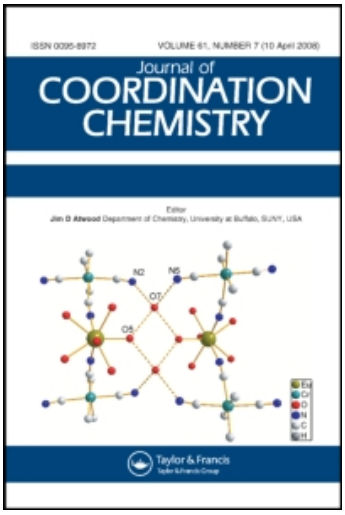

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Enantiomeric Recognition of Organic Ammonium Salts by Chiral Pyridino-18-Crown-6 Ligands: A Short Review

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ENANTIOMERIC RECOGNITION OF ORGANIC AMMONIUM SALTS BY CHIRAL PYRIDINO-18-CROWN-6 LIGANDS: A SHORT REVIEW

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A short review of enantiomeric recognition of chiral organic ammonium salts by chiral pyridino-18-crown-6 ligands is presented. Topics include preparation of chiral macrocycles and details of enantiomeric recognition as determined by ^{1}H NMR and calorimetry techniques. The chiral pyridino-18-crown-6 ligands containing two *tert*-butyl or two phenyl substituents on chiral macroring carbon atoms exhibited the highest recognition for the enantiomers of [α-(1-naphthyl)ethyl]ammonium perchlorate of any chiral pyridino-18-crown-6 ligands studied.

Keywords: Chiral pyridino-18-crown-6 ligands, chiral organic ammonium ions, enantiomeric recognition

INTRODUCTION

Molecular recognition is ubiquitous in nature. Examples include antibody-antigen interactions, biochemical catalysis reactions, the DNA double helix, and incorporation of single enantiomeric forms of amino acids and sugars in metabolic pathways. Perhaps the single most striking feature of these and similar host-guest systems is the remarkable level of specificity they exhibit. In many cases, this specificity must represent orders of magnitude recognition of one enantiomer over another by the host.

Molecular recognition is an active field of research. The present activity in this field is driven by the inherent interest in elucidating the remarkable ability of molecules to recognize one another with subsequent interaction and formation of stable organized structures.[1] Although this interest was evidenced in many early studies, it received a significant impetus when Pedersen[2] published his synthesis of a large number of crown ethers and identified their abilities to differentiate among similar metal cations. The rapid development of the field of molecular recognition as applied to macrocycles was recognized by the awarding of Nobel Prizes in 1987 to three of its pioneers, Pedersen,[3] Lehn[4] and Cram.[5]

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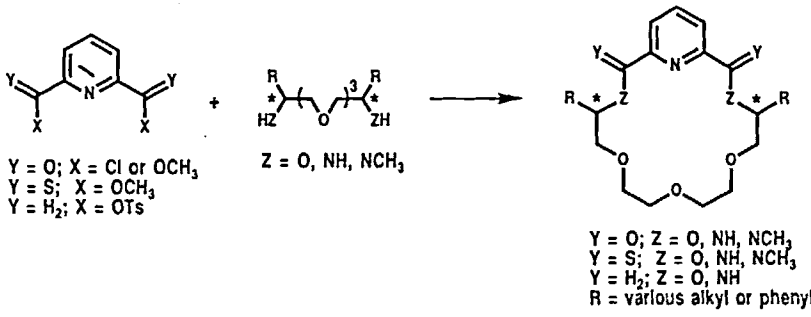
The enantiomeric recognition of organic amines by chiral macrocyclic ligands is an area of molecular recognition that is receiving considerable interest at the present time. Several research groups have carried out work involving these host-guest systems. Cram and his co-workers have reported chiral recognition of organic amines by a solvent extraction technique,[6–8] transport of amines through liquid membranes,[9] and partial resolution using chromatography of an amino acid on a silica gel or polystyrene bound chiral host material.[10] Lehn and his co-workers have studied reactivity differences when certain *p*-nitrophenyl esters were thiolyzed while complexed with chiral host molecules.[11] These researchers have studied many different molecular receptors.[12,13] Other research groups including our own have observed enantiomeric recognition of organic ammonium salts by chiral crowns derived from simple sugar molecules,[14,15] by chiral diaza-crowns,[16] by chiral crowns containing pyridine and triazole subcyclic units using the temperature-dependent ^{1}H NMR spectroscopy technique,[17–20] and by chiral pyridino-crowns using titration calorimetry.[17] An excellent review of chiral crown ethers in general and their interactions with organic ammonium salts has been published.[21]

Our interest in enantiomeric recognition has focused on the interaction of chiral crowns containing pyridine and triazole subcyclic units with organic ammonium salts.[17–20,22] The pyridino-crowns form strong complexes with certain organic ammonium salts.[17,23] The interations of chiral pyridino-crowns with organic ammonium salts were chosen because they show appreciable enantiomeric recognition in certain cases. Thus, they present the possibility of a systematic study of how the extent of enantiomeric recognition varies with crown substituent, guest type, and solvent. The results of such a study could lead to the ability to design specific information into hosts which would allow them to have superior recognition for one guest enantiomer over another. A short review of the preparation of the chiral pyridino-18-crown-6 ligands and their enantiomeric interactions with organic ammonium salts is presented herein.

PREPARATION OF CHIRAL PYRIDINO-18-CROWN-6 LIGANDS

The chiral pyridino-18-crown-6 ligands were prepared as shown in Scheme I. The chiral ligands that have been prepared are shown in Figure 1 with specific structural details, yields and references given in Table I.

As can be seen in Figure 1, the pyridino-crowns are of five types—diester-crowns



Scheme 1 Preparation of chiral pyridino-18-crown-6 ligands.

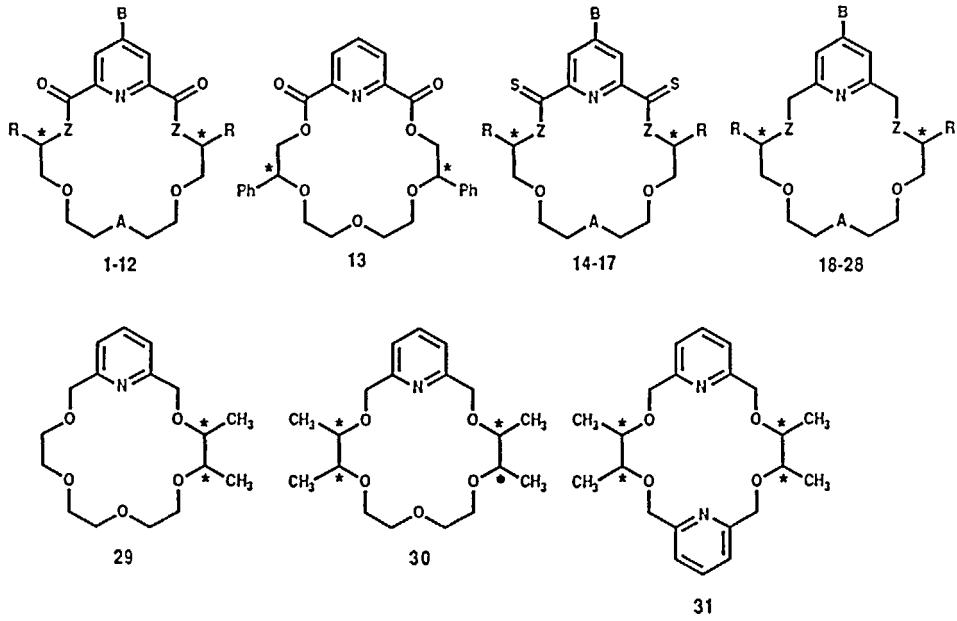


FIGURE 1 Chiral pyridino-18-crown-6 ligands (see Table I).

(**1–9** and **13**), bisamido-crowns (**10–12**), a thiono diester-crown (**14**), bis(thionoamido)-crowns (**15–17**), and the crown ethers (**18–31**). The diester-crowns were prepared by reacting the chiral dialkyl-substituted tetraethylene glycol with either 2,6-pyridinedicarbonyl chloride[24,28] (Scheme I, Y=O, X=Cl) or with dimethyl 2,6-pyridinedicarboxylate (Scheme I, Y=O, X=OHC_3).[18,20,25,29] The latter synthetic sequence is the well-known transesterification reaction and was driven to completion by removing the methanol by-product with molecular sieves. A similar reaction was used to prepare **14** from O,O'-dimethyl 2,6-pyridinedicarbothioate.[29] Bisamido-crowns **10** and **12** and bis(thionoamido)-crowns **15** and **17** were prepared by reacting the appropriate chiral diamine with either dimethyl 2,6-pyridinedicarboxylate (for **10** and **12**) or its dithiono derivative (Scheme I, Y=S, X=OCH_3) (for **15** and **17**).[26,27] This reaction is similar to the Tabushi method to prepare macrocyclic diamides.[30,31] Bisamido-crown **11** was made from 2,6-pyridinedicarbonyl chloride and the chiral diamine.[26] It is interesting to note that bis(thionoamido)-crowns **15** and **17** were also prepared by reacting bisamido-crowns **10** and **12** with 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (Lawesson's reagent).[26,27] Bis(thionoamido)-crown **16** was also prepared using Lawesson's reagent.[26] Lawesson's reagent has been used to convert open chain esters to thionoesters[32] and macrocyclic diesters to macrocyclic bis(thionoesters).[33] The majority of the chiral pyridino-crown ethers (**18–31**) were prepared by reacting 2,6-pyridinedimethyl ditosylate (Scheme I, Y=H_2, X=OTs) with the appropriate chiral dialkyl- or diphenyl-substituted tetraethylene glycol.[22,25] Macrocycle **18** was prepared by a Raney nickel reduction of thiono-crown **14**.[29] The syntheses of the many chiral dialkyl-substituted tetraethylene glycols used to prepare the chiral crowns are discussed fully in the referenced publications.

TABLE I
Chiral pyridino-18-crown-6 ligands (see Figure 1 for structures).

Comp	Z	A	B	R	Yld (%)	Reference
1	O	O	H	CH_3	49	24
2	O	O	Cl	CH_3	76	24
3	O	O	OCH_3	CH_3	17	24
4	O	O	$OCH_2C_6H_5$	CH_3	35	20
5	O	O	OH	CH_3	29 (from 4)	20
6	O	O	H	$C(CH_3)_3$	15	25
7	O	O	H	C_6H_5	17	18
8	O	O	$OCH_2C_6H_5$	C_6H_5	8	20
9	O	O	OH	C_6H_5	3 (from 8)	20
10	NH	O	H	C_6H_5	25	26
11	NCH_3	O	H	C_6H_5	53	26
12	NH	O	H	$CH_2C_6H_5$	29	27
13	see structure in Figure 1				51	28
14	O	O	H	CH_3	30	29
15	NH	O	H	C_6H_5	81 (from 10)	26
16	NHC_3	O	H	C_6H_5	90 (from 11)	26
17	NH	O	H	$CH_2C_6H_5$	28	27
18	O	O	H	CH_3	56 (from 14)	29
19	O	O	H	$(CH(CH_3)_2$	55	11
20	O	O	H	$CH_2CH_2CH{=}CH_2$	51	22
21	O	O	H	$CH_2CH(CH_3)_2$	43	22
22	O	O	H	$CH(CH_3)CH_2CH_3$	52	22
23	O	O	H	$C(CH_3)_3$	73	25
24	O	O	H	$CH_2C_6H_5$	38	22
25	O	O	H	C_6H_5	36	25
26	NH	O	H	$CH_2C_6H_5$	32 (from 17)	27
27	O	NH	H	CH_3	27	27
28	O	$(NC(O)CH_3)$	H	CH_3	82 (from 27)	27
29	see structure in Figure 1				43	25
30	see structure in Figure 1				47	22
31	see structure in Figure 1				15	22

ENANTIOMERIC RECOGNITION OF ORGANIC AMMONIUM SALTS AS DETERMINED BY TEMPERATURE DEPENDENT NMR TECHNIQUE

Complexation of the enantiomeric forms of various organic ammonium salts by some of these ligands has been studied by the temperature-dependent ^1H NMR technique[17–20,34,35] At low temperatures, the peaks in the ^1H NMR spectra of the complexes attributable to the hydrogen atoms on various groups of the chiral ligand of the complexes separate into two peaks of equal intensities. The low temperature peak separations were 40–140 Hz. At high temperatures, the appearance of a single peak is caused by a fast intermolecular or intramolecular face-to-face guest exchange. The kinetic parameters for the dissociation of these complexes were calculated as reported.[14,17,23,34,35] Table II shows the coalescence temperatures (T_c) and $\Delta G_c^{\ddagger}$ for the dissociation of the complexes of most of the chiral pyridino-18-crown-6 ligands

TABLE II

Free energies of activation, $\Delta G_c^{\ddagger}$ values (kcal/mol), in CD_2Cl_2[a] for the Interaction of chiral pyridino-18-crown-6 ligands with chiral alkylammonium salts.

Ligand	Value*	(*R*)-A[b]	(*S*)-A[b]	(*R*)-B[b]	(*S*)-B[b]	(*R*)-C[b]	(*S*)-C[b]	Reference
(*S*,*S*)-**1**	T_c	12	−19			−25	−36	17
	$\Delta G_c^{\ddagger}$	13.4	12.3			12.1	11.8	
(*R*,*R*)-**2**	T_c	−13	13			−36	−25	17
	$\Delta G_c^{\ddagger}$	12.5	13.4			11.8	12.1	
(*S*,*S*)-**2**	T_c					−34	−48	17
	$\Delta G_c^{\ddagger}$					11.6	11.1	
(*S*,*S*)-**3**	T_c					−11	−26	17
	$\Delta G_c^{\ddagger}$					12.7	12.4	
(*S*,*S*)-**4**	T_c	31	7					20
	$\Delta G_c^{\ddagger}$	14.5	13.1					
(*S*,*S*)-**5**	T_c	32	−8					20
	$\Delta G_c^{\ddagger}$	14.5	13.4					
(*S*,*S*)-**6**	T_c	−54	< −90					25
	$\Delta G_c^{\ddagger}$	10.3	<8.5					
(*S*,*S*)-**7**	T_c	11	−35			−21	−45	18,22
	$\Delta G_c^{\ddagger}$	13.3	12.0			11.9	10.8	
(*R*,*R*)-**9**	T_c	−1	27					20
	$\Delta G_c^{\ddagger}$	13.4	13.7					
(*S*,*S*)-**13**	T_c					−33	−28	17
	$\Delta G_c^{\ddagger}$					11.5	11.6	
(*S*,*S*)-**14**	T_c	0	−30			−38	−61	17
	$\Delta G_c^{\ddagger}$	13.0	11.8			11.4	11.0	
(*S*,*S*)-**18**	T_c	−56	−86			−40	−73	17
	$\Delta G_c^{\ddagger}$	10.3	8.7			11.3	10.0	
(*S*,*S*)-**20**	T_c	29	10					22
	$\Delta G_c^{\ddagger}$	14.2	13.3					
(*R*,*R*)-**22**	T_c	−20	5	−50	−15	−42	−48	22
	$\Delta G_c^{\ddagger}$	12.5	13.3	10.8	12.1	11.3	10.9	
(*S*,*S*)-**23**	T_c	−38	−95					25
	$\Delta G_c^{\ddagger}$	11.3	8.8					
(*R*,*R*)-**25**	T_c	6	−34					25
	$\Delta G_c^{\ddagger}$	14.2	11.4					
(*S*,*S*)-**29**	T_c	28	30					25
	$\Delta G_c^{\ddagger}$	14.9	14.6					
(*R*,*R*,*R*,*R*)-**30**	T_c	3	27	−21	25			22
	$\Delta G_c^{\ddagger}$	13.4	14.3	21.1	14.3			
(*R*,*R*,*R*,*R*)-**31**	T_c	−52	−43	−38	−46			22
	$\Delta G_c^{\ddagger}$	10.5	11.2	11.2	10.6			

[a] Varian Gemini-200 and SC-300 spectrometers were used to record all ^1H NMR spectra. Equimolar amounts of ligand and salt were dissolved in CD_2Cl_2. T_c = coalescence temperature (°C). $\Delta G_c^{\ddagger}$ values were ±0.2. [b] A = the hydrogen perchlorate salt of (*R*)- or (*S*)-α-(1-naphthyl)ethylamine; B = the hydrogen perchlorate salt of (*R*)- or (*S*)-α-phenylethylamine; C = the hydrogen perchlorate salt of methyl phenylalaninate.

with various chiral organic ammonium salts. The majority of the data are for complexes of these chiral ligands with the hydrogen perchlorate salts of (*R*)- and (*S*)-α-(1-naphthyl)ethylamine(A).

It is evident from the differences in the $\Delta G_c^{\ddagger}$ values in Table II that these chiral ligands exhibit enantiomeric recognition for chiral forms of various organic ammonium salts. All the *S,S* ligands formed kinetically more stable complexes with the *R* than with the *S* form of A. As expected, complexes of the *R,R* and *R,R,R,R* (**30** and **31**) ligands with the *S* form of A were more stable kinetically than those with the *R* form. It is interesting that chiral 4-hydroxypyridino-18-crown-6 ligands **5** and **9** are acidic enough to react with amines to form an ammonium cation complexed to the deprotonated hydroxypyridino-crown anion. The $\Delta G_c^{\ddagger}$ values for the (*S,S*)-**5**-(*R*)-A (amine form) was 11.0 kcal/mol while that for the complex with (*S*)-A (amine form) was 10.3. In the case of (*R,R*)-**9**, the complex with (*R*)-A (amine form) gave a $\Delta G_c^{\ddagger}$ value of 10.3 kcal/mol and with (*S*)-A (amine form) a $\Delta G_c^{\ddagger}$ value of 11.3. Thus, enantiomeric recognition was also observed for these interesting crown-amine interactions.

The degree of recognition was similar in all ligand-A complexes as shown by the $\Delta G_c^{\ddagger}$ values being about 1 kcal/mol or less except for **6**, **18**, **23** and **25** where the $\Delta G_c^{\ddagger}$ values were 1.6 kcal/mol or higher. An X-ray crystal study of the complexes of (*S,S*)-**1** with both (*R*)- and (*S*)-A showed that the methyl groups on the chiral carbons of (*S,S*)-**1** interact sterically with one of the naphthylene hydrogens of A in the (*S,S*)-**1**-(*R*)-A complex.[17] We had hoped that larger alkyl groups attached to the chiral centres, such as the *sec*-butyl groups of **22**, would cause even greater enantiomeric recognition. The large *tert*-butyl and phenyl substituents, on the other hand, provided the steric bulk necessary to cause ligands **6**, **23** and **25** to show excellent recognition for the enantiomers of A as shown in Table II.

In Table III, values for the difference in $\Delta G_c^{\ddagger}$ ($\Delta\Delta G_c^{\ddagger}$) for the interaction of various chiral ligands with A as observed by the temperature-dependent ^{1}H NMR technique (values from Table II) are compared with those calculated from the conformational equilibrium energies of the complexes.[36,37] These calculated energies included those for the ion-ligand interactions and the strain energy of the ligands that are the main components of $\Delta G_c^{\ddagger}$. They are therefore the main contributors to $\Delta\Delta G_c^{\ddagger}$. The other components that are temperature or solvent dependent are smaller and not much different for the *R* and *S* complex and therefore are mostly cancelled out in the calculated $\Delta\Delta G_c^{\ddagger}$ values.[36,37] Consequently, the calculated energy difference represents approximately the $\Delta\Delta G_c^{\ddagger}$ value. These calculated values are based on the empirical functions of bond lengths, bond angles, and interatomic Coulombic and Lennard-Jones Interactions.

As shown in Table III, the calculated and observed $\Delta\Delta G_c^{\ddagger}$ values are similar for all ligand-A complex interactions except for **7** and **22** where the calculated values were higher. Since the computer-calculated $\Delta\Delta G_c^{\ddagger}$ values generally agree with the observed $\Delta\Delta G_c^{\ddagger}$ values, those calculations can be used to predict which chiral disubstituted pyridino-18-crown-6 ligands would provide the best recognition for A. Indeed these calculations were done before **6**, **23** and **25** were prepared[22] and the calculations predicted that the di-*tert*-butyl- and diphenyl-substituted ligands would provide the best recognition. It is instructive to note that **6**, **23** and **25** gave the highest observed $\Delta\Delta G_c^{\ddagger}$ values.[25] Computer-generated stereoviews obtained from the force field calculations of the complexes of (*S,S*)-**23** with A show that for the *R* enantiomer, the *tert*-butyl substituent contacts the methyl part of the salt, the naphthyl

TABLE III

Differences in free energies of activation (($\Delta\Delta G_c^{\ddagger}$, kcal/mol) $[\Delta G_c^{\ddagger}(R) - \Delta G_c^{\ddagger}(S)]$ for the interaction of various chiral macrocyclic ligands with (*R*)- and (*S*)-[[α-(1-Naphthyl)ethyl]ammonium perchlorate (A in Table II) as determined experimentaly (NMR) and as calculated from empirical energy functions.[a]

	$\Delta\Delta G_c^{\ddagger}$	
Ligand	Obsd	Calcd[b]
(*S*,*S*)-**1**	1.1	0.7
(*S*,*S*)-**6**	<1.8	2.5
(*S*,*S*)-**7**	1.3	2.5
(*S*,*S*)-**13**	0.1	0.1
(*S*,*S*)-**18**	1.6	1.7
(*R*,*R*)-**22**	0.8	1.7
(*S*,*S*)-**23**	2.5	2.2
(*R*,*R*).**25**	2.8	
(*R*,*R*,*R*,*R*)-**30**	0.9	0.9

[a] Empirical calculations reported in references 22, 36 and 37. [b] Values as reported in reference 22.

substituent of the salt contracts the pyridine, and the three NH bonds are properly oriented toward their respective ligating groups, thus optimizing the salt-ligand electrostatic interaction.[22] The *S* enantiomeric salt appears to be less favourably bound to the ligand. The naphthyl substituent of the salt repels the *tert*-butyl substituent of the ligand, thus introducing distortion and strain in the complex, and the NH bonds are not well oriented toward their respective ligating group, thus weakening the salt-ligand interaction.[22]

ENANTIOMERIC RECOGNITION OF ORGANIC AMMONIUM SALTS AS DETERMINED BY LOG *K* VALUES

Complexation of the chiral forms of several chiral alkylammonium salts by the chiral disubstituted pyridino-18-crown-6 ligands was studied by determining the log *K* values by both a calorimetric technique in CH_3OH[17,39] and a direct ^1H NMR technique in CD_3OD–$CDCl_3$ mixtures.[25,38] Table IV lists the log *K* values for these interactions. It is clear from the data that enantiomeric recognition by these chiral crown compounds can be shown by the substantial differences in log *K* values. Thus, **1**, **7** and **23** exhibit log *K* differences of 0.41, 0.85 and 0.71 log *K* units for the interactions of the macrocycle with (*R*)-A versus the interaction with (*S*)-A. Varying degrees of enantiomeric recognition is also noted for the chiral ligands for other organic ammonium salts. In general, as shown by the $\Delta\Delta G_c^{\ddagger}$ data given above, the (*S*,*S*)- ligands form the most stable complexes with the (*R*)- salts [or (*R*,*R*)- ligands with (*S*)- salts]. The one exception is the complex of (*S*,*S*)- **7** with the hydrogen perchlorate salts of 2-amino-2-phenylethanol [see Table IV, (*R*)-F and (*S*)-F].

TABLE IV
Log K Values for the Interactions of Chiral Disubstituted Pyridino-18-crown-6 Ligands with several Chiral Alkylammonium Salts at 25°C

Crown	Salt[a]	Method	Solvent[b]	Log K	Reference
(*S*,*S*)-1	(*R*)-A	Cal	CH_3OH	2.47	17
	(*R*)-A	NMR	CD_3OD	2.47	38
	(*S*)-A	Cal	CH_3OH	2.06	17
	(*S*)-A	NMR	CD_3OD	2.08	38
	(*R*)-D	Cal	CH_3OH	1.73	17
	(*S*)-D	Cal	CH_3OH	1.76	17
	(*R*)-E	Cal	CH_3OH	2.02	17
	(*S*)-E	Cal	CH_3OH	1.78	17
(*S*,*S*)-7	(*R*)-A	NMR	70M-30C	2.15	25
	(*S*)-A	NMR	70M-30C	<1.30	25
	(*R*)-B	NMR	50M-50C	2.62	25
	(*S*)-B	NMR	50M-50C	2.06	25
	(*R*)-C	NMR	50M-50C	1.60	25
	(*S*)-C	NMR	50M-50C	1.28	25
	(*R*)-F	NMR	50M-50C	2.24	25
	(*S*)-F	NMR	50M-50C	2.95	25
	(*R*)-G	NMR	50M-50C	2.18	25
	(*S*)-G	NMR	50M-50C	1.76	25
(*S*,*S*)-13	(*R*)-D	Cal	CH_3OH	1.96	17
	(*S*)-D	Cal	CH_3OH	2.00	17
(*S*,*S*)-18	(*R*)-D	Cal	CH_3OH	2.43	17
	(*S*)-D	Cal	CH_3OH	2.29	17
(*S*,*S*)-23	(*R*)-A	NMR	10M-90C	1.33	25
	(*S*)-A	NMR	10M-90C	0.62	25
(*R*,*R*)-25	(*R*)-A	NMR	CD_3OD	2.92	25
	(*S*)-A	NMR	CD_3OD	3.10	25
	(*R*)-B	NMR	CD_3OD	2.91	25
	(*S*)-B	NMR	CD_3OD	3.05	25
(*R*,*R*)-29	(*R*)-A	NMR	CD_3OD	3.00	25
	(*S*)-A	NMR	CD_3OD	2.94	25

[a] See footnote *b* of Table II for the structures of A–C; D = the hydrogen chloride salt of (*R*)- or (S)-methyl tryptophanate; E = the hydrogen chloride salt of (*R*)- or (*S*)-methyl alaninate; F = the hydrogen perchlorate salt of 2-amino-2-phenylethanol; G = the hydrogenperchlorate salt of 2-amino-3-phenyl-1-propanol.
[b] Solvents M and C are given as percentages of CD_3OD(M) and $CDCl_3$(C).

It is important to note the correlation between the log K data obtained by calorimetry and that obtained by the direct ^{1}H NMR technique. The values listed in the first four entries in Table IV show this correlation.[38] Thus, the NMR-log K values are acceptable and can be used to show enantiomeric recognition in these systems. One great benefit of the ^{1}H NMR-log K technique is the greatly reduced amount of chiral crown ligand needed for these studies. The calorimetry process requires up to one gram of material while good NMR data can be obtained using 5 or 10 milligrams of crown. One drawback in the NMR technique is the inability to obtain good ΔH and ΔS data from plots of log K *vs* 1/T.[38] Thus, the NMR process can give acceptable log K data but the calorimetry technique must be used for the thermodynamic ΔH ΔS parameters.

SUMMARY

The chiral pyridino-18-crown-6 macrocycles are excellent ligands for the study of enantiomeric recognition of organic ammonium salts. They form reasonably strong complexes with the ammonium salts derived from primary amines as determined by the temperature dependent ^{1}H NMR and calorimetric log K techniques.[17,23] A variety of chiral disubstituted pyridino-18-crown-6 ligands have been prepared. The substituents were attached to two chiral ring carbon atoms located near the rigid pyridine portion of the molecule except for **13** where the two phenyl substituents were attached to chiral carbons in the flexible polyether portion of the macrocycle. The chiral pyridino-18-crown-6 ligands are shown in Figure 1 and described in Table I. The substituents varied from methyl to *tert*-butyl and phenyl. Two macrocycles containing four methyl substituents on chiral ring carbon atoms (**30** and **31**) were also prepared. A few chiral macrocyclic diamides and dithionoamides containing the pyridine subcyclic unit (**10–12** and **15–17**) were also prepared. The enantiomeric recognition of organic ammonium salts by these 6 new amide-containing ligands have not been studied.

This study has shown that the chiral disubstituted pyridino-18-crown-6 ligands recognize the enantiomers of certain organic ammonium salts. The complex is characterized by three interactions. First, the X-ray crystal study shows that the salt is anchored to the macrocycle by hydrogen bonds from the ammonium hydrogen atoms to the pyridine nitrogen and two ring oxygen atoms. Second, in the case of complexation of salt A, the naphthalene unit of the salt is directly over the pyridine ring. Third, the two substituents in chiral positions on the macrocycle must be close to the rigid pyridine ring to exert a steric interaction in the complex. This is clearly evident by the fact that compound **13** with large phenyl substituents away from the pyridine ring exhibited no enantiomeric recognition while **7–9** and **25** with the phenyls closer to the pyridine exhibited excellent recognition.

Enantiomeric recognition of the organic ammonium salts was most pronounced for the ligands containing two *tert*-butyl or two phenyl substituents. This high degree of recognition is evident by the difference in free energy ($\Delta\Delta G_c^{\ddagger}$) and log K values for the interactions of the diphenyl and di-*tert*-butyl macrocycles with A as shown in Table III and Table IV. Thus, recognition by (S,S)-**6** (di-*tert*-butyl) for A is shown by a $\Delta\Delta G_c^{\ddagger}$ value of <1.8 kcal/mol and a $\Delta \log K$ (NMR) value of <0.85 (70% CD_3OD in $CDCl_3$). Recognition factors of other di-*tert*-butyl and diphenyl-crowns for A were as follows: $\Delta\Delta G_c^{\ddagger}=2.5$ kcal/mol and $\Delta \log K$ (NMR)$=0.71$ (10% CD_3OD in $CDCl_3$) for **23** and $\Delta\Delta G_c^{\ddagger}=2.8$ kcal/mol and $\Delta \log K$ (NMR)$=0.18$ (CD_3OD) for **25**.

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