AD-A279 893

	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	15 May 1994	Technical Report

4. TITLE AND SUBTITLE
Thermodynamic and NMR Studies of Solvent Effect on Enantiomeric Recognition for a Chiral Organic Ammonium Cation by Chiral Diketopyridino-18-Crown-6 Type Ligands at 25.0°C

5. FUNDING NUMBERS
N00014-91-J-1710
R & T Code 313p002

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8. PERFORMING ORGANIZATION REPORT NUMBER
Technical Report No. 30

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Dr. H. Guard
Office of Naval Research
800 North Quincy Street
Arlington, VA 22217-5000

10. SPONSORING/MONITORING AGENCY REPORT NUMBER
N/A

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

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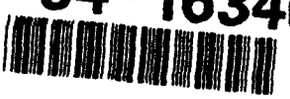

14. SUBJECT TERMS			15. NUMBER OF PAGES
			16. PRICE CODE N/A
17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	UL

OFFICE OF NAVAL RESEARCH

Grant N00014-91-J-1710

R&T Code 313p002

TECHNICAL REPORT NO. 30

Thermodynamic and NMR Studies of Solvent Effect on Enantiomeric Recognition for a Chiral Organic Ammonium Cation by Chiral Diketopyridino-18-Crown-6 Type Ligands at 25.0°C

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May 11, 1994

May 24, 1994

Thermodynamic and NMR studies of solvent effect on enantiomeric recognition for a chiral organic ammonium cation by chiral diketopyridino-18-crown-6 type ligands at 25.0°C

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Abstract: Three chiral diketopyridino-18-crown-6 type macrocycles have been shown to exhibit a high degree of enantiomeric recognition toward α-(1-naphthyl)ethylammonium perchlorate (NapEt) in various ratios of chloroform/methanol ($CDCl_3/CD_3OD$) and 1,2-dichloroethane/methanol ($C_2H_4Cl_2/CH_3OH$) solvent mixtures (from 100% to 10% methanol component). In most cases, differences in log *K* values (Δlog *K*) for (*R*)- and (*S*)-NapEt complexation with the chiral macrocycles are larger than 0.5. The degree of the enantiomeric recognition indicated by the Δlog *K* value changes noticeably with the binary solvent components. The recognition is better in the solvents having a moderate methanol component than in the binary solvents having either a high or a low methanol component. The highest degree of recognition is observed in 6/4 (v/v) $CDCl_3/CD_3OD$ and $C_2H_4Cl_2/CH_3OH$ solvent mixtures and in a 7/3 (v/v) $C_2H_4Cl_2/CH_3OH$ mixture for chiral (*S*,*S*)-1 macrocycle.

INTRODUCTION

Enantiomeric recognition, a special case of molecular recognition, involves discrimination between enantiomers of guest molecules by a chiral receptor. The successful design, synthesis, and use of molecules capable of enantiomeric recognition toward other species is of great interest to workers in asymmetric synthesis, enantiomeric separation, enzyme function, synthetic enzyme models, and other areas involving chiral recognition. The careful characterization of such synthetic systems could lead to a much improved understanding of natural systems. One area of recent interest is the enantiomeric recognition of chiral organic guests by chiral macrocyclic ligands. Many chiral macrocycles have been synthesized and their recognition properties toward organic enantiomers have been evaluated.[1-10] Our interest in enantiomeric recognition has focused on the interaction of chiral macrocycles containing pyridine units with chiral organic ammonium salts. Factors influencing the extent of enantiomeric recognition have been summarized.[11] They include rigidity of the macrocyclic frame, the bulkiness of the substituents on the ligand's chiral centers, the type and arrangement of the donor atoms on the ligands, the location of the chiral centers on the ligands, and the nature of the solvent. Among these factors, the structural effects have been studied much more thoroughly than the solvent effects.

Since molecular recognition normally occurs in solvent systems, solvent is an important factor which must be taken into consideration in understanding chiral interactions. In the study of enzyme models, for example, an enzyme exhibiting recognition toward a certain substrate is biologically active only in a solvent whose properties are very close to or the same as those of the biological medium.[12,13] On the other hand, a promising enzyme may never recognize any substrate if the solvent used is significantly different from that of the biological medium.[14] Because the process of molecular recognition involves steric contacts, the host-guest complex must have a proper conformation in order to maximize the recognition of the substrate by the host molecule. Therefore, the extent of molecular recognition is highly sensitive to the medium since the solvent molecules can influence not only the stability of the host-guest complexes but also the conformation of the complexes. It has been shown that the extent of enantiomeric recognition for organic ammonium

cations by pyridino-18-crown-6 type ligands is significantly affected by properties of the solvents in which the chiral interactions take place.[3,11,15] In chloroform/methanol ($CDCl_3/CD_3OD$) and 1,2-dichloroethane/methanol ($C_2H_4Cl_2/CH_3OH$) solvent mixtures, an improved degree of recognition usually can be observed compared with that in absolute methanol.[11,16] The ratio of $CDCl_3$ to CD_3OD also has an effect on recognition. For interactions between (*R*,*R*)-dimethyldiketopyridino-18-crown-6 (2, see Fig.1) and enantiomers of α-(1-naphthyl)ethylammonium perchlorate (NapEt, see Fig.1) in 100% CD_3OD, 5/5 and 9/1 $CDCl_3/CD_3OD$ mixtures, the highest degree of recognition was found in the 5/5 $CDCl_3/CD_3OD$ solvent mixture.[11]

In this paper, a systematic study of the solvent effect as demonstrated by different ratios of $CDCl_3/CD_3OD$ and $C_2H_4Cl_2/CH_3OH$ solvent mixtures (from 100% to 10% methanol component) on enantiomeric recognition is presented. The study shows that the solvent component has a significant effect on the degree of recognition. Dependence of enantiomeric recognition on the binary solvent systems whose properties change in a systematic way by successive change of the methanol component should be instructive not only in the study of enantiomeric recognition but also in other areas of molecular recognition.

EXPERIMENTAL

Materials

The diketopyridino-18-crown-6 type compounds (1, 2, 3, and K_2P18C6, Fig.1) and (*R*) and (*S*) enantiomers of NapEt were prepared as reported.[17,18] The purities of the chemicals used were checked by elemental analyses, ^{1}H NMR, and IR spectroscopy. The purities were also determined quantitatively by a thermometric titration technique.[19] By titrating enantiomers of NapEt with 18-crown-6 (SIGMA Chemical Company, its purity was 99.5% as determined by thermometric titration against a standard NaBr methanol solution.), the purities of the NapEt enantiomers were found to be (99.5 ± 0.3)%. The purities of 1, 2, 3, and K_2P18C6 were determined to be (99.0 ± 0.8)% with the same method. Methanol (Fisher, HPLC grade), 1,2-dichloroethane (EM Science,

Spectrograde), and deuterated methanol and chloroform were used as purchased without further purification.

Determination of Thermodynamic Quantities

Log K, ΔH, and ΔS values were determined as described earlier[20] by isoperibol titration calorimetry at 25.0 ± 0.1°C in $C_2H_4Cl_2/CH_3OH$ solvent mixtures. 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.[21] In order to avoid large heat losses caused by evaporation of $C_2H_4Cl_2$, 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 for several standard systems at 25°C, such as 18C6-Na^+ (log K = 4.36, ΔH = -8.32 kcal/mol) and 18C6-α-phenylethylammonium perchlorate (log K = 3.81, ΔH = -43.5 kJ/mol) complexation in methanol (the literature values: log K = 4.36, ΔH = -8.36 kcal/mol,[22] and log K = 3.82, ΔH = -43.7 kJ/mol,[16] respectively). The method of calculating log K and ΔH values from the calorimetric data has been described.[21]

Determination of Log K Values by A Direct ^1H NMR Method

In $CDCl_3/CD_3OD$ solvent mixtures, log K values for (*S*,*S*)-2 and (*S*,*S*)-3 interactions with NapEt enantiomers were determined by a ^1H NMR titration procedure using a Varian Gemini 200 (200 MHz) NMR spectrometer at 25.0 ± 0.1°C. The experimental technique has been described [23,24] and consistency of log K values determined by the ^1H NMR and calorimetric titration techniques has been verified.[23] The present study also shows excellent agreement between log K values for (*S*,*S*)-2 interactions with (*R*)- and (*S*)-NapEt (2.47 and 2.06 from calorimetric method and 2.46 and 2.06 from NMR experiments in absolute methanol, see Tables 1 and 2).

RESULTS AND DISCUSSION

In every case, (*R*)-NapEt forms thermodynamically more stable complexes with (*S*,*S*) macrocyclic ligands than (*S*)-NapEt. Thermodynamic quantities in Table 1 show that formation of the complexes is enthalpy driven. The entropy change is unfavorable in each case. The ΔH value is more negative for each (*R*)-NapEt complexation than that for (*S*)-NapEt complexation, indicating that the enthalpy changes always contribute to enantiomeric recognition in the systems studied. The recognition of NapEt enantiomers by the three chiral macrocyclic hosts is excellent in solvent mixtures of $CDCl_3/CD_3OD$ and $C_2H_4Cl_2/CH_3OH$. In most cases, differences in log *K* values (Δlog *K*) for (*R*)- and (*S*)-NapEt complexation with the chiral macrocycles are larger than 0.5. The largest Δlog *K* value observed is 0.72 (NapEt-(*S*,*S*)-**1** interactions in 7/3 $C_2H_4Cl_2/CH_3OH$), corresponding to a 5.3-fold difference in binding-constant values.

Dependence of log *K* and Δlog *K* values with the solvent components is plotted in Figures 2 and 3. In the figures, ϕ_D and ϕ_C are volume fractions of $C_2H_4Cl_2$ and $CDCl_3$ in the binary $C_2H_4Cl_2/CH_3OH$ and $CDCl_3/CD_3OD$ solvents, respectively. The stability of both (*R*)- and (*S*)-NapEt complexes increases with decreasing methanol component of the solvent mixtures (increasing ϕ_D and ϕ_C). This is expected since the low polarity of the solvent mixtures caused by decreasing methanol component should result in weaker solvent-solute interactions and the host-guest interactions should increase in magnitude as the polarity of the solvents decreases. It is worthy of note that the increasing rates of log *K* values with increasing ϕ_C and ϕ_D are different for the (*R*)- and (*S*)-NapEt interactions. This effect is significant in determining the degree of enantiomeric recognition, which will be discussed below.

Solvent Dependence of Enantiomeric Recognition

Log *K* values in Tables 1 and 2 show an appreciable solvent dependence of enantiomeric recognition. The degree of the recognition in the solvent mixtures having a moderate methanol component is higher than that in the solvent mixtures having either a high or a low methanol component. When the volume fraction of $C_2H_4Cl_2$ or $CDCl_3$ (ϕ_D or ϕ_C) increases from 0 to 0.9 (methanol component of the solvent mixtures decreases from 100% to 10%), the degree of

enantiomeric recognition in terms of $\Delta\log K$ values first increases to a peak value, then decreases. The highest degree of recognition for (*S*,*S*)-2 interactions with (*R*)- and (*S*)-NapEt is observed in both 6/4 $CDCl_3/CD_3OD$ and 6/4 $C_2H_4Cl_2/CH_3OH$ solvents. In the case of (*S*,*S*)-3, the peak recognition is also found in the 6/4 $CDCl_3/CD_3OD$ mixture. However, the best recognition of enantiomers of NapEt by (*S*,*S*)-1 occurs in a 7/3 $C_2H_4Cl_2/CH_3OH$ solvent mixture. These facts are shown in figures 2 and 3. The different recognition behavior of 1 from that of 2 and 3 can be attributed to the larger diameter of the sulfur atoms of 1 compared to that of the carbonyl oxygens of 2 and 3. The bulky sulfur atoms present stronger steric repulsion between the host and guest molecules, resulting in the best recognition occurring in the less polar 7/3 $C_2H_4Cl_2/CH_3OH$ solvent.

The peak recognitions are a result of different rates of increase in binding constants between (*R*)- and (*S*)-NapEt complexation with the macrocycles. Before the peak recognition ($\phi_C < 0.6$, $\phi_D < 0.6$ for 2, and $\phi_D < 0.7$ for 1), the increasing rates of log *K* with decreasing methanol component of the solvent mixtures are greater for (*R*)-NapEt than those for (*S*)-NapEt (see Figures 2 and 3). The slopes of the plots of log *K* vs. solvent composition for (*R*)-NapEt are larger than those for (*S*)-NapEt. This observation indicates that (*R*)-NapEt interaction with chiral macrocycles experiences less steric hindrance than the (*S*)-NapEt interaction when the host-guest interactions become stronger with decreasing polarity of the solvents. After the peak recognition ($\phi_C > 0.6$, $\phi_D > 0.6$ for 2, and $\phi_D > 0.7$ for 1), the opposite situation happens. The slopes in Figures 2 and 3 for (*R*)-NapEt are smaller than those for (*S*)-NapEt, indicating that in low polar solvents the log *K* values for (*S*)-NapEt complexation increase more quickly than those for (*R*)-NapEt complexation when the methanol component decreases.

In general, two kinds of interactions with opposite effects on the complex formation exist in chiral macrocycle-NapEt systems. A stable complex results from tripod hydrogen bonding and π-π overlap.[18,25,26] The tripod hydrogen bonding forms between three hydrogen atoms of the ammonium ion and a pyridine nitrogen and two alternate oxygen atoms of the macrocycle and π-π overlap happens between the pyridine ring of the macrocycle and naphthyl group of the NapEt molecule. The second kind of interaction is the steric repulsion between the groups at the chiral

centers of the organic ammonium ion and macrocyclic ligand, which results in a decrease in the complex stability. This repulsion is expected to be larger for (*S*)-NapEt interaction with the macrocycles than for (*R*)-NapEt interaction, so that the macrocyclic ligands display enantiomeric recognition toward the chiral organic ammonium cations. However, when the methanol component is decreased to a certain extent in the solvent mixtures, the interaction between NapEt and the macrocycle becomes so strong that the steric contact between host and guest species becomes unimportant as compared with the binding interactions. Thus, in low polar $C_2H_4Cl_2/CH_3OH$ and $CDCl_3/CD_3OD$ solvents (ratios of $C_2H_4Cl_2/CH_3OH$ and $CDCl_3/CD_3OD$ larger than 6/4) a faster increase in binding constants for (*S*)-NapEt than for (*R*)-NapEt interations is observed when polarity of the solvents is decreased (see Figures 1 and 2, the slopes for (*S*)-NapEt are larger than for (*R*)-NapEt in high ϕ_D and ϕ_C regions). As a result, the degree of the recognition decreases. Therefore, one role of the solvent is to keep a moderate interaction strength between host and guest species so that the chiral groups can perform their part well in enantiomeric recognition.

CONCLUSIONS

The chiral macrocycles exhibit the best recognition toward the enantiomers of NapEt in the $CDCl_3/CD_3OD$ and $C_2H_4Cl_2/CH_3OH$ solvent mixtures having a moderate methanol component. The degree of the recognition decreases in absolute methanol and in the binary solvents having a high or a low methanol component. The best recognition is achieved by regulating the conformation of the host-guest complexes in different binary solvent mixtures. There should be a most favorite conformation in which the chiral macrocyclic host can make full use of its chiral centers to perform optimum recognition toward the guest molecules. Both polarity of solvents and properties of solvent molecules have significant effects on modification of the complex conformation.

The medium is important in molecular recognition. An appropriate host molecule which has chiral center(s) and may display enantiomeric recognition toward chiral guest molecules can make full use of its recognition elements only in a certain medium. Therefore, a careful choice of the solvent system usually plays a key role in obtaining a maximum degree of molecular recognition. Two factors, the structure of the host and guest molecules and the medium, have different effects

on molecular recognition. The structure factor refers to whether or not a guest molecule exhibits recognition toward hosts. For example, the achiral K_2P18C6 can not display enantiomeric recognition in the $C_2H_4Cl_2/CH_3OH$ solvent systems of this study since it has no chiral center. The medium factor refers to the ability of the solvent to alter the degree of recognition. A good receptor is an essential prerequisite for molecular recognition, but maximum recognition can be obtained only by providing a proper medium.

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Table 1. log K, ΔH (kJ/mol), $T\Delta S$ (kJ/mol), and $\Delta\log K$ Values[a] Determined by Calorimetric Titration for Interactions of Macrocyclic Ligands with Enantiomers of NapEt[b] in Different Ratios (v/v) of 1,2-Dichloroethane/Methanol ($C_2H_4Cl_2/CH_3OH$) Mixtures at 25.0°C

$C_2H_4Cl_2/CH_3OH$			0/10[c]	3/7	5/5[c]	6/4	7/3	8/2	9/1
		ε[d]	32.7	26.0	21.5	19.3	17.1	14.8	12.6
(*S*,*S*)-1	(*R*)-NapEt	log K	1.72 ± 0.12	2.28 ± 0.08	2.69 ± 0.01	2.87 ± 0.05	3.08 ± 0.05	3.34 ± 0.04	3.86 ± 0.03
		ΔH	-13.7 ± 1.6	-16.0 ± 0.9	-17.95 ± 0.08	-20.5 ± 0.8	-22.4 ± 0.5	-25.3 ± 0.3	-28.7 ± 0.2
		$T\Delta S$	-3.8	-3.0	-2.57	-4.1	-4.8	-6.2	-6.7
	(*S*)-NapEt	log K	1.60 ± 0.05[e]	g	2.10 ± 0.12	2.25 ± 0.06	2.36 ± 0.05	2.74 ± 0.04	3.36 ± 0.01
		ΔH			-12.4 ± 1.8	-18.4 ± 0.7	-21.1 ± 0.9	-21.9 ± 0.8	-23.5 ± 0.2
		$T\Delta S$			-0.4	-5.5	-7.6	-6.3	-4.3
		$\Delta\log K$[f]	0.12		0.59	0.62	0.72	0.60	0.50
(*S*,*S*)-2	(*R*)-NapEt	log K	2.47 ± 0.01	2.76 ± 0.01	3.14 ± 0.02	3.35 ± 0.02	3.62 ± 0.02	3.88 ± 0.02	4.47 ± 0.04
		ΔH	-27.6 ± 0.3	-29.0 ± 0.3	-30.7 ± 0.2	-28.5 ± 0.3	-28.0 ± 0.2	-29.3 ± 0.3	-31.8 ± 0.4
		$T\Delta S$	-13.5	-13.3	-12.8	-9.1	-7.3	-7.2	-6.3
	(*S*)-NapEt	log K	2.06 ± 0.01	2.26 ± 0.05	2.54 ± 0.02	2.70 ± 0.02	3.01 ± 0.01	3.38 ± 0.01	4.01 ± 0.03
		ΔH	-26.4 ± 0.4	-26.9 ± 0.8	-27.5 ± 0.3	-27.6 ± 0.4	-27.1 ± 0.2	-26.5 ± 0.1	-28.6 ± 0.5
		$T\Delta S$	-14.7	-14.0	-13.0	-12.2	-9.9	-7.2	-5.7
		$\Delta\log K$[f]	0.41	0.50	0.60	0.65	0.61	0.50	0.46

Table 1 (Continued)

$C_2H_4Cl_2/CH_3OH$			0/10[c]	3/7	5/5[c]	6/4	7/3	8/2	9/1
ε[d]			32.7	26.0	21.5	19.3	17.1	14.8	12.6
K_2P18C6	(*R*)-NapEt	log *K*	3.05 ± 0.04	3.19 ± 0.04	3.38 ± 0.03	3.56 ± 0.03	3.77 ± 0.02	4.10 ± 0.02	4.56 ± 0.04
		ΔH	-30.8 ± 0.5	-25.6 ± 0.3	-24.0 ± 0.3	-22.5 ± 0.2	-23.5 ± 0.1	-23.5 ± 0.3	-26.2 ± 0.3
		$T\Delta S$	-13.4	-7.4	-4.7	-2.2	-2.0	-0.1	-0.2
	(*S*)-NapEt	log *K*	3.04 ± 0.01	3.20 ± 0.02	3.38 ± 0.04	3.57 ± 0.02	3.76 ± 0.01	4.08 ± 0.02	4.57 ± 0.02
		ΔH	-30.6 ± 0.5	-25.5 ± 0.2	-24.2 ± 0.4	-22.6 ± 0.2	-23.4 ± 0.1	-23.6 ± 0.2	-26.3 ± 0.2
		$T\Delta S$	-13.2	-7.2	-4.9	-2.2	-1.9	-0.3	-0.2

[a] Values are the averages taken from three determinations. Uncertainties are given as standard deviations.

[b] See Figure 1 for ligand and NapEt (α-(1-naphthyl)ethylammonium perchlorate) structures.

[c] Ref. 16.

[d] ε is dielectric constant. The values of the solvent mixtures were calculated according to the Onsager method (ref. 28).

[e] The log *K* value was determined by a direct ^{1}H NMR method in CD_3OD. Attempt to determine the log *K* and ΔH values by calorimetric titration failed due to small heat of reaction. The log *K* value for (*R*)-NapEt interaction with (*S*,*S*)-1 in 100% CD_3OD was also determined by the ^{1}H NMR method. The value of 1.69 ± 0.05 is in good agreement with the value 1.72 ± 0.12 determined by the calorimetric method.

[f] The Δlog *K* value is the difference between log *K* values for (*R*)- and (*S*)-NapEt interactions with a given chiral macrocyclic ligand.

[g] The heat of reaction is too small to evaluate the log *K* value.

Table 2. log K and Δlog K Values[a] Determined by ^{1}H NMR Method for (S,S)-2 and (S,S)-3 Interactions with Enantiomers of NapEt[b] in Different Ratios (v/v) of Chloroform/Methanol ($CDCl_3/CD_3OD$) Mixtures at 25.0°C

$CDCl_3/CD_3OD$			0/10	3/7	5/5	6/4	7/3	9/1
		ε[c]	32.7	24.3	18.8	16.0	13.2	7.65
(S,S)-2	(R)-NapEt	log K	2.46 ± 0.03	2.75 ± 0.02	2.96 ± 0.02	3.09 ± 0.03	3.18 ± 0.03	3.41 ± 0.04
	(S)-NapEt	log K	2.06 ± 0.04	2.29 ± 0.04	2.43 ± 0.04	2.51 ± 0.04	2.70 ± 0.03	2.98 ± 0.02
		Δlog K[d]	0.40	0.46	0.53	0.58	0.48	0.43
(S,S)-3	(R)-NapEt	log K	2.94 ± 0.03[e]	3.19 ± 0.05	3.35 ± 0.02	3.52 ± 0.04	3.62 ± 0.03	3.82 ± 0.02
	(S)-NapEt	log K	2.53 ± 0.04[e]	2.73 ± 0.05	2.85 ± 0.03	2.95 ± 0.04	3.11 ± 0.04	3.72 ± 0.03
		Δlog K[d]	0.41	0.46	0.50	0.57	0.51	0.10

[a] Values are the averages taken from two to three determinations. Uncertainties are given as standard deviations.

[b] NapEt = α-(1-naphthyl)ethylammonium perchlorate.

[c] ε is dielectric constant. The values of the solvent mixtures were calculated according to the Onsager method (ref. 28).

[d] The Δlog K value is the difference between log K values for (R)- and (S)-NapEt interactions with a given chiral ligand.

[e] Ref. 16.

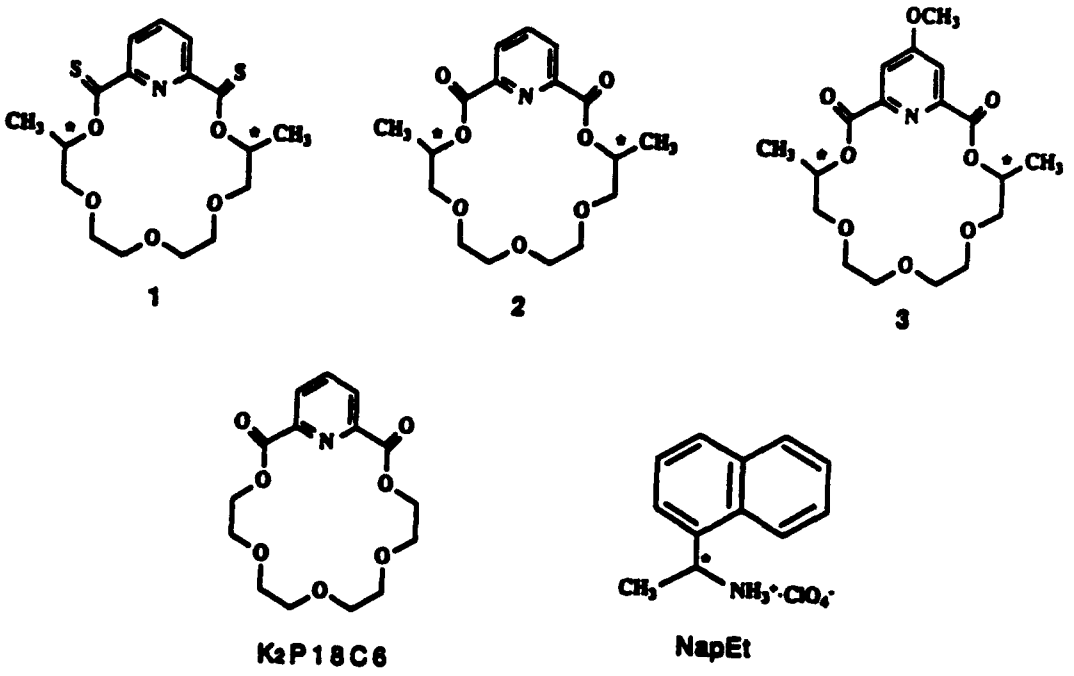

Figure 1. Structures of macrocyclic ligands and α-(1-naphthyl)ethylammonium perchlorate (NapEt).

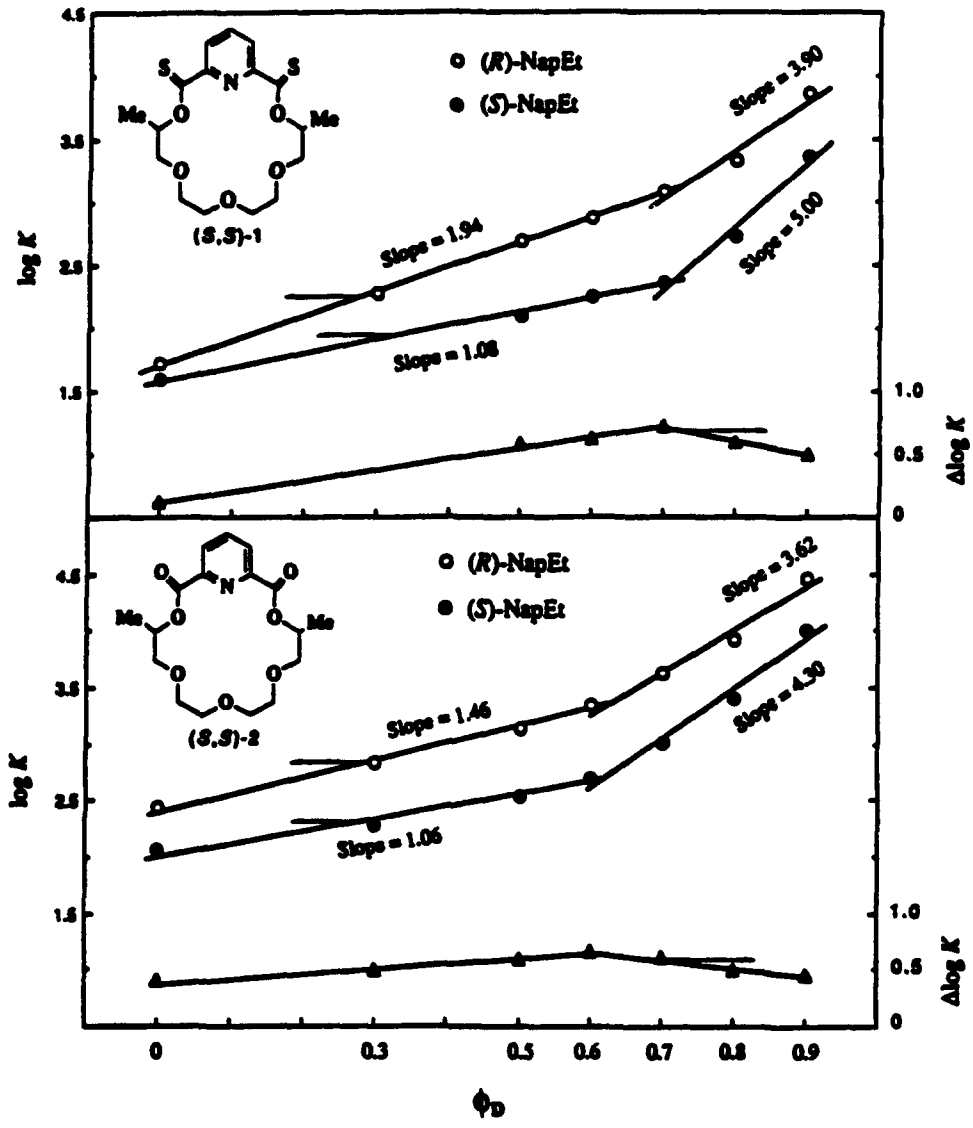

Figure 2. Plots of log K and $\Delta\log K$ values for interactions of (S,S)-1 and (S,S)-2 with (R)- and (S)-NapEt *vs.* the volume fraction of 1,2-dichloroethane (ϕ_D) in binary solvent mixtures of 1,2-dichloroethane/methanol ($C_2H_4Cl_2/CH_3OH$).

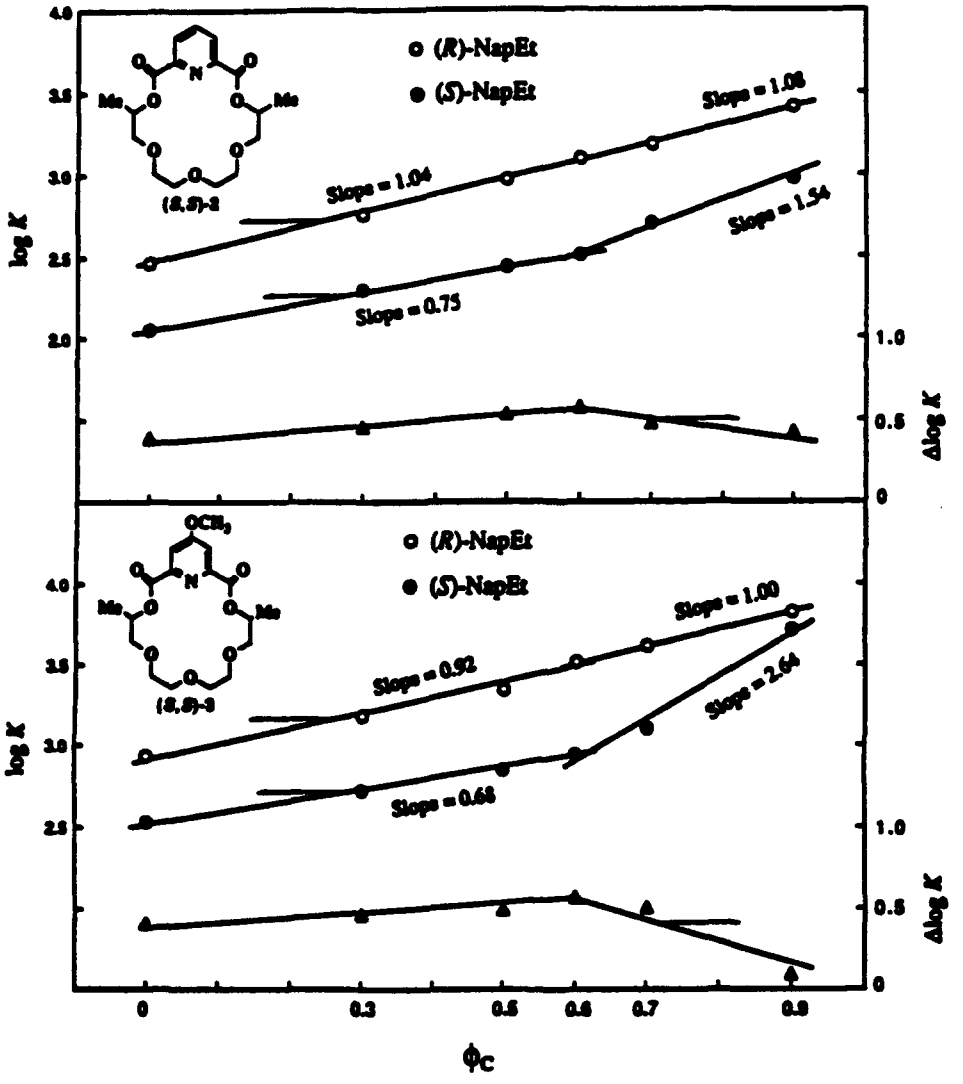

Figure 3. Plots of log K and $\Delta\log K$ values for interactions of (*S*,*S*)-2 and (*S*,*S*)-3 with (*R*)- and (*S*)-NapEt *vs.* the volume fraction of chloroform (ϕ_c) in binary solvent mixtures of chloroform/methanol ($CDCl_3/CD_3OD$).

Fig. 3