Chiral Pyridine-Based Macrobicyclic Clefts: Synthesis and Enantiomeric Recognition of Ammonium Salts

Paul C. Hellier, Jerald S. Bradshaw,* J. Jolene Young, Xian Xin Zhang, and Reed M. Izatt

Department of Chemistry and Biochemistry, Brigham Young University, Provo, UT 84602

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An achiral (**3**) and two chiral pyridine-based macrobicyclic clefts (**4** and **5**) have been prepared by treating 2,6-bis[[2′,6′-bis(bromomethyl)-4′-methylphenoxy]methyl]pyridine (**2**) with the appropriate achiral and chiral glycols. Starting **2** was prepared by first treating 2,6-bis(hydroxymethyl)-4-methylphenol with 2,6-[(tosyloxy)methyl]pyridine followed by phosphorus tribromide. Achiral macrobicyclic cleft **3** formed a complex at 25 °C in 50% CH_3OH/50% $CHCl_3$ (v/v) with a primary ammonium salt (log $K = 3.15$) as evidenced by a significant change in the ^{1}H NMR spectrum. Highly organized (*S*,*S*,*S*,*S*)-**4**, prepared by treating **2** with (1*S*,5*S*)-3-oxapentane-1,5-diol, exhibited recognition at 25 °C in 20% C_2H_5OH/80% 1,2-$C_2H_4Cl_2$ (v/v) for the (*S*)-enantiomer of α-(1-naphthyl)-ethylammonium perchlorate (NapEt) over its (*R*)-form (Δ log $K = 0.85$). This high recognition factor probably reflects an increase in molecular rigidity by the introduction of a second macro ring on the monocyclic pyridinocrown ligand.

Introduction

The study of chirality at the molecular level has emerged as a central theme in contemporary chemistry. Much of the stimulus for this interest originated from the chiral nature of many biomolecules and their interaction with other molecules. Chiral molecules find use in pharmaceuticals and agrochemicals. While the field of asymmetric synthesis has progressed at a tremendous rate in recent years,[1] there are still many instances where these methods do not provide a practical means for the preparation of pure homochiral compounds. Thus, there is a continuing interest in the chromatographic separation of racemic mixtures using chiral stationary phases.[2] Fundamental to the development of such materials is a thorough understanding of the factors affecting chiral recognition at the molecular level.[3] The knowledge gained through the study of this aspect of supramolecular chemistry is also of importance because of the insight it may give us into the forces driving biological recognition phenomena such as enzyme−substrate and antibody−antigen interactions.

The seminal work of Cram and co-workers[4] on the host−guest chemistry of primary ammonium salts and 1,1-binaphthol-derived chiral crown ethers illustrates clearly the validity of this approach. Enantiomeric recognition was optimized using a rational approach to host design. The subsequent covalent attachment of such compounds to an inert support resulted in systems capable of effecting the enantiomeric separation of racemic amino acid and ester salts.[5]

Our work has focused on the enantiomeric recognition of chiral organic ammonium salts by chiral crown ethers based on the pyridine-18-crown-6 structure.[3a] This host−guest pairing is particularly suited to such studies because of the strong intermolecular binding observed, arising from 3-point hydrogen bonding of the ammonium hydrogen atoms to the pyridine nitrogen atom and two of the oxygen atoms within the ring.[6] A further contribution to the overall stability of the supramolecular complex comes from the charge−dipole electrostatic interactions. The systematic introduction of various substituents around the macrocyclic ring has shed much light on the effect that such structural modifications have upon the differential binding of a pair of enantiomers. These studies have been guided by the characterisation of the host−guest interactions using a variety of physical techniques including ^{1}H NMR spectroscopy,[7−11] calorimetric titration,[7] X-ray crystallography,[7,10] and molecular mechanics calculations.[10,11] Crown ethers of this type, when bound to silica gel, have been shown to successfully effect the separation of the (*R*) and (*S*) forms of α-(1-naphthyl)ethylammonium perchlorate.[12]

As a result of their complexity, the synthesis of chiral macrobicyclic hosts has been left relatively unexplored.[13] Even less attention has been given to their use in enantiomeric recognition studies, even though they offer a number of potentially advantageous properties in comparison to macromonocyclic structures. Macrobi-

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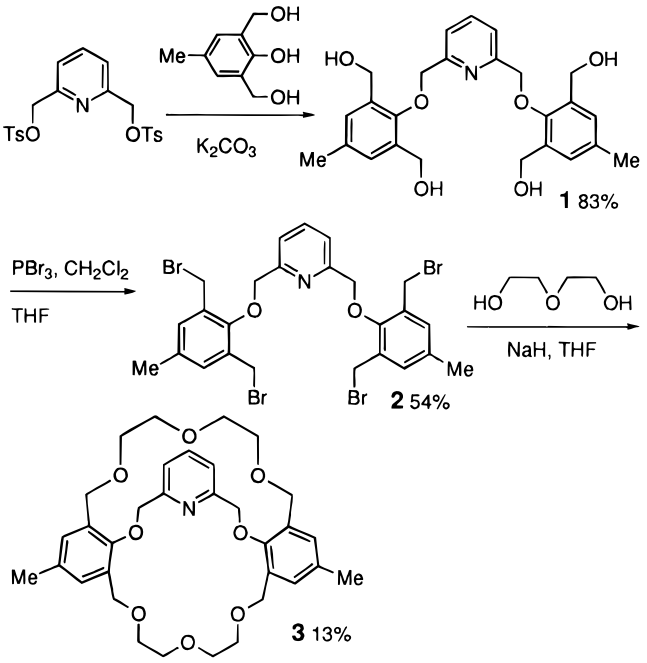
Scheme 1



cycles possess a three-dimensional cavity in which the recognition event may take place, thus, possibly leading to improved discrimination. In addition, recognition can be encouraged by the large degree of preorganization that is typically found in such molecules. The chiral recognition of amides and carboxylic acids has been demonstrated in macrobicyclic hosts by Still and co-workers[14] and Kilburn and co-workers,[15] respectively. The great potential of polycyclic structures in such studies is well illustrated in a recent publication of Yoon and Still,[16] where a macrotricyclic receptor showed binding of L-amino acid derivatives with enantioselectivites as high as 99% ee. Chiral cage-type cyclophanes of a similar topology have also been investigated by Murakami and co-workers.[17]

The present work is concerned with the synthesis of one achiral and two chiral macrobicylic hosts containing pyridine rings (**3**−**5**) (Schemes 1 and 2). This topology was chosen as previous studies on similar achiral compounds had shown that the 1,2,3-substitution pattern on the aromatic bridgeheads would result in the formation of a cleftlike structure.[18] This would allow ready access into the cavity for a guest organic ammonium salt. The incorporation of the rigid pyridine unit would impart a good deal of preorganization to the molecule resulting in a fixed conformation with the basic pyridine nitrogen atom directed toward the base of the cleft. The opening of the cleft is defined by the two polyether chains. Our synthesis of the achiral pyridine-containing cleft (Scheme 1) was flexible, thus allowing us to readily control the nature of the cavity through the use of the appropriate (*e.g.* chiral) diol in the final macrobicyclization step. An analagous pyridine-based macrobicycle was recently descibed by Lüning and co-workers,[19] although the potential to render their macrobicycle chiral has yet to be realized.

Results and Discussion

The key precursor in the planned syntheses of the chiral macrobicycles was the pyridine-bridged tetrabromide **2**. This material was prepared according to the route depicted in Scheme 1. 2,6-[(Tosyloxy)methyl]-pyridine was treated with 2 equiv of 4-methyl-2,6-bis-(hydroxymethyl)phenol in acetone using potassium carbonate as a base. Regioselective alkylation of the more acidic phenolic oxygen atoms occurred to give tetraalcohol **1** in an 83% yield. This gave access to **2** *via* bromination with phosphorus tribromide.

We decided to begin our studies by preparing the achiral pyridine-containing macrobicycle **3**. This would allow us to demonstrate the feasibility of the cyclization strategy and verify that successful complexation of organic ammonium salts would occur, before embarking on more lengthy syntheses of chiral hosts. Thus, **2** was treated with 2 equiv of diethylene glycol (Scheme 1) in THF using NaH as a base. The desired compound **3** was isolated as a white crystalline solid in a 13% yield. This represents a reasonable yield for such a reaction, probably the result of a convergent nature of the bromomethyl groups and the rigidity of precursor **2**. The ^{1}H NMR spectrum of this compound gave clear evidence that the expected cleftlike structure was maintained in solution. The bulk and rigidity of the pyridine group prevents the macrobicycle from inverting on itself. Thus, the two hydrogens of the benzylic methylene groups on the aromatic bridgeheads are magnetically inequivalent, giving rise to two doublets of an AB system in contrast to the singlet observed for the corresponding protons of acyclic precursor **2**.

^{1}H NMR spectroscopy gave clear evidence that achiral macrobicycle **3** could function as a host for primary ammonium salts. The addition of 1 equiv of (*R*)-(+)-(α-phenylethyl)ammonium perchlorate (PhEt) to a solution of the macrobicycle in a mixture of $CDCl_3$ and CD_3OD (1:1, v:v) resulted in substantial spectral changes. For instance, the doublet arising from the protons in the 3-position of the pyridine ring was shifted upfield from δ 7.538 to δ 7.381. More complex changes were observed in the spectrum reflecting the overall decrease in symmetry of the host−guest complex compared to the free host arising from the chiral nature of the ammonium salt. This could be seen clearly in the region δ 4.05 to δ 4.40 where the AB system, originating from the benzylic methylene protons adjacent to the benzene rings, was split into two distinctly separate AB patterns upon complexation. A log *K* value of 3.15 (See Table 1) for the complexation of (*R*)-(+)-PhEt was determined from the chemical shift changes induced by the incremental addition of the salt, according to the technique described by Zhu *et al.*[20] In a similar manner, the association constants for the binding of (*R*)-(−)-phenylglycinol hydrogen perchlorate (PhEtOH) and (*R*)-(+)-α-(1-naphthyl)-

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Table 1. Log *K*, Δ*H* (kJ/mol), and *T*Δ*S* (kJ/mol) Values[a] Determined by ^{1}H NMR and Calorimetric Titrations for Interactions of Chiral Macrocyclic Ligands with Enantiomers of Three Primary Ammonium Cations[b] in Various Solvents at 25 °C

ligand	cation	log *K*	Δ*H*	*T*Δ*S*	Δlog *K*[c]	solvent[d]
3	(*R*)-NapEt	2.32 ± 0.05				1 M/1 C
	(*R*)-PhEt	3.15 ± 0.05				1 M/1 C
	(*R*)-PhEtOH	2.95 ± 0.04				1 M/1 C
(*S*,*S*,*S*,*S*)-**4**	(*R*)-NapEt	ND				M
	(*S*)-NapEt	ND				M
	(*R*)-PhEt	ND				M
	(*S*)-PhEt	ND				M
	(*R*)-NapEt	2.49 ± 0.05	−13.6 ± 0.8	0.61		2Et/8DCE
	(*S*)-NapEt	3.34 ± 0.04	−15.7 ± 0.7	3.36	0.85	2Et/8DCE
	(*R*)-NapEt	2.26 ± 0.03				2M/8C
	(*S*)-NapEt	2.71 ± 0.03			0.45	2M/8C
	(*R*)-PhEt	2.47 ± 0.04				5M/95C
	(*S*)-PhEt	2.85 ± 0.02			0.38	5M/95C
	(*R*)-PhEt	2.48 ± 0.05				1M/9C
	(*S*)-PhEt	2.65 ± 0.05			0.17	1M/9C
	(*R*)-PhEt	1.77 ± 0.06				1M/1C
	(*S*)-PhEt	2.10 ± 0.04			0.33	1M/1C
(*S*,*S*)-**6**	(*R*)-NapEt[e]	2.47 ± 0.02	−27.6 ± 0.1	−18.9		M
	(*S*)-NapEt[e]	2.06 ± 0.02	−26.4 ± 0.1	−18.5	0.41	M
	(*R*)-NapEt	3.88 ± 0.03	−29.2 ± 0.4	−7.00		2Et/8DCE
	(*S*)-NapEt	3.42 ± 0.04	−23.5 ± 0.7	−3.98	0.46	2Et/8DCE
(*S*,*S*)-**6**	(*R*)-NapEt[f]	2.96 ± 0.02				1M/1C
	(*S*)-NapEt[f]	2.43 ± 0.04			0.53	1M/1C
	(*R*)-PhEt[g]	2.33 ± 0.05				M
	(*S*)-PhEt[g]	2.11 ± 0.05			0.22	M

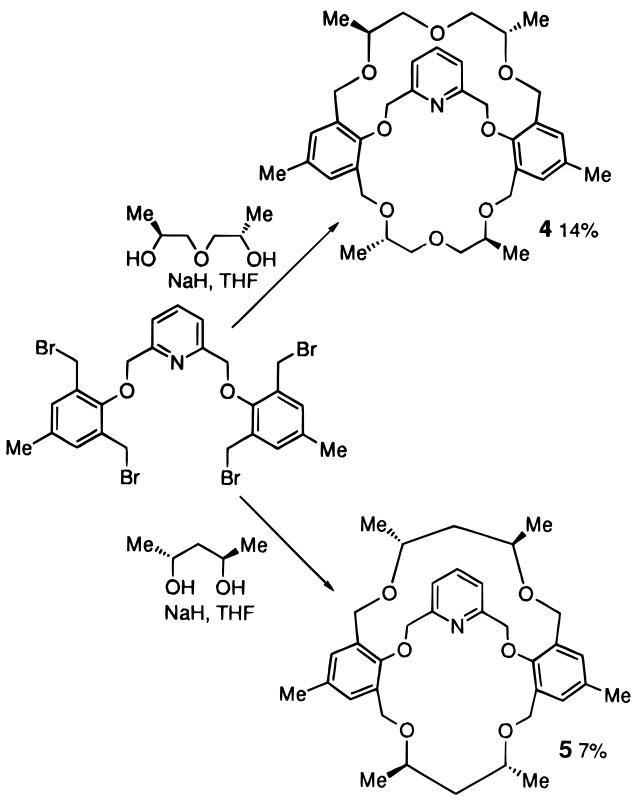
[a] Log *K* values without Δ*H* and *T*Δ*S* values were determined using the ^{1}H NMR mehod. ND means not determined because no significant chemical shift change was observed. [b] Perchlorate salts of the ammonium cations were used. The notations of ammonium cations are defined in Figure 2. [c] The Δlog *K* value is the difference between log *K* values for enantiomer interactions with a given chiral macrocyclic ligand. [d] M = methanol; C = chloroform; DCE = 1,2-dichloroethane; Et = ethanol. Solvent mixtures are indicated by volumetric ratios of their components. For example, 1M/1C = 50% methanol−50% chloroform (v/v). For NMR measurements, 100% deuterated solvents were used. [e] Reference 7. [f] Reference 23. [g] Reference 3a.

ethylammonium perchlorate (NapEt) were found to be 2.95 and 2.32, respectively. The lower value in the latter case probably reflects the bulkier nature of the guest.

Having established that achiral pyridine-containing macrobicycle **3** would effectively complex primary ammonium salts, we prepared the chiral analogues. For this purpose the homochiral methyl-substituted diethylene glycol, (1*S*,5*S*)-3-oxapentane-1,5-diol, was prepared in four steps from ethyl (*S*)-lactate according to the reported procedure.[21,22] Chiral tetramethyl-substituted macrobicycle **4** was synthesized in a 14% yield by treating the previously mentioned tetrabromide **2** with 2 equiv of the dianion derived from the chiral diol (Scheme 2). In a similar fashion a related chiral macrocycle **(5)**, with a smaller cavity, was prepared from (2*R*,4*R*)-pentanediol which is commercially available. The analogous reaction using (2*R*,3*R*)-butanediol was unsuccessful, possibly reflecting the increased strain in the still smaller cavity size.

The ^{1}H NMR spectrum of highly organized chiral host **4** is beautifully resolved (Figure 1), and clearly reflects the C_2 symmetry of the molecule that results from the introduction of chirality, in contrast to the C_{2v} symmetry of its achiral analogue **(3)**. Thus the benzylic methylene groups of the aromatic bridgeheads now give rise to two separate AB systems, resulting in a pair of doublets at δ 5.02 and 4.44; and δ 4.25 and 3.98. Similarly the protons of the methylene group adjacent to the pyridine ring are characterized by another AB system with signals at δ 5.33 and 4.97 instead of the usual singlet. The two

Scheme 2



distinct environments of the polyether ring methyl groups are identified by two doublets at δ 1.22 and 1.04. The ^{1}H NMR spectrum when recorded at 500 MHz shows, in the region δ 3.19 to 3.81, clear resolution of the remaining six inequivalent protons on a single dimethyl-substituted polyether section. Together with the two previously

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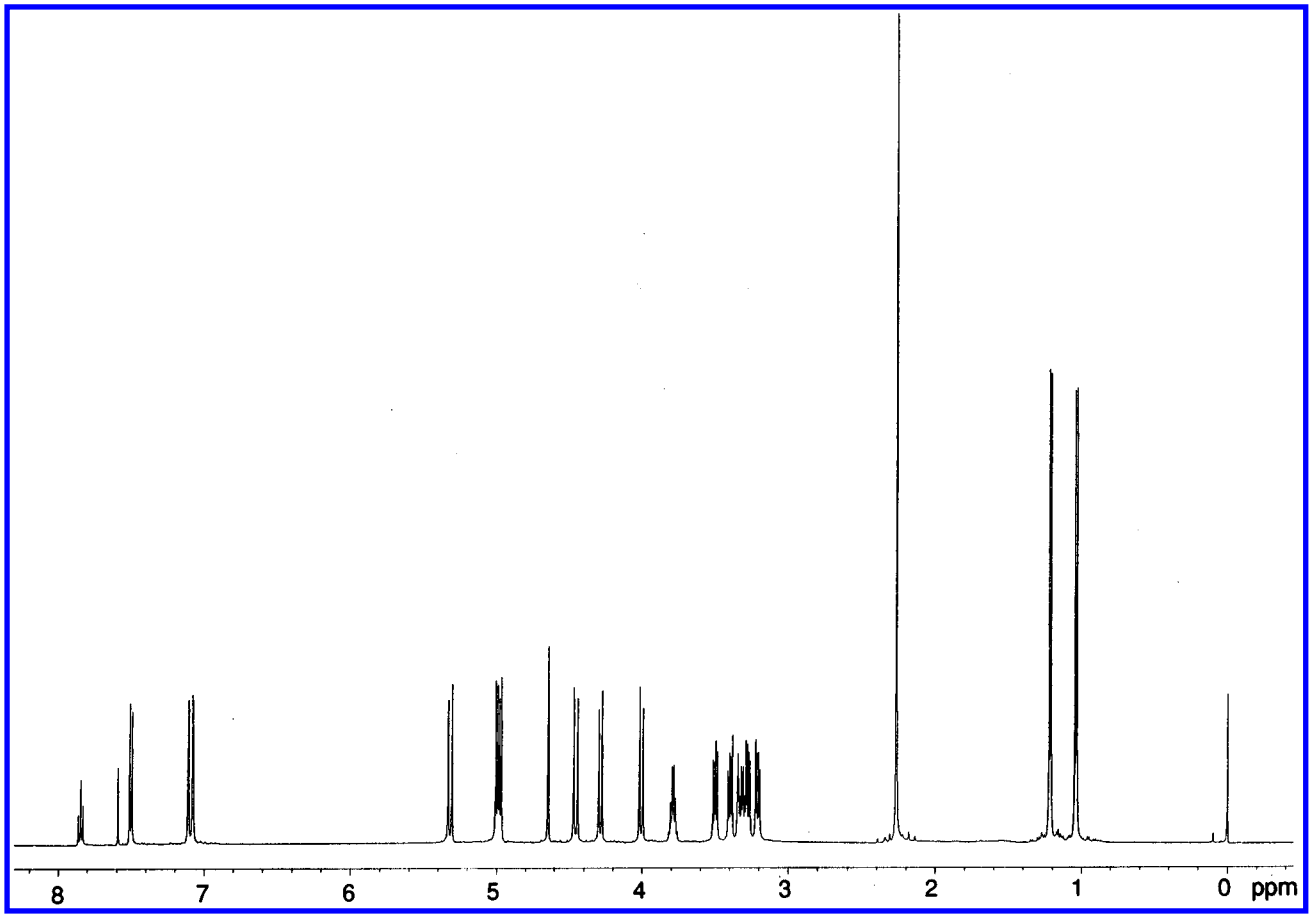

Figure 1. Proton NMR spectrum of **4**.

mentioned methyl groups these constitute two independent spin systems, the coupling interconnectivities of which have been clearly established by a 2D-COSY ^{1}H NMR experiment. An NOE ^{1}H NMR experiment aimed at unambiguously assigning the relative spatial positions of the ring methyl groups with respect to the pyridine ring was not successful. A similar logic to that detailed above allowed the interpretation of the ^{1}H NMR spectrum of the smaller macrobicyclic cleft **(5)**.

On complexing with (*R*)- and (*S*)-NapEt, the host pyridine proton signal at $\delta = 7.49$ ppm undergoes an upfield shift indicating an overlap between the naphthalene group of the guest ammonium salt and the pyridine group of host **4**. The benzene proton signals of **4** shift downfield in the NapEt complex. This downfield shift is believed to be a result of hydrogen bonding between the guest ammonium salt and the oxygen atoms adjacent to the benzene groups of **4**. Thus, the NMR data suggest that the ammonium guest interacts with the macrocyclic cleft through hydrogen bonding and that the naphthalene group of NapEt and the pyridine part of host **4** are close together.

Thermodynamic quantities for interactions of macrobicyclic compounds **3**, (*S*,*S*,*S*,*S*)-**4** and dimethylpyridino-18-crown-6 ligand (*S*,*S*)-**6** with three primary organic ammonium salts are listed in Table 1. The ligands and ammonium salts are shown in Figure 2. Compared with (*S*,*S*)-**6**, macrobicyclic (*S*,*S*,*S*,*S*)-**4** shows improved enantiomeric recognition toward NapEt. A large difference in stabilities between the complexes of (*R*)- and (*S*)-NapEt with (*S*,*S*,*S*,*S*)-**4** ($\Delta\log K = 0.85$) is observed in a 2:8 (v/v) EtOH/ClC_2H_4Cl (2Et/8DCE) solvent mixture, while the $\Delta\log K$ value for (*R*)- and (*S*)-NapEt interactions with

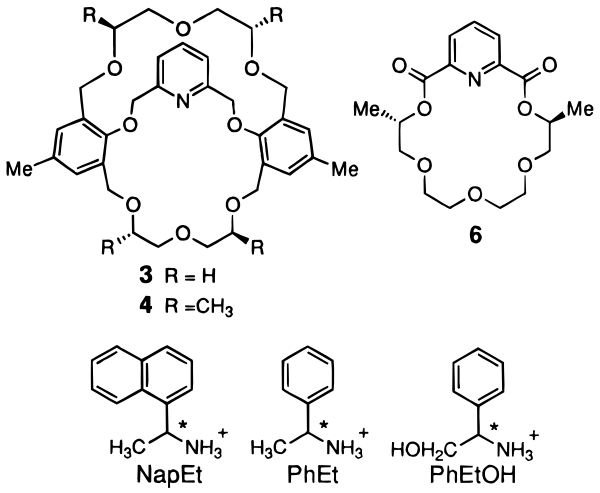

Figure 2. Macrocylic ligands and chiral organic ammonium perchlorates used in this study.

(*S*,*S*)-**6** is 0.46 in the same solvent mixture. The $\Delta\log K$ value of 0.85 indicates an excellent enantiomeric recognition. This high degree of enantiomeric recognition by (*S*,*S*,*S*,*S*)-**4** is probably due to an increase in molecular rigidity by introducing a second macro ring and two phenyl groups. Thermodynamic data provide evidence for this point. Positive values of entropy changes for **4**−NapEt interactions, as compared with **6**−NapEt interactions which show negative values of entropy changes, suggest a smaller conformational change of ligand **4** during complexation, indicating that **4** is more rigid than **6**.

It is interesting to note that (*S*,*S*,*S*,*S*)-**4** recognizes the (*S*) forms of NapEt and PhEt over their (*R*) forms, a reverse sequence of recognition as compared to (*S*,*S*)-**6** which recognizes the (*R*) forms of NapEt and PhEt over their (*S*) forms (see Table 1). Both enthalpic and entropic effects make contributions to the enantiomeric recognition of NapEt by (*S*,*S*,*S*,*S*)-**4**. The ΔH and $T\Delta S$ values for (*S*)-NapEt−(*S*,*S*,*S*,*S*)-**4** interaction are 2.1 and 2.75 (kJ/mol), respectively, more favorable than those for (*R*)-NapEt−(*S*,*S*,*S*,*S*)-**4** interaction. On the other hand, only the enthalpy change contributes to enantiomeric recognition of NapEt by (*S*,*S*)-**6**. In methanol for example, the ΔH value for (*R*)-NapEt−(*S*,*S*)-**6** interaction is 1.2 (kJ/mol) more favorable but the $T\Delta$S value is 0.4 (kJ/mol) more unfavorable than those for (*S*)-NapEt−(*S*,*S*)-**6** interaction.

As has been observed in other chiral recognition systems,[3,22−25] solvent has an effect on enantiomeric recognition with (*S*,*S*,*S*,*S*)-**4**. In MeOH/$CHCl_3$ solvent mixtures, the degree of enantiomeric recognition is lower than that in the 2Et/8DCE binary solvent. A high degree of enantiomeric recognition toward NapEt by (*S*,*S*,*S*,*S*)-**4** is observed in 2Et/8DCE while in 2:8 (v/v) $CD_3OD/CDCl_3$ (2M/8C) the $\Delta\log K$ value decreases to 0.45 and it further decreases to 0.38 with an increase in the $CDCl_3$ component of the solvent mixture (5M/95C). The recognition of (*S*,*S*,*S*,*S*)-**4** for PhEt enantiomers is not directly comparable with that of (*S*,*S*,)-**6** due to the different solvents used. As seen in Table 1, however, (*S*,*S*,*S*,*S*)-**4** does not show a significant improvement in enantiomeric recognition toward PhEt.

In MeOH, the interaction of macrobicycles **3** and **4** with NapEt and PhEt is very weak. No complexation could be detected by the ^{1}H NMR spectral method. In the solvent mixtures used, 1M/1C and 2Et/8DCE, **3** and **4**, form complexes with NapEt, PhEt, and PhEtOH but the complex stabilities are lower than those with **6**. This observation indicates that the second macro ring attached through the two phenyl groups and an enlargement of the pyridine-containing macro ring (from 18 members of **6** to 20 members for **3** and **4**) may result in a macrocyclic conformation which weakens tripod hydrogen bonding formed with the ammonium cations. The smaller $-\Delta H$ values for (*R*)- and (*S*)-NapEt interactions with (*S*,*S*,*S*,*S*)-**4** than those for (*R*)- and (*S*)-NapEt interactions with (*S*,*S*)-**6** support this explanation.

Experimental Section

^{1}H NMR spectra were recorded at 200 and 500 MHz. Solvents and starting materials were puchased from commercial sources where available.

2,6-Bis[[2′,6′-bis(hydroxymethyl)-4′-methylphenoxy]-methyl]pyridine (1) (Scheme 1). A solution of 4-methyl-2,6-bis(hydroxymethyl)phenol (50.9 g, 0.30 mol) and K_2CO_3 (45.4 g, 0.33 mol) in 1.5 L of acetone was refluxed for 30 min. 2,6-[(Tosyloxy)methyl]pyridine (67.82 g) was added to the reaction mixture and rinsed in with 0.5 L of acetone. The reaction mixture was heated at reflux for 16 h. H_2O (680 mL) was added, and the reaction mixture was filtered hot. The volume of the filtrate was reduced to 1 L on a rotary evaporator. The analytically pure product precipitated as white crystals on standing at 4 °C to give 53.7 g (83%) of **1**; mp 180 °C; IR (KBr) 3407, 2917, 1599, 1481, 1203, 1155, 1039, 1017, 995 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 2.30 (s, 6H), 4.55 (d, 8H, J = 4.5 Hz), 4.95 (s, 4H), 5.13 (t, 4H, J = 4.5 Hz), 7.17 (s, 4H), 7.65 (d, 2H, J = 8.2 Hz), 8.00 (t, 1H, J = 8.2 Hz); ^{13}C NMR (DMSO-d_6) δ 20.7, 58.1, 76.1, 120.6, 127.9, 132.7, 134.7, 138.1, 151.2, 156.7; MS (CI) m/z 440 ($M^+ + 1$). Anal. Calcd. for $C_{25}H_{29}NO_6$: C, 68.32; H, 7.47; N, 3.19. Found: C, 68.13; H, 7.34; N, 3.12.

2,6-Bis[2′,6′-bis(bromomethyl)-4′-methylphenoxy]-methyl]pyridine (2) (Scheme 1). A 1.0 M solution of PBr_3 in CH_2Cl_2 (90 mL) was added to a solution of **1** (9 g, 0.02 mol) in THF (700 mL) under a nitrogen atmosphere at 0 °C over a period of 30 min. Stirring was continued at 0 °C for 3 h. The reaction mixture was evaporated under vacuum. The residue was added to a mixture of ice-water (300 mL) and CH_2Cl_2 (250 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 250 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried (Mg_2SO_4), filtered, and evaporated under vacuum. The crude product was recrystallized from $ClCH_2CH_2Cl$/MeOH (2:3.5) to give 7.06 g (54%) of **2** as a white solid; mp 155−156 °C; IR (KBr) 2920, 1595, 1480, 1365, 1236, 1210, 1160, 972, 792 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.31 (s, 6H), 4.60 (s, 8H), 5.29 (s, 4H), 7.21 (s, 4H), 7.69 (d, 2H, J = 8.1 Hz), 7.91 (t, 1H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 21.2, 28.4, 77.0, 121.4, 132.3, 133.4, 135.6, 139.6, 153.5, 156.9; MS (CI) m/z 691 (M^+). Anal. Calcd. for $C_{25}H_{25}Br_4NO_2$: C, 43.44; H, 3.64; N, 2.03. Found: C, 43.66; H, 3.81; N, 1.88.

13,27-Dimethyl-3,6,9,17,20,23,30,38-octaoxa-40-aza-hexacyclo[23.3.1.$9^{29,39}$.$3^{11,15}$.$1^{11,15}$.$1^{32,36}$]tetraconta-1(29),11,13,15(39),25,27,32,34,36(40)-nonaene (3) (Scheme 1). A solution of diethylene glycol (0.95 mL, 10 mmol) in THF (90 mL) was added to a suspension of 95% NaH (0.76 g, 30 mmol) in THF (90 mL) under N_2 over 10 min. The reaction mixture was heated at reflux for 1 h. After cooling to rt, a solution of **2** (3.45 g, 5 mmol) in THF (190 mL) was added with vigorous stirring over a period of 3 h. The reaction mixture was stirred at rt for a further 16 h. After cooling to 0 °C, H_2O (20 mL) was added. The reaction mixture was evaporated under vacuum. The residue was dissolved in a mixture of H_2O (100 mL) and CH_2Cl_2 (200 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried (Mg_2SO_4), filtered, and evaporated under vacuum. The residue was chromatographed on silica gel eluting with first MePh/$MeCO_2Et$ (20:1) and then MePh/MeOH (100:1). The crude product was isolated by evaporation of the second eluant under vacuum. The isolated product was further purified by chromatography on silica gel eluting with MeOH/30% aqueous NH_3 (20:1) to give 0.37 g (13%) of **3** as a white crystalline solid; mp 57 °C; IR(KBr) 2919, 1596, 1452,1242, 1097, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.27 (s, 6H), 3.23−3.60 (m, 16H), 4.19 (d, 4H, J = 11.5 Hz), 4.61 (d, 4H, J = 11.0 Hz), 5.25 (s, 4H), 7.07 (s, 4H), 7.54 (d, 2H, J = 8.0 Hz), 7.80 (t, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ: 20.6, 68.6, 68.7, 69.9, 78.5, 121.4, 130.6, 131.1, 132.7, 136.8, 154.1, 156.9; MS (CI) m/z 578 ($M^+ + 1$). Anal. Calcd. for $C_{33}H_{41}NO_8$: C, 68.37; H, 7.13; N, 2.42. Found: C, 68.05; H, 7.22; N, 2.27.

(4*S*,8*S*,18*S*,22*S*)-4,8,13,18,22,27-Hexamethyl-3,6,9,17,20,23,30,38-octaoxa-40-azahexacyclo-[23.3.1.$9^{29,39}$.$3^{11,15}$.$1^{11,15}$.$1^{32,36}$]tetraconta-1(29),11,13,15(39),25,27,32,34,36(40)-nonaene (4) (Scheme 2). (2*S*,6*S*)-4-Oxaheptane-2,6-diol[21,22] (1.34 g, 10 mmol) was treated with **2** (3.45 g, 5 mmol) according to the procedure described above for the synthesis of **3**. The crude product was purifed by chromatography on silica gel eluting with MePh/$MeCO_2Et$ (20:1) to give 0.454 g (14.2%) of **4** as a white crystalline solid; mp 131−2 °C; $[\alpha]^{25}_D$ = +11.2 (c = 1.70, CH_2Cl_2); IR(KBr) 2922, 1592, 1453, 1372, 1207, 1108 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.04 (d, 6H, J = 5.9 Hz), 1.22 (d, 6H, J = 6.2 Hz), 2.27 (s, 6H), 3.18−3.23 (m, 2H), 3.25−3.36 (m, 4H), 3.37−3.42 (m, 2H), 3.47−3.52 (m, 2H), 3.75−3.82 (m, 2H), 3.98 (d, 2H, J = 11.6 Hz), 4.25 (d, 2H, J = 11.6 Hz), 4.44 (d, 2H, J = 12.5 Hz), 4.97 (d, 2H, J = 12.5 Hz), 5.02 (d, 2H, J = 12.5 Hz), 5.37 (d, 2H, J = 12.5 Hz), 7.04 (s, 2H), 7.10 (s, 2H), 7.49 (d, 2H, J = 7.6 Hz),

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7.79 (t, 1H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ: 16.5, 17.2, 20.9, 65.5, 66.1, 70.0, 74.3, 74.6, 75.8, 77.2, 120.9, 129.8, 129.9, 131.3, 132.5, 132.9, 137.1, 153.3, 156.9; MS (CI) m/z 636 (M^+). Anal. Calcd. for $C_{37}H_{49}NO_8$: C, 69.89; H, 7.77; N, 2.20. Found: C, 70.02; H, 7.94; N, 2.35.

(4*R*,6*R*,16*R*,18*R*)-4,6,11,16,18,23-Hexamethyl-3,7,15,19,-26,34-hexaoxa-36-azahexacyclo[19.3.1.1^{25,35}.3^{9,13}.1^{9,13}.1^{28,32}]-hexatriconta-1(25),9,11,13(35),28,30,32(36)-nonaene (5) (Scheme 2). (2*R*,4*R*)-Pentanediol (0.99 g, 9.5 mmol) was reacted with **2** (3.28 g, 4.75 mmol) according to the procedure described above for the synthesis of **3**. The crude product was purifed by chromatography on silica gel eluting with MePh/$MeCO_2Et$ (40:1) to give 0.191 g (7.0%) of **5** as a white crystalline solid; mp 62−65 °C; $[\alpha]^{25}_D$ = −307.8 (c = 3.84, CH_2Cl_2); IR(KBr) 2928, 1591, 1458, 1372, 1287, 1204, 1153, 1093, 1029 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 0.92 (d, 6H, J = 6.2 Hz), 1.32 (d, 6H, J = 5.9 Hz), 2.25 (s, 6H), 3.56 (2H, m), 3.95 (d, 2H, J = 13.8 Hz), 4.18 (2H, m), 4.27 (d, 2H, J = 13.8 Hz), 4.44 (d, 2H, J = 12.8 Hz), 4.92 (d, 2H, J = 12.8 Hz), 5.25 (d, 2H, J = 12.4 Hz), 5.67 (d, 2H, J = 12.4 Hz), 6.78 (s, 2H), 6.84 (s, 2H), 7.24 (d, 2H, J = 7.7 Hz), 7.71 (t, 1H, J = 7.7 Hz); ^{13}C NMR ($CDCl_3$) δ: 18.6, 20.3, 21.2, 46.3, 63.6, 64,9, 67.0, 73.2, 77.5, 121.3, 126.2, 126.9, 131.2, 133.3, 137.2, 154.3, 158.1; MS (CI) m/z 576 (M^+). Anal. Calcd. for $C_{35}H_{45}NO_6$: C, 73.01; H, 7.88; N, 2.43. Found: C, 73.17; H, 8.00; N, 2.27.

Determination of Thermodynamic Quantities. The log K values in Table 1 were determined at 25.0 ± 0.1 °C by either a direct ^{1}H NMR titration procedure at 200 MHz or titration calorimetry using a Tronac Model 450 calorimeter. The experimental techniques for direct ^{1}H NMR[3a,20,24] and calorimetric[3a,23] titrations have been described in detail. The calorimetric method determined ΔH and ΔS values besides the log K values and these values are also reported in Table 1. The calorimeter was calibrated according to the procedures described in the literature.[26] Concentrations of ammonium salt solutions were 0.11−0.13 M and those of chiral macrocycles were (2.4−3.8) × 10^{-3} M. The ammonium solutions were titrated continuously at a rate of 1.75 × 10^{-3} mL/s into the macrocycle solutions. The correction for heat of dilution was performed by a separate experiment in which the pure ammonium salt solution was titrated into pure solvent. The method used to process the calorimetric data and to calculate the log K and ΔH values has been described.[26]

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