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A Thermodynamic Study of Enantiomeric Recognition of Organic Ammonium Cations by Pyridino-18-Crown-6 Type Ligands in Methanol and a 1 : 1 Methanol-1,2-Dichloroethane Mixture at 25.0 °C

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Abstract. Log K, ΔH, and $T\Delta S$ values for interactions of (R) and (S) enantiomers of α-(1-naphthyl)ethylammonium perchlorate (NapEt), α-phenylethylammonium perchlorate (PhEt), and the hydrogen perchlorate salt of 2-amino-2-phenylethanol (PhEtOH) with a series of chiral and achiral pyridino-18-crown-6 type ligands and 18-crown-6 (18C6) were determined from calorimetric titration data valid in methanol and in a 1 : 1 (v/v) methanol–1,2-dichloroethane (MeOH–1,2-DCE) mixture at 25.0 °C. In the MeOH–1,2-DCE solvent mixture, the chiral macrocyclic ligands exhibit excellent recognition for enantiomers of the three organic ammonium cations as shown by large differences in log K values (Δ log K) which range from 0.4 to 0.6 (2.5- to 4.0-fold difference in binding constants). The Δ log K values in the solvent mixture MeOH–1,2-DCE are increased by 0.1 – 0.5 log K units over those in absolute methanol, indicating a favorable effect of 1,2-dichloroethane on enantiomeric recognition. In 1,2-dichloroethane, however, the interactions are too strong (log $K > 6$) to observe the degree of recognition by a direct calorimetric method. Complexation of organic ammonium cations by these macrocyclic ligands is driven by favorable enthalpy changes. The entropy changes are unfavorable in all cases. The thermodynamic origin of enantiomeric recognition for NapEt in 1 : 1 (v/v) MeOH–1,2-DCE is enthalpic, but those for PhEt and PhEtOH are entropic. Effects of the ligand structure and flexibility and of the organic cation structure on recognition and complex stability are discussed on the basis of the thermodynamic quantities. Different thermodynamic behaviors of achiral **5** and 18C6 from those of chiral macrocyclic ligands indicate a difference between chiral and achiral macrocycle interactions with the chiral organic ammonium cations. The different thermodynamic behavior of NapEt enantiomers compared to those of PhEt and PhEtOH enantiomers supports the idea that the solution complex conformation of NapEt is different from those of PhEt and PhEtOH. π–π interaction is absent for the PhEt and PhEtOH complexes with diesterpyridino-18-crown-6 ligands in solution. Therefore, the higher degree of enantiomeric recognition for NapEt than for either PhEt or PhEtOH by these chiral macrocyclic ligands is a result of the presence of π–π interaction in the NapEt system.

Key words: Enantiomeric recognition, thermodynamics, crown ether, chiral organic ammonium salt.

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1. Introduction

Enantiomeric recognition of chiral organic guests by chiral macrocyclic ligands is an active research field. Several research groups have carried out work involving these host-guest systems. Cram and his co-workers did the pioneering work on the use of chiral macrocyclic compounds in enantiomeric recognition and studied many chiral interaction systems [1]. Some macrobicyclic and macrotricyclic molecules were shown to have significant recognition toward certain chiral amides [2]. Naemura and his coworkers examined the enantiomeric recognition behavior of chiral crown ethers toward racemic primary ammonium salts through bulk liquid membranes [3]. Echegoyen and his co-workers showed that chiral 18-membered-ring crown ethers containing substituted triazole subcyclic units displayed a modest degree of enantiomeric recognition toward two organic ammonium cations [4]. They concluded from ^{1}H-NMR titration data that the positions of the naphthyl and phenyl rings of the ammonium cations were different in diastereomeric complexes. Enantiomeric recognition of organic ammonium cations by chiral macrocyclic compounds in the gas phase has been investigated recently by Fourier transform ion cyclotron resonance mass spectrometry [5] and fast atom bombardment mass spectrometry [6]. Moderate to excellent recognitions were found. Moreover, chiral crown ethers have been successfully used to chromatographically resolve underivatized small peptides [7], amino acids [8], aminophosphoalkanoic acids [9], and other amino derivatives [10].

In our laboratory, chiral crown ethers containing pyridine subcyclic units were demonstrated to form strong complexes with certain organic ammonium cations in various single and mixed organic solvents and to exhibit good to excellent enantiomeric recognition in certain cases [11–14]. We have characterized such host-guest interactions by ^{1}H-NMR spectroscopy [11–16], calorimetric titration [11, 14, 17], X-ray crystallography [11, 16–18], and molecular mechanics calculations [15, 16]. It has been well established that tripod hydrogen bonding involving a pyridine nitrogen and two alternate oxygen atoms of the macrocycle and three hydrogen atoms of the ammonium cation (see Figure 1) provides the fundamental interaction between pyridino-18-crown-6 type ligands and organic ammonium cations [11, 16–18]. A secondary bonding may occur between the pyridine ring of the crown ether and the aromatic group of the ammonium cation through $\pi - \pi$ interaction. Our recent studies show that $\pi - \pi$ interaction exists in complexes involving α-(1-naphthyl)ethylammonium perchlorate (NapEt) and, in limited cases, α-phenylethylammonium perchlorate (PhEt) and the hydrogen perchlorate salt of 2-amino-2-phenylethanol (PhEtOH) [16, 17]. These two kinds of interactions anchor the guest ammonium cation on the host macrocyclic ligand. The enantiomeric recognition stems principally from the steric effect between the chiral groups of the macrocycle and the chiral ammonium cation. Greater steric hindrance may occur with one enantiomer of an ammonium cation than with the other enantiomer so that the enantiomers can be recognized by the crown ether. Pirkel

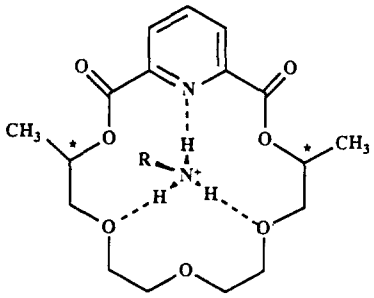

Fig. 1. Tripod hydrogen bonding.

and Pochapsky pointed out that the chiral recognition requires a minimum of three simultaneous interactions with at least one of these interactions being stereochemically dependent [19]. Many good-to-excellent enantiomeric recognitions have been observed for complexation of organic ammonium cations by pyridino-18-crown-6 type compounds, and the results have been summarized in two recent reviews [20, 21].

Thermodynamic parameters are important in identifying and understanding the driving forces of host-guest interactions and the origins of chiral recognition. Although thermodynamics does not provide direct structural information about the processes occurring in solution, accurate thermodynamic data must fit the proposed model for reaction systems. Therefore, a thermodynamic study usually provides insight into the nature of chiral host-guest interactions. We have determined some thermodynamic parameters for chiral interactions, but enthalpic and entropic data are relatively scarce as compared to the binding-constant data. In this paper, a systematic thermodynamic study on chiral interactions of three guest enantiomers (NapEt, PhEt, and PhEtOH) with four chiral pyridino-18-crown-6 type hosts in a 1 : 1 (v/v) methanol-1,2-dichloroethane (MeOH-1, 2-DCE) solvent mixture is presented. Our previous ^{1}H-NMR study showed that a higher degree of enantiomeric recognition can be obtained in methanol-chloroform solvent mixtures than in absolute methanol [12]. Because of the large heat loss caused from evaporation of volatile chloroform, the methanol-chloroform mixtures are difficult to use as solvents for titration calorimetry. Therefore, the 1 : 1 MeOH-1,2-DEC mixture was chosen as the solvent, and a high degree of enantiomeric recognition was also found in this solvent mixture.

2. Experimental

2.1. MATERIALS

The pyridino-18-crown-6 type compounds (**1, 2, 3, 4**, and **5**, see Figure 2 for structures) were prepared as reported [22, 23]. 18-Crown-6 (18C6) was obtained

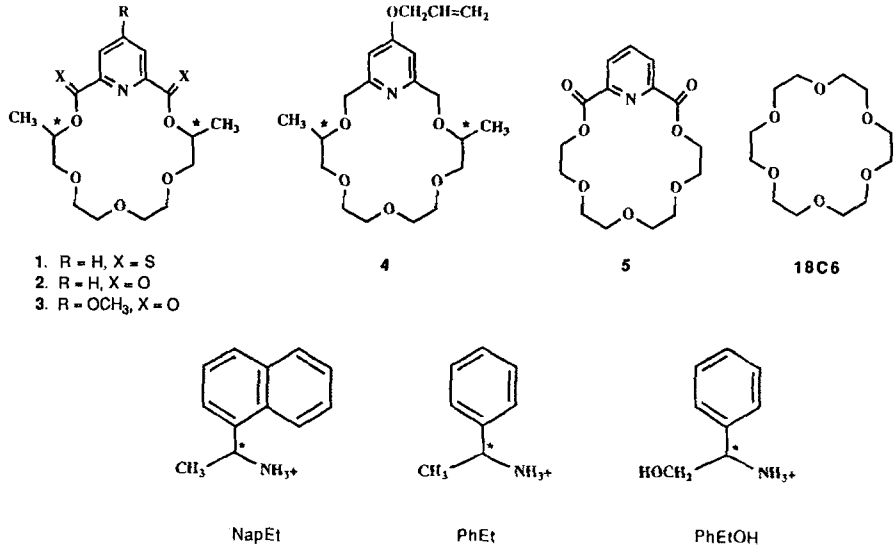

Fig. 2. Structures of macrocyclic ligands and chiral primary ammonium cations.

from SIGMA Chemical Company. (*R*) and (*S*) enantiomers of NapEt and PhEtOH were prepared as reported [11, 14]. (*R*) and (*S*) enantiomers of PhEt were prepared by treating the free amines (Aldrich) with 1M $HClO_4$ in an ethanol solution. After the solvent was removed under reduced pressure, the residue was dissolved in 1,4-dioxane and the solvent was removed again under reduced pressure. The residue was dried overnight in an oven at 40°C under reduced pressure. Then, the raw product was crystallized from butyl acetate and carbon tetrachloride to give white crystals. Highly pure products were obtained by recrystallization several times from the same solvents.

Each of the chemicals used was standardized by thermometric titration according to the method developed by Lamb and co-workers [24] to establish the purities and concentrations in solutions. The purity of 18C6 was found to be 99.2% by thermometric titration in absolute methanol against standard NaBr which had been dried overnight at 120°C. By titrating enantiomers of NapEt, PhEt and PhEtOH with 18C6, their purities were determined to be (99.0 ± 0.8)%. The purities of **1, 2, 3, 4**, and **5** were between 94% and 99% established by thermometric titration with either standard NaBr or ammonium salts. In these cases, the impurities were found to have no effect on the complexation. 1,2-Dichloroethane (EM Science, Spectrograde), methanol (Fisher, HPLC grade), and deuterated methanol were used as purchased without further purification.

2.2. DETERMINATION OF THERMODYNAMIC QUANTITIES

Log K, ΔH, and ΔS values were determined as described earlier [25] by isoperibol titration calorimetry at 25.0 ± 0.1°C. The initial solution volume in the Dewar was 20 mL. The calorimeter (Tronac Model 450) was calibrated according to the procedures described in the literature [26]. In order to avoid large heat losses caused by evaporation of 1,2-DCE, the reaction vessel of the calorimeter was modified so that an immersible magnetic stirrer, instead of a glass stirrer normally inserted into the reaction vessel from above, was used to stir the solution from underneath. The reliability of the equipment was tested by determining the thermodynamic quantities in absolute methanol for interactions of 18C6 with NaBr and with (R)- and (S)-PhEt. The values of log K (4.36) and ΔH (-8.32 kcal/mol) for NaBr interaction with 18C6 are in excellent agreement with the literature values of 4.36 ± 0.02 and -8.36 ± 0.37 kcal/mol [27]. The log K values for 18C6 interaction with (R)- and (S)-PhEt (3.82 and 3.81, see Table I) are also in excellent agreement with the literature value (3.84 ± 0.01) [28]. The ΔH values for PhEt interactions with 18C6 (-43.6 and -43.8 kJ/mol, see Table I) are higher than the literature value (-39.8 kJ/mol) [28], probably due to the different anions used. Perchlorate salts were used in this study but iodide was used in the literature for PhEt [28]. In addition, the purities of (R)- and (S)-PhEt used in this work were > 99% but that of $PhCH(CH_3)NH_3^+ \cdot I^-$ in the literature was (95.6 ± 0.9)%.

2.3. DETERMINATION OF LOG K VALUES BY A DIRECT ^{1}H-NMR METHOD

Some of the log K values were determined by a ^{1}H-NMR titration procedure [29, 30] either because of the limited amounts of sample or because the heats of reaction were too small to allow accurate calorimetric measurement (interactions of **1** with NapEt and PhEt in methanol). The NMR experiments were done on a Varian Gemini 200 (200 MHz) NMR spectrometer at 25.0 ± 0.1°C. Consistency of log K values determined by the direct ^{1}H-NMR method and by the direct calorimetric titration technique has been verified [29], confirming that the NMR technique produces log K values in agreement with those obtained from the calorimetric method. Also, using the NMR technique to verify the log K values determined by calorimetric titration was another objective of the present study. The log K values obtained from these two different methods are in excellent agreement (see Table I).

3. Results and Discussion

The thermodynamic data valid in absolute methanol (Table I), in the 1 : 1 (v/v) MeOH-1,2 DCE mixture (Table II), and in 1,2-DCE (Table III) indicate that the complexation of the organic ammonium cations by the macrocyclic ligands is driven by favorable enthalpy changes. The entropy changes are unfavorable in all cases. The (S,S) ligands form thermodynamically more stable complexes with

TABLE I. Log K, ΔH (kJ/mol), and $T\Delta S$ (kJ/mol) values[a] for interactions between chiral organic ammonium cations[b] and pyridino-18-crown-6 type ligands in methanol at 25.0 °C.

ligand[c]	value	(*R*)-NapEt	(*S*)-NapEt	(*R*)-PhEt	(*S*)-PhEt
(*S*, *S*)-**1**	log K	1.72 ± 0.12	1.60 ± 0.05	1.65 ± 0.06	1.58 ± 0.07
	ΔH	-13.7 ± 1.6			
	$T\Delta S$	-3.8			
	Δ log K[d]		0.12		0.07
(*S*, *S*)-**2**	log K	2.47 ± 0.01[e]	2.06 ± 0.01[e]	2.33 ± 0.05[f]	2.11 ± 0.05[f]
	ΔH	-27.6 ± 0.3	-26.4 ± 0.4		
	$T\Delta S$	-13.5	-14.7		
	Δ log K		0.41		0.22
(*R*, *R*)-**2**	log K	2.08 ± 0.04[f]	2.50 ± 0.03[f]	ND	ND
	Δ log K		0.42		
(*S*, *S*)-**3**	log K	2.94 ± 0.03	2.53 ± 0.04	2.85 ± 0.03[f]	2.66 ± 0.03[f]
	ΔH			-25.6 ± 0.3	-21.6 ± 0.2
	$T\Delta S$			-9.3	-6.4
	Δ log K		0.41		0.19
(*S*, *S*)-**4**	log K	3.07 ± 0.02	2.81 ± 0.03		
	ΔH	-28.3 ± 0.3	-20.8 ± 0.9	ND	ND
	$T\Delta S$	-10.8	-4.8		
	Δ log K		0.26		
5	log K	3.05 ± 0.04	3.04 ± 0.01	2.96 ± 0.02	2.95 ± 0.02
	ΔH	-30.8 ± 0.5	-30.6 ± 0.5	-33.4 ± 0.7	-33.3 ± 0.8
	$T\Delta S$	-13.4	-13.2	-16.5	-16.4
18C6	log K	3.68 ± 0.01	3.68 ± 0.01	3.82 ± 0.02	3.81 ± 0.03
	ΔH	-39.9 ± 0.3	-39.5 ± 0.3	-43.6 ± 0.5	-43.8 ± 0.6
	$T\Delta S$	-18.9	-18.5	-21.8	-22.0

[a] Values are the averages taken from three to four determinations; uncertainties are given as standard deviations. Log K values without ΔH and $T\Delta S$ values listed were determined using the ^{1}H-NMR technique, and they are averages taken from two determinations. ND means not determined. The following log K values were also determined using the ^{1}H-NMR method: (*S*, *S*)-**1**–(*R*)-NapEt (1.69 ± 0.05), (*S*, *S*)-**2**–(*R*)-NapEt (2.45 ± 0.03), **5**–(*R*)-NapEt (3.03 ± 0.05), **5**–(*S*)-NapEt (3.02 ± 0.04), **5**–(*R*)-PhEt (2.98 ± 0.05), and **5**–(*S*)-PhEt (2.98 ± 0.05).

[b] Perchlorate salts were used. The notations of ammonium cations are defined in Figure 2.

[c] See Figure 2 for structures.

[d] The Δ log K value is the difference between log K values for enantiomer interactions with a given chiral macrocyclic ligand.

[e] Ref. 11.

[f] Ref. 14.

(R)-NapEt and (R)-PhEt than with (S)-NapEt and (S)-PhEt. (R,R)-**2** forms a more stable complex with (S)-NapEt than with (R)-NapEt.

The recognition sequence of (R) and (S) enantiomers of PhEtOH is reversed as compared with that of PhEt, i.e., (S,S) ligands recognize the (S)-PhEtOH over (R)-PhEtOH (see Table II). This is due to a reversal of priority in the nomenclature of PhEtOH as compared with PhEt, so that the absolute configuration of (R)-PhEt is the same as that of (S)-PhEtOH. In the MeOH-1,2-DCE mixture, **1** and **2** exhibit the same extent of recognition toward the enantiomers of PhEt and PhEtOH (Table II).

3.1. ACHIRAL MACROCYCLIC LIGANDS

Achiral **5** and 18C6 show no recognition for the three enantiomers either in methanol or in MeOH-1,2-DCE mixture (see Tables I and II). Stability constants of 18C6 complexes are larger than those of **5** complexes, which is attributed to larger enthalpy gains (ΔH values for 18C6 interactions are -35.4 to -40.2 kJ/mol in MeOH-1,2-DCE and -39.5 to -43.8 kJ/mol in methanol, but those for **5** interactions are -24.0 to -33.4 kJ/mol). The larger entropy losses observed for 18C6 interactions with ammonium ions compared to those for **5** interactions are expected because of the greater flexibility of the 18C6 molecule, indicating that the conformation change upon complexation with ammonium ions is greater for 18C6 than for **5**. This is consistent with the expected increase in molecular rigidity resulting from the introduction of a pyridine ring and two carbonyl groups in **5**. Since the rigid molecules have better recognition properties than the flexible ones, the pyridino-18-crown-6 type hosts are a good choice for enantiomeric recognition studies. On the other hand, the fact that **5** does not exhibit chiral recognition due to the absence of chiral center(s) indicates that the chiral center(s) is indispensable for enantiomeric recognition.

3.2. STRUCTURAL EFFECTS OF MACROCYCLES AND AMMONIUM CATIONS ON ENANTIOMERIC RECOGNITION

The degree of recognition ($\Delta \log K$) for enantiomers of NapEt by chiral marocyclic ligands in the 1 : 1 MeOH-1,2-DCE mixture has the sequence $\mathbf{1} \sim \mathbf{2} \geq \mathbf{3} > \mathbf{4}$ (see Table II).

Dithiono-macrocycle **1** and diester-macrocycles **2** and **3** are less flexible and show higher recognition for enantiomers of NapEt than the more flexible **4** in the 1 : 1 MeOH-1,2-DCE mixture. This is expected since a flexible ligand can adjust its conformation to accommodate both enantiomers of a guest molecule, lowering the recognition ability. On the other hand, a less flexible ligand will have a better fit for one enantiomer than for the other, thus displaying greater chiral recongition. The larger difference in $T\Delta S$ values for **4** interactions with (R)- and (S)-NapEt than those for **1**, **2**, and **3** interactions with (R)- and (S)-NapEt is evidence of the large conformational change of **4** upon complexation with the cations.

TABLE II. Log K, ΔH (kJ/mol), and $T\Delta S$ (kJ/mol) values[a] for interactions between chiral organic ammonium cations[b] and pyridino-18-crown-6 type ligands in 1 : 1 (v/v) 1,2-dichloroethane-methanol at 25.0 °C.

ligand[c]	value	(*R*)-NapEt	(*S*)-NapEt	(*R*)-PhEt	(*S*)-PhEt	(*R*)-PhEtOH	(*S*)-PhEtOH
(*S*, *S*)-**1**	log K	2.69 ± 0.01	2.10 ± 0.09	2.27 ± 0.03	1.86 ± 0.08	1.96 ± 0.08	2.34 ± 0.06
	ΔH	-17.95 ± 0.08	-12.4 ± 1.8	-23.5 ± 0.3	-24.2 ± 0.6	-24.3 ± 0.8	-23.4 ± 0.7
	$T\Delta S$	-2.57	-0.4	-10.5	-13.6	-13.2	-10.0
	Δ log K[d]		0.59		0.41		0.38
(*S*, *S*)-**2**	log K	3.14 ± 0.02	2.54 ± 0.02	2.80 ± 0.02	2.37 ± 0.04	2.41 ± 0.04	2.83 ± 0.03
	ΔH	-30.7 ± 0.2	-27.5 ± 0.3	-32.0 ± 0.3	-35.5 ± 0.4	-32.7 ± 0.2	-30.7 ± 0.2
	$T\Delta S$	-12.8	-13.0	-16.0	-22.0	-18.9	-14.5
	Δ log K		0.60		0.43		0.42
(*R*, *R*)-**2**	log K	2.53 ± 0.07	3.11 ± 0.03				
	ΔH	-26.9 ± 0.9	-30.4 ± 0.5	ND	ND	ND	ND
	$T\Delta S$	-12.5	-12.7				
	Δ log K		0.58				
(*S*, *S*)-**3**	log K	3.52 ± 0.02	2.96 ± 0.01	3.17 ± 0.03	2.76 ± 0.04		
	ΔH	-29.3 ± 0.2	-24.9 ± 0.1	-29.7 ± 0.4	-32.0 ± 0.5	ND	ND
	$T\Delta S$	-9.2	-8.0	-11.6	-16.2		
	Δ log K		0.56		0.41		
(*S*, *S*)-**4**	log K	3.96 ± 0.02	3.50 ± 0.01				
	ΔH	-32.4 ± 0.3	-24.6 ± 0.2	ND	ND	ND	ND
	$T\Delta S$	-9.8	-4.6				
	Δ log K		0.46				

TABLE III.

TABLE II. (Continued.)

ligand[c]	value	(*R*)-NapEt	(*S*)-NapEt	(*R*)-PhEt	(*S*)-PhEt	(*R*)-PhEtOH	(*S*)-PhEtOH
5	log K	3.38 ± 0.03	3.38 ± 0.04	3.24 ± 0.04	3.21 ± 0.05	3.24 ± 0.05	3.25 ± 0.01
	ΔH	-24.0 ± 0.3	-24.2 ± 0.4	-26.1 ± 0.5	-26.3 ± 0.6	-26.0 ± 0.5	-25.8 ± 0.4
	$T\Delta S$	-4.8	-4.9	-7.6	-7.9	-7.5	-7.3
18C6	log K	4.43 ± 0.03	4.44 ± 0.03	4.52 ± 0.01	4.50 ± 0.04	4.30 ± 0.03	4.28 ± 0.04
	ΔH	-35.4 ± 0.4	-35.7 ± 0.3	-40.2 ± 0.2	-40.2 ± 0.4	-37.5 ± 0.5	-38.2 ± 0.7
	$T\Delta S$	-10.1	-10.4	-14.4	-14.5	-12.9	-13.8

[a] Values are the averages taken from three to four determinations; uncertainties are given as standard deviations.
ND means not determined.
[b] Perchlorate salts were used for all ammonium cations listed in the table. The notations of the ammonium cations are defined in Figure 2.
[c] See Figure 2 for structures.
[d] The Δ log K value is the difference between log K values for enantiomer interactions with a given chiral macrocyclic ligand.

TABLE III. Log K, ΔH (kJ/mol), and $T\Delta S$ (kJ/mol) values[a] for interactions between enantiomer PhEt[b] and chiral pyridino-18-crown-6 type ligands in 1,2-Dichloroethane at 25.0 °C.

ligand[b]	value	(*R*)-PhEt	(*S*)-PhEt
(*S*, *S*)-**1**	log K	> 6	> 6
	ΔH	51.4 ± 0.9	-48.7 ± 0.9
	$T\Delta S$	> -17	> -14
(*S*, *S*)-**3**	log K	> 6	> 6
	ΔH	-55.5 ± 0.9	-54.9 ± 0.8
	$T\Delta S$	> -21	> -21

[a] Values are the averages taken from two determinations.
[b] See Figure 2 for structures. Perchlorate salts were used for PhEt.

Recognition by the chiral macrocycles for the enantiomers of PhEt and PhEtOH is poorer than that for the enantiomers of NapEt, which probably results from a difference in the effectiveness of the $\pi - \pi$ interactions of these systems. A striking difference in $T\Delta S$ values between chiral interactions involving NapEt and those involving PhEt and PhEtOH is seen in Table II. In each case, the entropy change for PhEt and PhEtOH interactions is more negative than that for NapEt complexation, while the enthalpy change for PhEt and PhEtOH interactions is more favorable than that for NapEt interactions. A similar observation has been noted for NapEt and PhEt interactions with **5** in 9 : 1 (v/v) MeOH-H_2O solvent [17]. It has been pointed out that $\pi - \pi$ overlap is present for both NapEt and PhEt complexes of pyridino-18-crown-6 ligands. But only NapEt shows $\pi - \pi$ overlap in the interactions with diesterpyridino-18-crown-6 compounds [16, 17]. The thermodynamic data in the present study allow us to better understand this observation. The extensive desolvation caused by $\pi - \pi$ interaction between the naphthyl group of NapEt and the pyridine and carbonyl groups of the ligands results in less negative entropy changes. This same process consumes heat produced by the complexation so that smaller $-\Delta H$ values are observed. The π electrons of the phenyl group apparently are not energetic enough to allow the phenyl group to replace the solvent molecules from the keto oxygens of the ligand [16]. This has been considered to be the main reason for absence of $\pi - \pi$ interaction. The large negative $T\Delta S$ values for PhEt and PhEtOH interactions with macrocyclic ligands in MeOH-1,2-DCE mixture (Table II) support this idea. If one kind of interaction is absent among others (hydrogen bonding, $\pi - \pi$ interaction, steric hindrance, etc.), the guest molecule has more orientation choices in interacting with the host molecule and the host-guest interactions become less selective. Therefore, the absence of $\pi - \pi$ interaction is a main factor in causing the lower degree of enantiomeric recognition for PhEt and PhEtOH.

3.3. THERMODYNAMIC ORIGIN OF ENANTIOMERIC RECOGNITION

In 1 : 1 MeOH-1,2-DCE solvent, more favorable enthalpy and more unfavorable entropy changes for (S, S) ligand interactions with (R)-NapEt than with (S)-NapEt indicate that the recognition for (R)-NapEt over (S)-NapEt by (S, S) ligands originate from an enthalpy effect. On the other hand, the less unfavorable entropy and less favorable enthalpy changes for (S, S) ligand interactions with (R)-PhEt and (S)-PhEtOH than with (S)-PhEt and (R)-PhEtOH indicate that the recognition for enantiomers of PhEt and PhEtOH is entropic in origin.

Because of $\pi - \pi$ interaction, both (R)- and (S)-NapEt complexation with the ligands probably involves nearly the same extent of desolvation. The evidence is seen by small differences in $T\Delta S$ values for **1, 2,** and **3**. (The large difference in $T\Delta S$ values for **4** interaction with (S)- and (R)-NapEt is due to large differences in conformational change between (R)- and (S)-NapEt complexes because of the flexibility of **4**). Therefore, the sterically less hindered interactions of (R)-NapEt with (S, S) ligands show large negative enthalpy changes, resulting in more stable complexes.

The phenyl groups of PhEt and PhEtOH are more likely to direct away from the pyridine ring owing to absence of strong π -- π interaction [16, 17, 29]. For this type of complexation, the (S)- and (R)-complexes may experience different desolvation processes [17]. The sterically less hindered interactions of (R)-PhEt and (S)-PhEtOH with (S, S) ligands can replace more solvent molecules from the ammonium cations and the ligands. Thus, the more extensive desolvation of (R)-PhEt and (S)-PhEtOH complexes results in the higher log K values.

3.4. EFFECT OF MACROCYCLE STRUCTURE ON COMPLEX STABILITY

The stability order for the (R)-NapEt complexes is 18C6 > **4** > **3** > **5** > **2** > **1**, and that for the (S)-NapEt complexes is a little different, i.e., 18C6 > **4** > **5** > **3** > **2** > **1** (Table II). According to these sequences, the following conclusions about complex stability can be drawn: (1) 18C6 > pyridino-18C6; (2) pyridine group with an electron-donating substitution (**3** and **4**) > unsubstituted pyridine group (**1** and **2**); (3) pyridino-18C6 (**4**) > diesterpyridino-18C6 (**1**, **2**, and **3**); and (4) diestersubstitution (**2**) > dithiono-substitution (**1**). For interactions with ammonium cations, both $-\Delta H$ and log K values are smaller in all cases for **1** than for **2**, indicating that the bulky sulfur atoms of **1** weaken host-guest interaction through steric repulsion.

It has been noted that the addition of the electron-donating groups -OMe and $-OCH_2CH{=}CH_2$ to the pyridine ring of the ligands enhances the complex stability [14]. Comparisons of (S, S)-**3** with (S, S)-**2** complexes in MeOH-1,2-DCE mixture and of (S, S)-**4** with (S, S)-dimethylpyridino-18-crown-6 (**1** in ref. 14) in methanol show that the increase in log K values is a result of the entropy effect. The enthalpy changes for interactions of (S, S)-**3** and (S, S)-**4** are less favorable than those for interactions of corresponding unsubstituted ligands. These facts indicate that the

oxygen-containing substituents of the pyridine ring result in extensive desolvation upon complexation with the ammonium cations.

Although the presence of the electron-donating substituents of the pyridine ring increases complex stability, no significant change in the extent of enantiomeric recognition has been observed. However, the introduction of the -$OCH_2CH{=}CH_2$ group makes it possible to chemically bond the ligand to silica gel so that a chromatographic separation of enantiomers can be carried out [23].

3.5. SOLVENT EFFECT

Solvents have a significant effect on enantiomeric recognition and complex stability [14]. In methanol, good recognition is observed in some cases as seen from Table I. Values of log K and $-\Delta H$ in methanol are usually not large. In the low polar solvent 1,2-DCE, the values of log K and $-\Delta H$ are large (Table III) due to low Gutmann donicity of the solvent [31]. However, the degree of recognition could not be observed by a direct calorimetric method owing to too strong interactions.

In the 1 : 1 (v/v) MeOH-1,2-DCE mixture, both degree of recognition, in terms of Δ log K, and log K and $-\Delta H$ values are larger than those in methanol. The Δ log K values are 0.1–0.5 log K units higher than those in absolute methanol. The largest increase in Δ log K values occurs for (S,S)-**1** (a $\sim$ 0.5 log K unit increase is observed for enantiomers of NapEt). The poor recognition of **1** for chiral ammonium cations in methanol is probably due to weak interaction of **1** with the cations, which should be caused by bulky sulfur atoms as mentioned above. In MeOH-1,2-DCE mixture, however, the decreased solvation energy results in strong complexation reactions, allowing the enantiomeric recognition of **1** to be determined. Our earlier kinetic study showed that (S,S)-**1** exhibited enantiomeric recognition for (R)-NapEt over the (S) form in CD_2Cl_2 by 1.2 kcal/mol in the $\Delta\Delta G_c^{\neq}$ value [11]. The kinetic conclusion is now confirmed by the thermodynamic results in MeOH-1,2-DCE mixture.

From Tables I and II, it can be seen that the increase in log K values from methanol to 1 : 1 MeOH-1,2-DCE mixture is mostly attributed to enthalpy changes for the interactions involving chiral ligands, i.e., the ΔH values are more negative in 1 : 1 MeOH-1,2-DCE mixture than in methanol. This is expected since the complexation reactions become stronger in MeOH-1,2-DCE mixture due to decreases in solvent-cation and solvent-ligand interactions. However, the enthalpy changes become less negative in MeOH-1,2-DCE mixture for achiral **5** and 18C6 interactions with enantiomers of NapEt and PhEt. The increase in log K values from methanol to MeOH-1,2-DCE mixture for **5** and 18C6 complexation results from less negative $T\Delta S$ values. Thus, the thermodynamic data reveal a very different behavior between the chiral and the achiral ligands.

In general, decreasing the polarity of the solvent causes host-guest interactions to be stronger due to a decrease in solvation energy of host and guest molecules. This results in more solvent molecules being released during the formation of the

diastereomeric complexes between organic ammonium cations and macrocyclic ligands. The result is that a positive or less negative entropy change is observed. Hence, it is not surprising to find less negative $T\Delta S$ values for **5** and 18C6 complexation in 1 : 1 MeOH-1,2-DCE mixture than in absolute methanol, and this results in the enhancement of the binding constants. For chiral macrocyclic ligands, however, more stereochemical limits are present and these limits lead to large conformational changes in both host and guest molecules when their interactions increase in the less polar solvent. Thus, the large entropy loss caused by the large conformational change compensates the entropy gain arising from desolvation, resulting in a small or even negative change of $T\Delta S$ values in the less polar solvent MeOH-1,2-DCE. Therefore, the increase in binding constants from polar methanol to less polar MeOH-1,2-DCE for complexation of the chiral ligands comes mostly from the enthalpic contribution.

The increase in extent of enantiomeric recognition from absolute methanol to 1 : 1 MeOH-1,2-DCE mixture originates from either entropy or enthalpy effects depending on different systems. A primary observation is that the increased recognition for NapEt by diesterpyridino-18-crown-6 (**2**) is due to an enthalpy effect while that for other interactions is attributed to an entropy effect. In methanol, both enthalpy (1.2 kJ/mol difference in the ΔH values) and entropy (1.1 kJ/mol difference in the $T\Delta S$ values) make contributions to chiral recognition of NapEt enantiomers by (S,S)-**2** (a 0.41 Δ log K value). But in MeOH-1,2-DCE mixture, the enthalphic effect (a 3.2 kJ/mol difference in the ΔH values) makes the primary contribution to a Δ log K value of 0.60. The increase in Δ log K values for **4** interaction with enantiomers of NapEt is attributed to an entropy effect. The differences in ΔH values for (R)- and (S)-NapEt complexation with **4** in methanol and MeOH-1,2-DCE are almost the same ($\sim$ 8 kJ/mol), but a 1 kJ/mol less negative $T\Delta S$ value for (R)-NapEt-(S,S)-**4** interaction in MeOH-1,2-DCE causes a 0.2 log K unit increase in extent of recognition. The less negative $T\Delta S$ value for (R)-NapEt-(S,S)-**4** interaction should result from greater desolvation in MeOH-1,2-DCE mixture due to decreasing solvation energy. The increased recognition for enantiomers of PhEt by (S,S)-**3** is also attributed to the entropy effect. In methanol, the entrophy change for **3**-(R)-PhEt interaction is more negative than for **3**-(S)-PhEt interaction, but in MeOH-1,2-DCE mixture the $T\Delta S$ value for (R)-PhEt interaction is less negative than that for (S)-PhEt interaction. Only the entropy effect contributes to enantiomeric recognition of PhEt in 1 : 1 MeOH-1,2-DCE mixture.

Whether the enthalpy or entropy effect contributes to the increase in degree of enantiomeric recognition in the MeOH-1,2-DCE mixture is probably related to the conformation of the diastereomeric complexes. The complexes of **2** with (R)- and (S)-NapEt have a relatively rigid structure because of the tripod hydrogen bonding and $\pi-\pi$ interaction. The increase in the Δ log K value for this recognition system is attributed to an enthalpy effect. The complex structures for **3**-PhEt and **4**-NapEt are less rigid than that for **2**-NapEt due to absence of either $\pi-\pi$ interaction (PhEt

complexes) or carbonyl groups (ligand **4**). The entropy effect contributes to the increase in Δ log K values for these systems.

4. Conclusions

Excellent enantiomeric recognition for NapEt, PhEt, and PhEtOH by chiral pyridino-18-crown-6 type ligands is observed in 1 : 1 (v/v) MeOH-1,2-DCE solvent mixture. The degree of enantiomeric recognition can be enhanced in solvent mixtures of alcohol/alkylhalide (methanol/chloroform and methanol/1,2-dichloroethane) as compared with that in methanol. Recognition for enantiomers of NapEt is always better than that for enantiomers of PhEt and PhEtOH.

Different thermodynamic behavior of achiral macrocyclic ligands from those of chiral ones and of NapEt enantiomers from those of PhEt and PhEtOH reveals different types of interactions. For example, the thermodynamic origin of enantiomeric recognition for (R)- and (S)-NapEt is enthalpic, while that for (R) and (S) enantiomers of PhEt and PhEtOH is entropic. Presence or absence of $\pi - \pi$ interaction in the diastereomeric complexes is a main cause for this difference.

Either enthalpy changes or entropy changes may be responsible for increasing the degree of enantiomeric recognition from methanol to 1 : 1 MeOH-1,2-DCE mixture. For the rigid (S, S)-**2**-NapEt systems, enthalpy effects contribute to an increasing Δ log K value. For other less rigid systems, the entropy effect results in increasing the degree of recognition. Therefore, thermodynamic parameters reflect the different structural features of host-guest complexes and different enantiomeric recognition mechanisms and, consequently, lead to a better understanding of chiral recognition.

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