (Table II). The phenyl substituents of **6** are further from the nitrogen binding site in the less rigid polyether portion of the macrocycle, while the methyl substituents of **1** are next to the rigid ester–pyridine groups. We infer from the structures shown in Figure 3 that if complexation with the various guests studied results in a similar conformation of the macrocycle and similar placement of the guest side groups, then the phenyl substituents on the macrocycle are not in a position to interfere in a manner that would differentiate between the enantiomers.

The electron-withdrawing 4-chloro group of (*S,S*)-**2** caused a diminished kinetic stability for the complex with Bnz, while the electron-donating 4-methoxy group of (*S,S*)-**3** showed enhanced kinetic stability over that shown for the complex (*S,S*)-**1** with Bnz as we reported previously for the derivatives of **7**.[29] Similar effects on the kinetic stability were shown by the complexes of (*S,S*)-**2** and (*S,S*)-**3** with both forms of PheOMe as compared to the (*S,S*)-**1**–PheOMe complexes.

The $\Delta G_c^{\ddagger}$ data in Table II for the interaction of the *S,S* forms of **2**–**4** with the *S* and *R* forms of PheOMe always favor the *R* form. This result is consistent with the preceding discussion and indicates that the presence of chloro and OMe groups on the pyridine moiety and the substitution of thiono groups for keto groups have little effect on enantiomer recognition.

The (*S,S*)-**5**–TrpOMe complexes were more stable thermodynamically than the corresponding (*S,S*)-**1**–TrpOMe complexes (Table I). This result is expected since removal of the electron-withdrawing carbonyl groups from the macrocycle ring should allow the (*S,S*)-**5** to complex more strongly with ammonium salts.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. Support from National Science Foundation Grant No. CHE-8000059 is also gratefully acknowledged. Salary for F.G.M. for the ^{1}H NMR work was provided by the Division of Chemical Sciences, Office of Basic Energy Sciences, Department of Energy Contract No. DE-AC02-78ER05006. We thank Dr. J. F. Stoddart for his supply of (*R*)- and (*S*)-PheOMe.

Registry No. (*S,S*)-**1**, 82468-65-3; (*R,R*)-**1**, 83780-63-6; (*S,S*)-**2**, 83725-75-1; (*S,S*)-**3**, 83725-76-2; (*S,S*)-**4**, 88034-45-1; (*S,S*)-**5**, 88034-46-2; (*S,S*)-**6**, 80656-07-1; benzene, 18720-46-2; (*S*)-NapEt, 82431-48-9; (*R*)-NapEt, 82456-17-5; (*S*)-PheOMe, 75444-51-8; (*R*)-PheOMe, 75444-50-7; (*S*)-TrpOMe, 7524-52-9; (*R*)-TrpOMe, 14907-27-8; (*S*)-AlaOMe, 2491-20-5; (*R*)-AlaOMe, 14316-06-4; NH_4Cl, 12125-02-9; Ag^+, 14701-21-4.

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