Recognition by A New Chiral Dimethyl-substituted Phenanthrolino-18-Crown-6 Diester Ligand of the Enantiomers of Various Organic Ammonium Perchlorates

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Two new chiral dimethyl-substituted phenanthrolino-18-crown-6 diester ligands [(*S,S*)-**3**] and [(*S,S*)-**4**] (see Figure 1) were prepared through the reactions of 1, 10-phenanthroline-2,9-dicarboxylyl dichloride with (*S,S*)-dimethyl-substituted triethylene glycol and (*S,S*)-dimethyl-substituted benzotriethylene glycol, respectively. The complexation of (*S,S*)-**3** with the enantiomers of various organic ammonium perchlorates in various solvent systems was studied by ^{1}H nmr spectral techniques and molecular mechanics. The degree of enantiomeric recognition was determined by the difference in the free energy of activation values ($\Delta\Delta G^{\ddagger}_{c}$) and the difference in log *K* values for these interactions. The extensive π system in the ligand plays an important role for the strong interaction and recognition. The ^{1}H nmr NOESY spectra and molecular mechanics calculations for the interactions of the new ligand with the organic ammonium salts further proved the existence of a π–π interaction.

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Introduction.

Since Cram and his co-workers published their pioneering study on the use of chiral macrocyclic ligands in enantiomeric recognition [1], a great number of chiral macrocycles have been synthesized and their use in enantiomeric recognition has been studied. Most of this work has been reviewed [2-8]. In the past decade, our interest in enantiomeric recognition has focused on the interaction of chiral macrocycles with chiral organic ammonium salts [2,3,9-14]. We have chosen interactions of the chiral pyridino-18-crown-6 ligands because they form relatively strong complexes with organic ammonium salts [15] and they can be prepared with various substitutents at chiral positions on the macroring. We have made a systematic study of how the extent of enantiomeric recognition varies with crown substituent, guest type and solvent [2, 3, 12, 16, 17].

In our effort to identify, understand, and quantitate the factors responsible for enantiomeric recognition of selected chiral organic ammonium salts by chiral pyridine-containing macrocycles, we have found that the following factors play important roles in enantiomeric recognition [4,16]. First, the ligand should be able to form stable complexes with chiral guests. Electrostatic interaction and hydrogen bonding are the primary forces involved in the formation of complexes. Molecular conformation is also an important factor because only ligands that have an appropriate structure and conformation for forming three-point hydrogen-bonding with the primary ammonium salt can form stable complexes. Second, the ligand molecule should be rigid. Rigid molecules can form strong complexes with guests. Flexible ligands can match both guest enantiomers by adjusting its conformation, and therefore, provides little or no recognition [4,16]. For example, (*S,S*)-diphenylpyridino-18-crown-6 diester (**1**) exhibited strong complexation toward (*R*)-naphthylethylammonium perchlorate (NapEt) over (*S*)-NapEt (Δlog *K* > 0.85) and toward (*R*)-phenylethylammonium perchlorate (PhEt) over (S)-PhEt (Δlog *K* = 0.56), while the less rigid chiral crown without carbonyl groups on the ring, (*S,S*)-diphenylpyridino-18-crown-6 (**2**), exhibited a much smaller chiral recognition toward either NapEt (Δlog *K* = 0.18) or PhEt (Δlog *K* = 0.14) enantiomers [3,4]. In this case, the carbonyl oxygen atoms in **1** make the ligand less flexible so that it is relatively difficult for the ligand to adjust its conformation to accommodate either enantiomer of the guest ammonium cation with equal ease. Third, there should be a π–π interaction between the ligand and the guest. The role of π–π interaction in stabilizing synthetic host-guest complexes has attracted considerable interest in recent years both in theoretical [18-21] and experimental studies [22-27] . The π–π interaction energy is believed to include electrostatic, polarization and charge-transfer interactions as well as dispersion energy [18]. A variety of experimental studies suggest that π–π interaction may contribute to specific complexation in biological systems [28,29]. A few theoretical models have been suggested to explain the π–π interaction [19]. In the case of interactions of pyridino-18-crown-6 with organic ammonium salts studied by us, π–π interaction plays a role to position the complex conformation, leading to different steric environments for different complexes. The presence of π–π interaction in these complexes has been illustrated by ^{1}H nmr NOESY spectra, ^{1}H nmr chemical shift changes, X-ray structural analyses and molecular mechanics calculations [14,17,30]. The π–π interactions become increasingly favorable with extensive π systems [18] .

In order to investigate the effect of the size of the π system on complexation and enantiomeric recognition, two new chiral macrocycles containing phenanthroline, (*S*,*S*)-**3** and (*S*,*S*)-**4**, have been prepared (see Figure 1). These systems have a more rigid molecular frame and a more extensive π system. This paper describes the synthesis of new chiral macrocycles (*S*,*S*)-**3** and (*S*,*S*)-**4** (see Scheme 1). Enantiomeric recognition of various organic ammonium salts by (*S*,*S*)-**3** as determined by temperature dependent ^{1}H nmr measurements and by a direct ^{1}H nmr determination of log *K* values as well as molecular mechanics calculations is also reported.

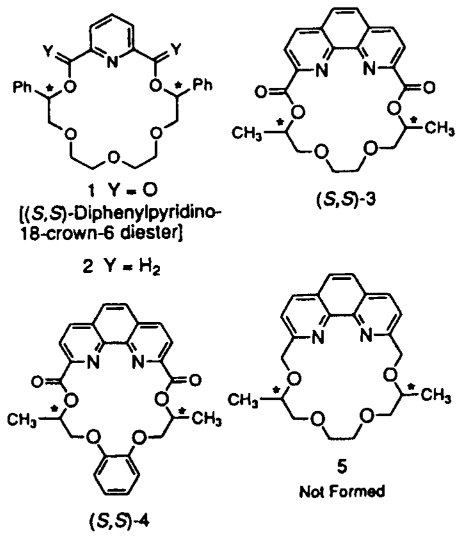
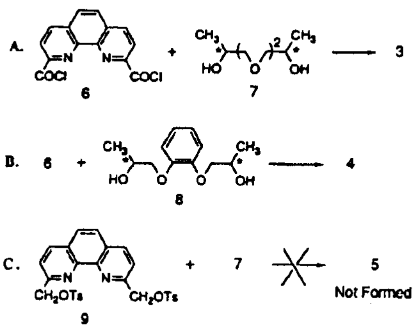


Figure 1. Chiral Macrocycle Structures.

Scheme 1
Preparation of Chiral Crowns.

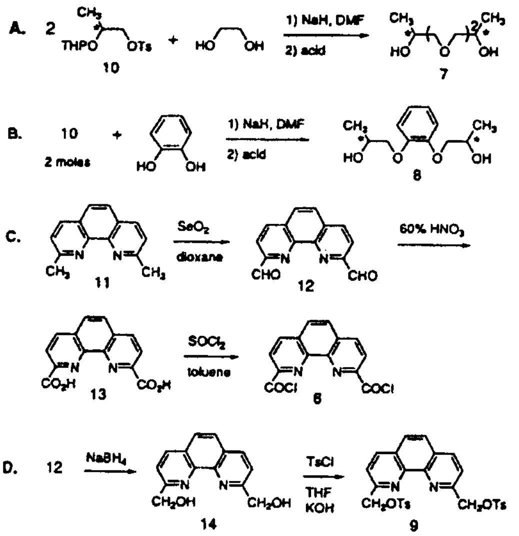


Results and Discussion.

New chiral macrocycles (*S*,*S*)-**3** and (*S*,*S*)-**4** were prepared as shown in Scheme 1. Chandler and coworkers reported the synthesis of many phenanthroline-containing macrocycles without chiral centers on the ring [31,32]. We used the same procedure for the synthesis of our new chiral macrocycles. Cyclization of the appropriate diol **7** or **8** with 1,10-phenanthroline-2,9-dicarboxylyl dichloride (**6**) in refluxing toluene gave chiral macrocycles (*S*,*S*)-**3** and (*S*,*S*)-**4** in yields of 32% and 10%, respectively. An attempt to improve yields and the reaction rate using dimethylaminopyridine (DMAP) as catalyst [33] gave no significant improvement. The structure proposed for (*S*,*S*)-**3** is consistent with data obtained from ^{1}H nmr, ms and ir spectra, an X-ray structure determination, and the elemental analysis. The structure proposed for (*S*,*S*)-**4** is consistent with the data obtained from the ^{1}H nmr and ms spectra and an elemental analysis. We were unable to prepare chiral macrocycle (*S*,*S*)-**5** through the cyclization of ditosylate **9** with chiral dimethyl-substituted triethylene glycol in the presence of NaH (Scheme 1C). It is possible that the phenanthroline ring was destroyed by a reductive process under these conditions as has been reported for similar reactions [34-36].

Chiral dimethyl-substituted triethylene glycol **7** and dimethyl-substituted benzotriethylene glycol **8** needed for the preparation of the chiral macrocycles were obtained as shown in Scheme 2. Compound **7** was formed in a 55% yield by treating mono THP-protected methyl-substituted ethylene glycol tosylate (**10**) [12] with ethylene glycol using NaH as the base and removing the THP protecting group in a second step. Compound **8** was obtained in a 36% yield in a similar manner.

Scheme 2
Preparation of Starting Materials



1,10-Phenanthroline-2,9-dicarboxylyl dichloride **6** was prepared as reported [37] with some improvements (Scheme 2C). First, acetone was used to recrystallize dialdehyde **12** to give better crystals. Second, dilute nitric acid (60%) was used to oxidize dialdehyde **12** to the corresponding dicarboxlic acid **13** to give a very high yield (97%) with good product purity. Concentrated nitric acid (80%), as reported in the literature [37], gave many byproducts which were very difficult to remove. 2,9-Bis(tosyloxymethyl)-1,10-phenanthroline (**9**) was prepared in a 42% yield by treating the corresponding dialcohol **14** with tosyl chloride in THF in the presence of KOH (Scheme 2D).

In an effort to convert diester **3** to the corresponding dithiono macrocycle, (*S,S*)-**3** was refluxed with Lawesson's reagent in xylene for one day. No conversion was observed. Lawesson's reagent has been used to convert furano-18-crown-6 diesters to the corresponding furano-18-crown-6 dithionoesters in good yields [38,39]. Lawesson's reagent also was used successfully by us to convert pyridino-18-crown-6 diamides to the corresponding pyridino-18-crown-6 dithionodiamides in high yields [12]. Compounds with electron-withdrawing substitutents conjugated to the ester carbonyl group failed to react with Lawesson's reagent, while conjugated electron-donating groups increased the reaction rate [38]. Failure of diester **3** to react in this case is probably a result of the strong electron-withdrawing ability of the nitrogen atoms in the phenanthroline ring.

A computer drawing of the solid state structure of (*S,S*)-**3** is shown in Figure 2. In addition to that molecule, the crystal structure also contains two molecules of water. The role of the water molecules will be discussed below. In Figure 2, one water molecule, OW2, and the hydrogen atoms of the macrocycle are omitted for clarity. The crystal structure clearly establishes the structural formula and conformation of (*S,S*)-**3**. The positional and isotropic thermal parameters of the atoms of this molecule are listed in Table 1. The bond lengths and angles are included in Table 2. Because of the few observed data used in the refinement and possible disorder (see experimental), these values are of rather poor quality. This is indicated by the large estimated standard deviations reported for the bond lengths and angles.

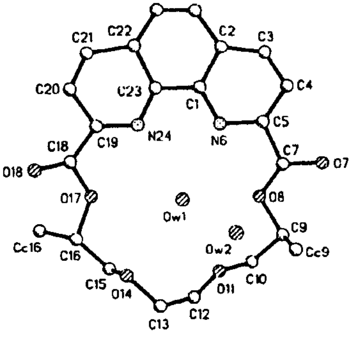


Figure 2. X-ray crystal structure of the unprimed molecule of (*S,S*)-3 drawn with SHELXTL-PLUS [47]. One water molecule, OW2, and the hydrogen atoms were omitted for clarity.

Table 1

Atomic Coordinates (x 10^4) and Isotropic (Nonhydrogen Atoms) and Fixed Istropic (Hydrogen Atoms) Displacement Coefficients ($Å^2$ X 10^3) for (*S,S*)-3

	x	y	z	U
C1	-613(22)	1205(19)	4763(16)	41(8)
C2	-301(20)	848(19)	5608(16)	39(7)
C3	904(21)	889(19)	5678(17)	58(8)
H3	1126	696	6237	80
C4	1739(21)	1140(20)	5150(15)	56(9)
H4	2541	1161	5290	80
C5	1255(22)	1452(21)	4369(17)	50(8)
N6	123(18)	1506(16)	4149(12)	53(7)
C7	2070(25)	1828(24)	3682(20)	70(10)
O7	3111(18)	1655(17)	3837(12)	97(7)
O8	1668(12)	2182(12)	2996(11)	51(5)
C9	2502(21)	2410(21)	2330(15)	64(9)
H9	3203	2713	2549	80
Cc9	2775(20)	1375(21)	1891(14)	90(11)
H1C9	3329	1520	1460	80
H2C9	3081	841	2276	80
H3C9	2085	1088	1644	80
C10	1889(22)	3178(22)	1789(16)	82(10)
H10A	2412	3458	1377	80
H10B	1621	3784	2125	80
O11	998(17)	2674(17)	1376(13)	103(7)
C12	496(28)	3373(31)	855(21)	162(16)
H12A	1024	3664	451	80
H12B	140	3975	1151	80
C13	-395(26)	2819(26)	438(16)	119(13)
H13A	-7	2171	234	80
H13B	-646	3245	-34	80
O14	-1470(20)	2439(20)	866(15)	144(10)
C15	-1966(32)	3292(34)	1068(25)	198(21)
H15A	-1543	3738	1457	80
H15B	-2139	3724	580	80
C16	-3017(27)	2913(26)	1436(22)	112(13)
H16	-3295	2328	1083	80
Cc(16)	-4074(24)	3771(27)	1616(18)	168(16)
H1C16	-4282	4119	1099	80
H2C16	-4711	3348	1824	80
H3C16	-3869	4329	2017	80
O17	-2886(16)	2475(15)	2313(12)	89(7)
C18	-3608(27)	1791(28)	2777(21)	85(11)
O18	-4428(19)	1502(20)	2394(14)	146(10)
C19	-3144(28)	1461(25)	3527(20)	76(10)
C20	-4036(25)	1137(20)	4092(17)	72(10)
H20	-4827	1102	3926	80
C21	-3792(22)	819(23)	4820(17)	60(9)
H21	-4339	660	5252	80
C22	-2617(28)	753(27)	5167(22)	99(12)
C23	-1772(23)	1208(22)	4517(19)	58(9)
N24	-2075(18)	1497(17)	3759(13)	53(7)
C25	-2241(27)	477(22)	5935(20)	88(12)
H25	-2824	211	6309	80
C26	-1224(22)	514(21)	6147(16)	61(9)
H26	-1015	334	6711	80
Ow1	-482(13)	722(13)	2263(9)	73(6)
Ow2	886(17)	-974(16)	1511(11)	119(8)

Table 2

Bond Lengths and Angles for Nonhydrogen Atoms of (*S,S*)-**3**

1	2	3	1-2(Å)	1-2-3 (°)
C2	C1	N6	1.46(4)	126(2)
C23	C1	C2	1.41(4)	120(2)
N6	C1	C23	1.35(3)	114(2)
C1	C2	C3		108(2)
C26	C2	C1	1.44(4)	117(2)
C3	C2	C26	1.41(3)	135(2)
C2	C3	C4		134(2)
C3	C4	C5	1.32(4)	109(2)
C4	C5	N6	1.42(4)	128(2)
C4	C5	C7		118(2)
N6	C5	C7	1.37(3)	114(2)
C1	N6	C5		114(2)
C5	C7	O7	1.52(4)	114(2)
C5	C7	O8		120(2)
O7	C7	O8	1.26(4)	126(3)
C7	O8	C9	1.27(4)	117(2)
O8	C9	Cc9	1.47(3)	109(2)
O8	C9	C10		103(2)
Cc9	C9	C10	1.47(3)	111(2)
C9	C10	O11	1.46(4)	112(2)
C10	O11	C12	1.37(3)	111(2)
O11	C12	C13	1.32(4)	109(3)
C12	C13	O14	1.40(4)	123(2)
C13	O14	C15	1.50(4)	105(3)
O14	C15	C16	1.22(5)	104(3)
C15	C16	Cc16	1.43(5)	121(3)
C15	C16	O17		114(3)
Cc16	C16	O17	1.63(4)	98(2)
C16	O17	C18	1.51(4)	130(2)
O17	C18	O18	1.39(4)	113(3)
O17	C18	C19	1.19(4)	114(3)
O18	C18	C19		133(3)
C18	C19	C20	1.38(5)	110(3)
N24	C19	C18	1.30(4)	128(3)
C20	C19	N24	1.43(4)	122(3)
C19	C20	C21		120(3)
C20	C21	C22	1.26(4)	125(3)
C21	C22	C23	1.48(4)	109(3)
C21	C22	C25		131(3)
C23	C22	C25	1.53(4)	120(3)
C1	C23	C22		115(2)
N24	C23	C1	1.31(4)	121(2)
C22	C23	N24		123(2)
C19	N24	C23		121(2)
C22	C25	C26	1.35(5)	124(3)
C25	C26	C2	1.23(4)	124(3)

The aromatic portion of (*S,S*)-**3** causes rigidity in the molecule. A least-squares plane was calculated for the 14 atoms of the fused rings, C7 and C18. The average deviation from the plane of an atom used in the calculation of this plane is 0.035Å. Both carbonyl oxygens are on the same side of the least-squares plane with O7 and O18 being 0.24Å and 0.44Å, respectively, above the plane. The methyl carbon Cc9 is 1.51Å above the plane while Cc16, the other methyl carbon, is 1.71Å below that plane. The view of Figure 2 was drawn to be similar to the view of the ligand in the low energy conformation of the complex shown in Figure 4. Using this figure as a reference, the carbonyl oxygens and Cc9 would be on the side of the molecule towards the organic cation guest.

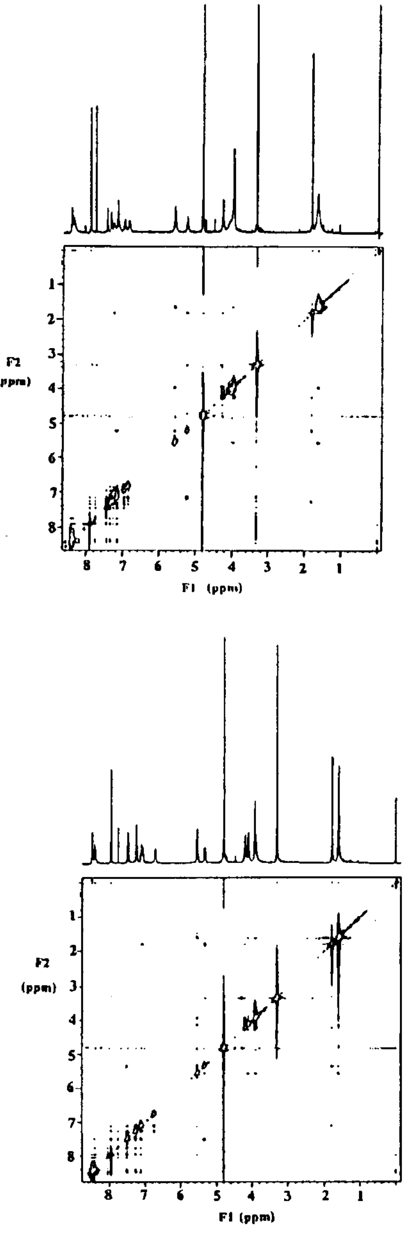


Figure 3. ^{1}H nmr NOESY spectra of the complexes of (*S,S*)-**3** with (*R*)-1-(naphthyl)ethylammonium perchlorate (a) and the (*S*)-perchlorate salt (b) in a mixed solvent of 75% CD_3OD + 25% $CDCl_3$ at 25°.

The role of the water molecules is of interest. Unfortunately, as indicated in the experimental, the hydrogen atoms of the waters could not be found. However, the water O-donor atom of the ligand interatomic distances do indicate some water-ligand interaction. These interatomic distances are shown in Table 3. These distances indicate that OW1 is located above the

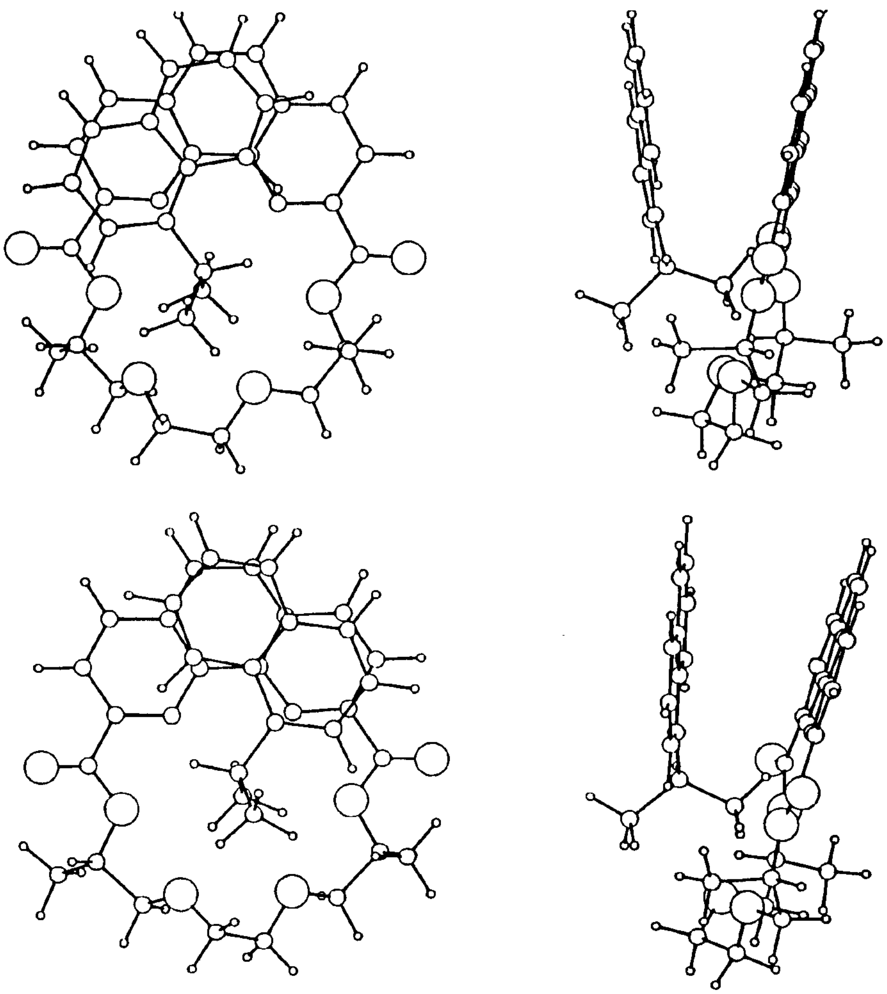


Figure 4. Computer-generated views obtained from molecular mechanics calculations of the complexes of (*S,S*)-**3** with (*R*)-1-(naphthyl)ethylammonium perchlorate (a) and with the (*S*)-perchlorate (b) using X-ray coordinates as the starting coordinates of the (*S,S*)-**3**.

cavity approximately equidistant from 5 of the 6 donor atoms of the ligand. It is 1.76Å above the least-square plane of the rigid portion of the molecule and on the same side of the host as the organic cation would be as shown in the low energy calculation, Figure 4. The OW1-donor atom of (*S,S*)-**3** interatomic distances are rather long for hydrogen bonds and are all likely polar-polar interactions. The OW1-OW2 interatomic distance (2.86Å) is typical of that found in hydrogen bonds and suggests that the two water oxygens are linked by such an interaction. Finally, OW2 interacts weakly (probably weak polar-polar interactions) with the nitrogen atoms of a symmetry related (-x, 0.5 + y, 0.5 - z) host molecule. The result is chains of molecules which are weakly linked by hydrogen bonded water molecules.

The OW1 appears to organize the host molecule as all the oxygens are somewhat directed into the cavity of the host (Figure 2). However, it is not possible to compare this structure with either an empty host or a host complexing a cation, as neither of these materials have been crystallized.

Table 3

Water Oxygen-(*S,S*)-**3** Donor Atom Interatomic Distances

Water Oxygen	(*S,S*)-**3** Donor Atom	Interatomic Distance(Å)
OW1	N24	3.17
OW1	N6	3.24
OW1	O11	3.24
OW1	O14	3.26
OW1	O8	3.28
OW1	O17	3.51
OW2	N24[a]	3.38
OW2	N6[a]	3.43

[a] Symmetry related host molecules by -x, 0.5 + y, 0.5 - z.

Complexation of the enantiomeric forms of various organic ammonium perchlorates by ligand (*S,S*)-**3** has been studied by the temperature-dependent ^{1}H nmr technique [2,9-11,40,41] and by determining the log *K* values for the association of the chiral ligand and the salt enantiomers by a direct ^{1}H nmr technique [13]. The kinetic parameters for the dissociation of those complexes were calculated as reported [2,40,41]. Table 4 shows the coalescence temperature (T_C) and ($\Delta\Delta G^{\ddagger}_{c}$) values for the dissociation of the complexes of (*S,S*)-**3** with the (*R*)- and (*S*)-forms of various ammonium perchlorates in CD_2Cl_2.

Table 4

Free Energies of Activation Values ($\Delta\Delta G^{\ddagger}_{c}$)(kcal/mole) for the Interactions of Chiral Crown Ligand (*S,S*)-**3** with the Enantiomers of Various Organic Ammonium Perchlorates in CD_2Cl_2

Salts [a]	Salt Configuration	T_c (K)	$\Delta G^{\ddagger}_{c}$	$\Delta\Delta G^{\ddagger}_{c}$
NapEt	*R*	264	12.26	
	S	245	11.79	0.47
PheMe	*R*	295	14.17	
	S	286.5	13.66	0.51
PhEt	*R*	>303	>15.05	
	S	>303	>14.91	
PhEt(OH)	R	272	12.41	
	S	261	12.73	-0.32

[a] NapEt = α-(l-naphthyl)ethylammonium perchlorate; PheMe = the hydrogen perchlorate salt of methyl phenylalaninate; PhEt = α-phenylethylammonium perchlorate; PhEt(OH) = the hydrogen perchlorate salt of 2-amino-2-phenylethanol.

The data in Table 4 show that new chiral ligand **3** exhibits enantiomeric recognition for the chiral forms of NapEt and the hydrogen perchlorate salts of methyl phenylalaninate (PheMe) and 2-amino-2-phenylethanol [PhEt(OH)]. (*S,S*)-**3** formed stronger complexes with the (*R*)-forms of NapEt and PheMe over the (*S*)-forms as is typical for the pyridino crowns [2-4] but formed the stronger complex with the (*S*)-form of PhEt(OH). The (*R*)-forms of NapEt and PheEt have the same configuration in space as the (*S*)-form of PhEt(OH) since the priority of the substituents on the chiral carbon atom changes in PhEt(OH). The $\Delta\Delta G^{\ddagger}_{c}$ values are smaller than those obtained for the pyridine-containing system.

Log *K* values, as determined by the direct ^{1}H nmr technique, are accurate indicators of enantiomeric recognition. Table 5 shows the log *K* values for the interactions of (*S,S*)-**3** with various organic ammonium perchlorates in a 50% CD_3OD-50% $CDCl_3$ mixed solvent system. The best enantiomeric recognition was observed for the interaction of the new ligand with (*R*)- and (*S*)-NapEt, with less recognition for the interaction with (*R*)- and (*S*)-PhEt. The more extensive π-system in NapEt could provide a stronger interaction with the phenanthroline ring system of the ligand and, therefore, provide greater recognition. Similar results were observed in other systems [42]. There was essentially no enantiomeric recognition for the interactions of the new ligand with the enantiomers of PhEt(OH) and PheMe. This lack of recognition was also observed for the interactions of the chiral pyridine-containing 18-crown-6 ligands with those two ammonium salts [4].

Table 5

Log *K* Values for the Interactions of Chiral Crown Ligand (*S,S*)-**3** With the Enantiomers of Organic Ammonium Perchlorates in 50% CD_3OD + 50% $CDCl_3$ at 25°

Salts [a]	Salt Configuration	log *K*	Δlog *K*
NapEt	*R*	4.56	
	S	4.16	0.40
PhEt	*R*	4.00	
	S	3.78	0.22
PhEt(OH)	*R*	3.52	
	S	3.57	-0.05
PheMe	*R*	3.34	
	S	3.38	-0.04

[a] See footnote a in Table 4.

The effect of solvent on the interactions of (*S,S*)-**3** with the (*R*)- and (*S*)-NapEt, PhEt, and PheMe has been examined in a number of different solvents and solvent mixtures (see Table 6). The data show two important facts. First, complex stability varies significantly as the solvent changes. Log *K* values increased for the interactions of (*S,S*)-**3** with NapEt, PhEt and PheMe when the solvent changed from 20% DMSO-D_6-80% CD_3OD to CD_3OD to increasing amounts of $CDCl_3$ in CD_3OD and finally to CD_3CN. Solvent parameters which might have an effect on complex stabilities are dielectric constant [43], empirical solvent polarity [43] and Gutmann donor and acceptor numbers [44]. Examination of the various solvent parameters indicates that complex stability changes are inversely proportional to changes in the Gutmann donor number as has been observed in the chiral pyridino-18-crown-6 system [4]. DMSO has the largest donor number (29.8) so the log *K* values in 20% DMSO and 80% CD_3OD are the smallest. $CDCl_3$ has the smallest donor number (4.0) so log *K* values in 70% $CDCl_3$ and 30% CD_3OD are the largest. Solvents of high donicity have a stronger solvation power towards ammonium cations. Hence, they destablize the complexes formed between the macrocycle ligand and the ammonium cations.

A second fact is the extent of chiral recognition, as measured by the Δlog *K*, increases with increasing log *K* values. As shown in Table 6, log *K* values increase from 3.47 and 3.36 in 20% DMSO-D_6-80% CD_3OD to 5.18

Table 6

Log *K* Values for the Interactions of Chiral Crown Ligand (*S,S*)-**3** with the Enantiomers of Various Organic Ammonium Perchlorates in Various Solvents at 25°

		NapEt. [b]		PhEt. [b]		PheMe. [b]	
Solvents [a]	Salt Configuration	log *K*	Δlog *K*	log *K*	Δlog *K*	log *K*	Δlog *K*
20% D + 80% M	*R*	3.47					
	S	3.36	0.11				
100% M	*R*	4.05					
	S	3.88	0.17				
70% M + 30% C	*R*	4.31					
	S	3.97	0.34				
50% M + 50% C	*R*	4.56		4.00		3.34	
	S	4.16	0.40	3.78	0.22	3.38	-0.04
30% M+70% C	*R*	5.18		4.33		3.53	
	S	4.66	0.52	4.12	0.21	3.64	-0.11
100% CN	*R* [c]						
	S [c]						

[a] D = DMSO-D_6, M = CD_3OD, C = $CDCl_3$, CN = CD_3CN. [b] See footnote a in Table 4. [c] The log *K* values were too large to obtain accurate values.

and 4.66 in 30% CD_3OD-70% $CDCl_3$ for the interactions of the (*S,S*)-**3** with the (*R*)- and (*S*)-NapEt, respectively. The resulting Δlog *K* values increase from 0. 11 to 0. 52. This is in contrast to complexation by the pyridino analog of **3** where, even though the log *K* values increased as the solvent donor number decreased, the Δlog *K* values did not change [16]. The main factor that contributes to chiral recognition is steric. As the log *K* value increases, the host and guest form a tighter complex and the steric interaction will become more important. Obviously, the (*S,S*)-(*R*) complex has the least steric repulsion. As the host and guest distance decreases in the less polar solvents, the steric fit in the (*S,S*)-(*S*) complex should become more unfavorable and the Δlog *K* should be even greater. The fact that the π-π interaction between phenanthroline and naphthalene in the complexes of (*S,S*)-**3** with the enantiomers of NapEt should be much greater than in the complexes of the pyridino crowns should also play a major role in recognition. This stronger π-π interaction may mean that the guest naphthalene in the (*S,S*)-**3**-(*S*)-NapEt complex cannot avoid steric strain as easily as in the case of the pyridino crown. This could explain why we see an increase in Δlog *K* values for the (*S,S*)-**3** complexes in less polar solvents but not for the pyridino-crown complexes.

As shown in Table 7, diester (*S,S*)-**3** forms stronger complexes with (*R*)- and (*S*)-NapEt than does (*S,S*)-dimethypridino-18-crown-6 diester [(*S,S*)-Me_2K_2P18C6] and (*S,S*)-dimethylpyridino-18-crown-6 [(*S,S*)-Me_2P18C6], and it exhibits similar but lower enantiomeric recognition. The stronger complexation results from the fact that the new ligand is more rigid and flat as shown by the X-ray structure (Figure 2). The more rigid molecule should more readily form complexes because of a decreased cost to adjust its conformation for complexation. The similar enantiomeric recognition of the new ligand as compared to the other two ligands is because the steric interactions between (*S,S*)-**3** and the guests are similar to those with the pyridino ligands.

Table 7

Log *K* Values for the Interactions of Various Crown Ethers with NapEt [a] in 50% CD_3OD + 50% $CDCl_3$ at 25°C

Crowns	Salt Configuration	log *K*	Δlog *K*	Ref
(*R,R*)-Me_2K_2P18C6 [b]	*R*	2.20		16
	S	2.80	0.60	
(*S,S*)-Me_2P18C6 [c]	*R*	3.96		48
	S	3.42	0.54	
(*S,S*)-**3**	*R*	4.56		
	S	4.16	0.40	

[a] See footnote a in Table 4. [b] (*R,R*)-Me_2K_2P18C6 = (*R,R*)-Dimethylpyridino-18-crown-6 diester. [c] (*S,S*)-Me_2P18C6 = (*S,S*)-Dimethylpyridino-18-crown-6.

Information on the conformation of the complexes of the new ligand with the (*R*)- and (*S*)-NapEt in 75% CD_3OD-25% $CDCl_3$ has been obtained by analysis of the ^1H nmr NOESY spectra and molecular mechanics calculations. The ^1H nmr NOESY spectra (Figure 3) for the interactions of (*S,S*)-**3** with (*R*)- and (*S*)-NapEt show that the off-diagonal peaks appear at 7.1 to 8.6 ppm. This is an indication of the overlap of the two π systems of the host and guest. Molecular mechanics calculations for the interactions of (*S,S*)-**3** with (*R*)- and (*S*)-NapEt in the absence of solvent gave the lowest energy conformations containing $\pi-\pi$ stacking as shown in Figure 4. The (*S,S*)-(*R*) complex is 1.51 kcal/mole more stable than (*S,S*)-(*S*) complex.

Table 8

Crystal Data and Structure Solution Data for (*S,S*)-**3**

Formula	$C_{22}H_{22}N_2O_6 \bullet 2H_2O$
Formula weight	446.4
Crystal size	0.12 x 0.15 x 0.40 mm
F(000)	944
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a	11.647(4) Å
b	12.058(3) Å
c	16.010(5) Å
V	2248.4 Å^3
Density	1.32 Mg/m^3
Absorption coefficient	0.101 mm^{-1}
Index ranges	$0 \leq h \leq 12$, $0 \leq k \leq 12$, $0 \leq l \leq 17$
Reflections collected	1720
Independent Reflections	1701
Observed Data used in refinement	655 ($F > 3.5\ \sigma$ (F))
Weighting Scheme	$w\text{-}l = \sigma^2 (F) + 0.0002\ F^2$
R Values	R = 0. 124, R_W = 0.092
Goodness of fit	2.77
Largest and mean Δ/σ	0.002, 0.001
Data to parameter ratio	5:1:1
Largest difference peak	0.41 eÅ^{-3}
Largest difference hole	-0.38 eÅ^{-3}

EXPERIMENTAL

The ^{1}H nmr spectra were obtained at 200 MHz in $CDCl_3$ with TMS as the internal standard (for structural determinations) and at 500 MHz (for recognition studies). Melting points are uncorrected. Starting materials were used as purchased from Aldrich Chemical Co. unless otherwise noted. The hydrogen perchlorate salts of the chiral amines used in the study were prepared as reported [9,16]. Starting materials **6** [37], **10** [12], and **14** [37] were prepared as reported.

(1*S*,8*S*)-(+)-1,8-Dimethyl-3,6-dioxaoctane-1,8-diol (**7**) (Scheme IIA).

To a stirred suspension of 5.8 g of sodium hydride (NaH) (0.24 mole, 80% dispersion in mineral oil) in 200 ml of dry and pure dimethylformamide (DMF) was added dropwise 5.38 g (87 mmoles) of dry ethylene glycol dissolved in 200 ml of DMF at room temperature under Ar. After addition, the reaction mixture was stirred at room temperature for 10 minutes and then at 85° for 2.5 hours. The reaction solution was cooled to 0° and 55 g (175 mmoles) of (*S*)-2-(tetrahydropyranyloxy)propyl *p*-toluenesulfonate **10** dissolved in 200 ml of DMF was added dropwise. The reaction mixture was stirred at 0° for 10 minutes, at room temperature for 60 minutes and then at 85° for two days. The solvent was evaporated under reduced pressure and the residue was dissolved in a mixture of methylene chloride (CH_2Cl_2), ice and water. The mixture was shaken well and the phases were separated. The aqueous phase was extracted with CH_2Cl_2. The organic phases were combined, dried over anhydrous magnesium sulfate ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give an oil product. The crude product was dissolved in 600 ml of methanol containing 6 ml of 37% hydrochloric acid (HCl). The solution was stirred at room temperature for two days. After the reaction was completed, 18 g of sodium carbonate (Na_2CO_3) was added and the mixture was stirred at room temperature for two hours. After neutralization, the solvent was evaporated. The residue was dissolved in a mixture of water and CH_2Cl_2. The mixture was shaken well and the phases were separated. The aqueous phase was extracted with CH_2Cl_2. The organic phases were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated. The residue was purified by fractional distillation under reduced pressure to give 8.5 g (55%) of **7**, bp 86-89°/0.2 mm Hg; $[\alpha]_D^{20}$ +41.5 (c = 1.282, $CHCl_3$); ir (neat): 3406, 2869, 1455, 1374, 1122 cm^{-1}; ^{1}H nmr: δ 1.05 (d, 6 H), 3.20-3.70 (m, 10 H), 3.92 (m, 2 H); ms: (CI) m/z 179 (M^++1). A satisfactory elemental analysis was obtained for **3**, a derivative of **7**.

(1*S*,8*S*)-(+)-1,8-Dimethyl-4,5-benzo-3,6-dioxaoctane-1,8-diol (**8**) (Scheme IIB).

A mixture of 1.0 g (9.1 mmoles) of catechol and 0.87 g (36.3 mmoles, 80% dispersion in mineral oil) of NaH in 35 ml of dry and pure tetrahydrofuran (THF) was stirred at room temperature under Ar for 30 minutes. Compound **10** (9.0 g, 28.7 mmoles) dissolved in 20 ml of THF was added dropwise to the reaction solution. After addition, the reaction mixture was stirred at room temperature for an hour and then at reflux temperature for two days. The solvent was evaporated under reduced pressure and the residue was dissolved in a mixture of water and CH_2Cl_2. The mixture was shaken well and the phases were separated. The aqueous phase was extracted with CH_2Cl_2. The organic phases were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated. The residue was dissolved in a mixture of 80 ml of methanol containing 1 ml of 37% HCl. The mixture was stirred at room temperature for one day. After the reaction was completed, 3.0 g of Na_2CO_3 was added and the mixture was stirred at room temperature for two hours. After neutralization, the solvent was evaporated under reduced pressure. The residue was dissolved in a mixture of water and CH_2Cl_2. The mixture was shaken well and the phases were separated. The aqueous phase was extracted with CH_2Cl_2. The organic phases were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated. The residue was purified by recrystallization from hexane to give 0.74 g (36%) of **8**, mp 84-84.5°; $[a]_D^{20}$ +63.7 (c = 0.164, $CHCl_3$); ir (KBr): 3420, 1506, 1262, 1227, 1125 cm^{-1}; ^{1}H nmr: δ 1.25 (d, 6 H), 3.55 (s, 2 H, disappeared in D_2O), 3.74-4.28 (m, 6 H), 6.96 (s, 4 H); ms: m/z 226 (M^+). A satisfactory elemental analysis was obtained for **4**, a derivative of **8**.

1,10-Phenanthroline-2,9-dicarbaldehyde (**12**) (Scheme 2C).

Aldehyde **12** was prepared as reported [37,45]. Compound **12** was purified by recrystallization from pure acetone to give needles.

1,10-Phenanthroline-2,9-dicarboxylic acid (**13**) (Scheme 2C).

Compound **12** (5.8 g, 24.5 mmoles) in 115 ml of 60% nitric acid (HNO_3) was heated to reflux for four hours. The mixture was cooled and poured onto ice. The precipitated solid was filtered and washed with water to give 6.35 g (96%) of compound **13**. This compound was used for the preparation of **6** without further purification. The ir and ^1H nmr spectra were the same as reported [37].

2,9-Bis (tosyloxymethyl)-1,10-phenanthroline (9) (Scheme 2D).

To a stirred mixture of 3.0 g (12.5 mmoles) of 2,9-bis(hydroxylmethyl)-1,10-phenanthroline **14** [37] and 6.0 g (93.2 mmoles) of powered potassium hydroxide (KOH) in 80 ml of pure and dry THF at 0° under Ar, was added dropwise 7.2 g (37.8 mmoles) of tosyl chloride dissolved in 50 ml of THF. After addition, the reaction mixture was stirred at 0° for four hours, and then at room temperature for two hours until the tosyl chloride disappeared. The solvent was evaporated under reduced pressure and the residue was dissolved in a mixture of CH_2Cl_2, ice and water. The mixture was shaken well and the phases were separated. The aqueous phase was extracted with CH_2Cl_2. The organic phases were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated. The residue was recrystallized from benzene to give 2.9 g (42%) of compound **9**, mp 128° dec; ir (KBr): 1605, 1371, 1174 cm^{-1}; ^1H nmr: δ 2.45 (s, 6 H), 5.50 (s, 4 H), 7.35 (d, 2 H), 7.80 (d, 2 H), 7.82-7.95 (m, 4 H), 8.30 (d, 2 H); ms: (CI) m/z 549 (M^++1).

(4*S*,11*S*)-(-)-4,11-Dimethyl-3,6,9,12-tetraoxa-23,26-diazatetracyclo[12.8.4.$0^{17,25}$.$0^{20,24}$]hexacosa-14,16,18,20,22(1),23,25-heptaene-2,13-dione (3) (Scheme 1A).

To a refluxing solution of 1.72 g (5.6 mmoles) of compound **6** in 1800 ml of dry and pure toluene, was added dropwise 1.0 g (5.6 mmoles) of compound **7** dissolved in 200 ml of dry toluene. The reaction mixture was stirred at reflux temperature for one hour. The mixture was cooled, filtered and the solvent was evaporated under reduced pressure. The residue was dissolved in chloroform ($CHCl_3$). The solution was washed with saturated Na_2CO_3 and then water. The organic phase was dried over $MgSO_4$ and filtered. The solvent was evaporated. The residue was recrystallized from a mixed solvent of water and ethanol to give 0.69 g (32%) of **3**, mp 76-77°; $[\alpha]_D^{20}$ -84.6 (c = 0.364, $CHCl_3$); ir (KBr): 1719, 1312, 1152 cm^{-1}; ^1H nmr: δ 1.52 (d, 6 H), 3.82-4.12 (m, 8 H), 5.4 (m, 2 H), 7.92 (s, 2 H), 8.35-8.56 (q, 4 H); ms: m/z 410 (M^+);

Anal. Calcd. for $C_{22}H_{22}N_2O_6$: C, 64.39; H, 5.37. Found: C, 64.18; H, 5.38.

(4*S*,11*S*)-4,11-Dimethyl-7,8-benzo-3,6,9,12-tetraoxa-23,26-diazatetracyclo[12.8.4.$0^{17,25}$.$0^{20,24}$]hexacosa-14,16,18,20,22(1),23,25-heptaene-2,13,-dione (4) (Scheme IB).

To a refluxing solution of 0.26 g (0.85 mmole) of compound **6** in 350 ml of dry and pure toluene, was added dropwise 0.19 g (0.84 mmole) of compound **8** dissolved in 200 ml of dry toluene. The reaction solution was stirred at reflux temperature for one hour. The reaction mixture was cooled, filtered and the solvent was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$. The solution was washed with saturated Na_2CO_3 and then water. The organic phase was dried over $MgSO_4$ and filtered. The solvent was evaporated. The product was purified by column chromatography on neutral aluminum oxide using $CHCl_3$ as eluent to give 40 mg (10%) of **4**; ^1H nmr: δ 1.5 (s, H_2O peak), 1.65 (d, 6 H), 4.50 (d, 4 H), 5.60 (m, 2 H), 6.93 (m, 4 H), 7.93 (s, 2 H), 8.39-8.51 (q, 4 H); ms: m/z 458 (M^+).

Anal. Calcd. for $C_{26}H_{22}N_2O_6 \cdot 1.5\ H_2O$: C, 64.32; H, 5.19. Found: C, 64.67; H, 5.03.

Determination of $\Delta G_c^\ddagger$ Values.

$\Delta G_c^\ddagger$ values listed in Table 4 were determined as reported [2,3,9-11,41].

Determination of Log *K* Values.

The log *K* values listed in Tables 5-7 were determined by the direct ^1H nmr method as reported [3,13].

^1H nmr NOESY Experiments.

2D ^1H nmr NOESY spectra of the (*S,S*)-**3** complexes with the (*R*)- and (*S*)-NapEt were obtained on a Varian VXR 500 MHz nmr spectrometer at 25°. Stoichiometric amounts of the host and the guest were weighted on a high precision balance and dissolved in a mixed solvent of 75% CD_3OD + 25% $CDCl_3$ (v/v). The 90 degree pulse width was always calibrated. Delay time was set to about 3 times the maximum T_1 value.

Molecular Mechanics Calculations.

The search and the comparison of the lowest energy conformation of the (*S,S*)-**3** complexes with the (*R*)- and (*S*)-NapEt was accomplished using QUANTA/CHARMm software from Molecular Simulation, Inc. on a Silicon Graphics Personal IRIS Workstation. X-ray coordinates were used as the starting coordinates to obtain the lowest energy conformation of (*S,S*)-**3**.

X-ray Structural Determination.

It was not possible to obtain crystals of (*S,S*)-**3** that diffracted well. Two possible reasons for this are the rather small size of the crystals and the large thermal motion (Table 2) and possible disorder of many of the atoms. Despite this problem, crystal data and single crystal intensity data were collected using a Siemens R3m/V automated diffractometer which utilized MoKα graphite monochromated radiation (λ = 0.71073Å). The crystal data were obtained using a least-squares procedure involving 28 carefully centered reflections. Intensity data were collected using a $2\theta-\theta$ variable speed scanning procedure. Crystal data and structure solution data are summarized in Table 8.

The solid state was solved using the direct method. The solution revealed that the structure included two water molecules for every (*S,S*)-**3** molecule. Because there were so few observed data compared to the number of parameters (Table 8), the non-hydrogen atoms were refined isotropically. Positions for all the hydrogens of (*S,S*)-**3** were calculated and isotropic displacement coefficients were assigned to these atoms. During the refinement process, the hydrogens were allowed to ride on their neighboring carbon atoms and the thermal parameters were not refined. It was not possible to locate or calculate positions for hydrogens of the water molecules. Atomic scattering factors for all the atoms were obtained from the International Tables for X-ray Crystallography [46]. All programs used in the solving, refining and displaying of the structure are contained in the SHELXTL-PLUS program package. [47].

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