Journal of Inclusion Phenomena and Molecular Recognition in Chemistry **17:** 157–175, 1994.

Factors Influencing Enantiomeric Recognition of Primary Alkylammonium Salts by Pyridino-18-Crown-6 Type Ligands

REED M. IZATT,* TINGMIN WANG, JON K. HATHAWAY, XIAN X. ZHANG, JANET C. CURTIS, JERALD S. BRADSHAW[a] and CHENG Y. ZHU
Marion Merrell Dow, Inc., Analytical Chemistry, Kansas City, MO, U.S.A.
[a] *Department of Chemistry, Brigham Young University, Provo, UT 84602, U.S.A.*

and

PETER HUSZTHY
Institute of Organic Chemistry, Technical University, Budapest, Hungary.

(Received: 9 August 1993; in final form: 24 December 1993)

Abstract. Equilibrium constant (K), enthalpy change (ΔH), and entropy change (ΔS) values were determined for the interactions of a series of chiral pyridino-18-crown-6 type ligands with enantiomers of several primary alkylammonium salts in various solvents. Good enantiomeric recognition in terms of $\Delta \log K$ was observed in many systems with $\Delta \log K$ values greater than 0.4. The extent of enantiomeric recognition and the stabilities of the chiral crown ether-ammonium salt complexes were found to depend on the rigidity of the macrocyclic frame of the ligand, the type and arrangement of the donor atoms on the ligand, the bulkiness of the substituents on the ligand's chiral centers, the location of the chiral centers on the ligand, and the solvent. The effects of these factors on the extent of enantiomeric recognition and on the stabilities of the complexes were examined for the systems studied.

Key words: Enantiomeric recognition, pyridino-18-crown-6 type ligands, primary alkylammonium salts, equilibrium constant (K), enthalpy change (ΔH), entropy change (ΔS), NMR, titration calorimetry.

1. Introduction

Host-guest chiral recognition is important in a variety of physical, chemical, and biological processes including sensing, purification and resolution of enantiomers, asymmetric catalysis reactions, and incorporation of single enantiomeric forms of amino acids and sugars in biochemical pathways. Therefore, the design, synthesis, and use of molecules capable of enantiomeric recognition of other molecules are of great interest to workers in these fields. Cram and his co-workers first described the syntheses and characterization of a number of chiral crown ethers capable of enantiomeric recognition toward primary ammonium salts in 1973 [1,

* Author for correspondence.

2]. Since then, the study of enantiomeric recognition by crown ethers and other molecules has been blossoming. An excellent review of chiral crown ethers and their interactions with chiral organic ammonium salts has been published [3]. Enantiomeric recognition using a variety of open chain molecules has also been reported [4–6]. The successful separation of a large array of chiral guest molecules by Pirkle's chiral stationary phases (CSPs) which were derived from amino acid derivatives is a notable example of chiral recognition using open-chain chiral ligands [7, 8].

Our interest in enantiomeric recognition focuses on the interaction of chiral macrocyclic ligands containing a pyridine subunit with chiral primary alkylammonium salts. These macrocycles are chosen for study because they form thermodynamically stable complexes with chiral primary ammonium cations in a number of solvents and solvent mixtures, and they also exhibit appreciable enantiomeric recognition in many cases [9–13]. Thus, these complexes present the possibility of a systematic study on how the extent of enantiomeric recognition varies as factors such as the ligand structure and the solvent are changed. The results of the study could lead to improved understanding of the origin of chiral recognition in these systems, and improved ability to design specific information into ligand molecules, which would allow them to have superior recognition for one guest enantiomer over another. In our efforts to identify, understand, and quantify the factors responsible for enantiomeric recognition in chiral macrocycle-chiral ammonium salt systems, a series of novel chiral macrocycles, **1–16** (Figure 1), with their structures varying in a systematic manner have been synthesized.

This paper focuses on the characterization of the host-guest interactions involving these chiral ligands and chiral primary ammonium salts. Log K, ΔH, and ΔS values for these host-guest interactions are reported. The effects of the ligand and ammonium cation structures and solvent on enantiomeric recognition as measured by $\Delta \log K$ are examined.

2. Experimental Section

2.1. Materials

The syntheses of chiral **2–16** have been described [9–11, 13–17]. Compound **1** was prepared using a new procedure, superior to the one reported earlier [16] in terms of product yield and purity, described under SYNTHESES in the following paragraphs. The purities of **1–16** were found to be greater than 95% according to TLC (thin layer chromatography), IR and ^{1}H NMR spectroscopy, elemental analyses, and calorimetric titration analyses. (R) and (S) enantiomers of $NapCH(CH_3)NH_3^+ \cdot ClO_4^-$ were prepared from $NapCH(CH_3)NH_2$ (Aldrich) according to the procedure reported earlier [9, 17, 18]. (R) and (S) enantiomers of $PhCH(CH_3)NH_3^+ \cdot ClO_4^-$ were prepared according to the literature [9] and were recrystallized from a butylacetate-carbon tetrachlo-

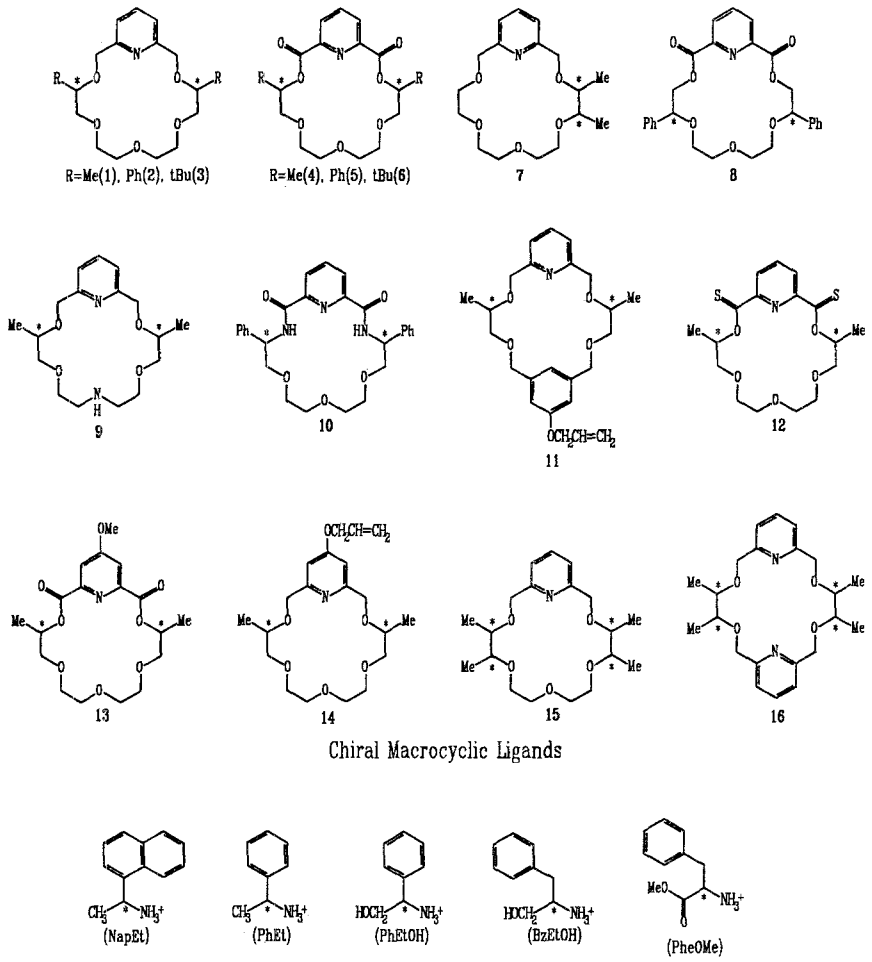

Fig. 1. Chiral macrocycles and primary ammonium cations studied in this paper.

ride mixture. $PhCH(CH_2OH)NH_3^+ \cdot ClO_4^-$, $PhCH_2CH(CH_2OH)NH_3^+ \cdot ClO_4^-$, and $PhCH_2CH(COOMe)NH_3^+ \cdot ClO_4^-$, were prepared according to the procedures described under SYNTHESES. Deuterated solvents (Aldrich) and non-deuterated solvents (HPLC grade, Fisher) were used as purchased without further purification.

2.2. SYNTHESES

The starting material (2*S*, 12*S*)-(+)-4,7,10-trioxatridecane-2,12-diol needed to synthesize **1** was prepared as reported [14, 19].

(4*S*, 14*S*)-(+)-4,14-*Dimethyl*-3,6,9,12,15-*pentaoxa*-21-*azabicyclo*[15.3.1]*heneicosa*-1(21),17,19-*triene*, **1**. To a stirred suspension of 4.0 g (134 mmol, 80% dispersion in mineral oil) of NaH in 75 mL of pure and dry THF was added, dropwise and under Ar at 0°C, 10.7 g (48 mmol) of (2*S*, 12*S*)-(+)-4,7,10-trioxatridecane-

2,12-diol dissolved in 450 mL of dry and pure THF. After addition, the reaction mixture was stirred at 0°C for 10 min, at room temperature for 30 min, and was refluxed for 4 h. The reaction mixture was cooled to −10°C and then a solution of 22.7 g (51 mmol) of 2,6-pyridinedimethyl ditosylate in 525 mL of pure and dry THF was added dropwise in 30 min. After addition of ditosylate, the reaction mixture was stirred at −10°C for 10 min, then at room temperature for 2 days. The solvent was removed under reduced pressure, and the residue was dissolved in a mixture of 200 g of ice, 200 mL of water, and 1000 mL of CH_2Cl_2. The phases were well shaken and separated. The aqueous phase was shaken twice with 400 mL portions of CH_2Cl_2. The combined organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The crude product was purified first by column chromatography on Al_2O_3 (neutral, activated, Brockman I) using toluene and C_2H_5OH/toluene (1/80) as eluents, then by fractional distillation under reduced pressure to give 8.74 g (56%) of a white, clear oil; bp 141-2°C (0.02 mmHg); $[\alpha]_D^{22} + 40.97°$ (c 1.06, $CHCl_3$) [lit. value: +40.7° (c 1.00, $CHCl_3$)] [16]; IR (neat) 3061, 2968, 2868, 1592, 1578, 1456, 1371, 1350, 1333, 1112 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, δ) 1.18 (d, 6H, J=6Hz), 3.37–3.72 (m, 12H), 3.73–3.93 (m, 2H), 4.81 (s, 4H), 7.25 (d, 2H, J=10Hz), 7.65 (t, 1H, J=10Hz); MS (low volt) m/e 325 (M^+); *Anal.* calcd. for $C_{17}H_{27}NO_5$: C 62.75, H 8.36. Found: C, 62.92; H, 8.19.

Hydrogen perchlorate salts of (R)- and (S)-2-amino-2-phenyl-1-ethanol (PhCH-(CH$_2$OH)-NH$_3^+\cdot$ClO$_4^-$). To a stirred solution of 1.51 g (10.0 mmol) of the amine in 20 mL of pure and dry MeOH were added dropwise, 3.1 mL of 3.2 M $HClO_4$ in acetic acid at 0°C for 10 min. After addition, the reaction mixture was stirred at 0°C for 10 min and then at room temperature for 10 min. The solvent was removed under reduced pressure and the residue was recrystallized from an acetonitrile-chloroform mixture to give pure white crystals. The 3.2 M $HClO_4$ in acetic acid solution was prepared as follows. To 85 g (0.83 mol) of acetic anhydride was added at 0°C under Ar 50 g (0.35 mol) of 70% aqueous perchloric acid dropwise with stirring. After the addition, the mixture was stirred at 0°C for 10 min, and then at room temperature for 10 min.

The hydrogen perchlorate salts of the (*R*) and (*S*) $PhCH_2CH(CH_2OH)NH_2$ were prepared following the same procedure as above. The hydrogen perchlorate salts of methyl phenylalaninate ($PhCH_2CH(COOMe)NH_3^+\cdot ClO_4^-$) were prepared from the corresponding hydrochloride salts following a procedure similar to that described above.

2.3. Determination of log K and ΔH values by calorimetry

When the quantity of a chiral macrocyclic ligand permitted, calorimetric experiments were carried out to determine the log K and ΔH values for the interactions of this ligand with its guests. Titration calorimetry is advantageous because it allows for the simultaneous determination of log K and ΔH values [20]. In

this work, an isoperibol titration calorimeter (Tronac model 450) with a 20 mL reaction vessel was used for the calorimetric determination of log K and ΔH values. For each data run, 20 lead points, 100 titration points and 20 trail points were taken. Each system was measured independently a minimum of two times and usually three in order to calculate the precision of the results. The operation of the calorimetric system was tested using several standard systems at 25°C, i.e., HCl-THAM neutralization in aqueous solution (log K = 8.075, $\Delta H = -11.36$ kJ/mol) [21], 18-crown-6-Pb^{2+} complexation in aqueous solution (log K = 4.27, $\Delta H = -21.6$ kJ/mol) [22], and 18-crown-6-Na^{+} complexation in methanol (log K = 4.36, $\Delta H = -35.1$ kJ/mol^{-1}) [22]. The log K and ΔH values for these standard systems were reproduced. Because of our interest in reactions in organic solvents, the heat effects for the evaporation of the volatile organic solvents posed serious problems during the calorimetric experiments. To overcome this evaporation problem, we modified the reaction vessel of the calorimeter so that an immersible magnetic stirrer, instead of a glass stirrer normally inserted into the reaction vessel from above, could be used to stir the solution from underneath. Such design of the reaction vessel allows a better sealing from the top where the glass stirrer used to be inserted. With such modification, we have successfully determined log K and ΔH values using solvents as volatile as methanol or a methanol/chloroform (1:1,v/v) mixture. However, in more volatile solvents such as acetone and chloroform, accurate calorimetric measurements were not possible. Other methods for log K determinations such as those involving use of NMR were employed in those cases.

2.4. Determination of log K by NMR

A ^{1}H NMR titration procedure [23] was used to determine some of the log K values. The NMR experiments were done on either a Varian Gemini 200 (200 MHz) or a Varian VXR 500 (500 MHz) NMR spectrometer. Each of the NMR spectrometers was equipped with a temperature control device which was accurate to 0.1°C. Since the exchange rates between the free and complexed macrocyclic ligand in all of our macrocycle-ammonium cation systems are fast in terms of the ^{1}H NMR time scale at 25°C [24], well resolved ^{1}H NMR spectra for the macrocycles in the presence of the ammonium salts can be obtained from either the 200 MHz or the 500 MHz NMR spectrometer. Therefore, the accuracy of the log K values determined on the 200 MHz spectrometer is equivalent to those determined on the 500 MHz spectrometer. Although the NMR method generally provides less accurate log K values than calorimetry and does not give ΔH values directly [23], it does have two advantages over isoperibol titration calorimetry. First, the NMR method can handle systems in relatively volatile solvents because the evaporation of small amounts of solvent does not affect the chemical shifts of a molecule. Second, the NMR method requires much smaller amounts of sample than a standard isoperibol titration calorimeter (with reaction vessel size 20 mL or up). In case of a mostly

entropy driven reaction where the heat effect during the reaction is too small to allow an accurate calorimetry measurement, the NMR method may still be valid for log K determination if an NMR chemical shift of the sample changes significantly as a result of the reaction. Fortunately, all of the chiral ligands studied had at least one pyridine proton whose chemical shift changes upon formation of the complex between the ligand and the guest ammonium cation. Therefore, we used the NMR method to determine the log K values and estimate ΔH values for systems where only limited amounts of sample were available.

3. Results and Discussion

The log K, ΔH, and ΔS values for the interactions of **1–16** with enantiomers of the ammonium salts studied are listed in Tables I–III. Table I contains the thermodynamic values for interactions either in pure methanol or in methanol/chloroform mixtures. The effect of the ligand and ammonium cation structures on the ligand-ammonium salt interaction strengths and the extent of enantiomeric recognition are emphasized in Table I. Tables II and III focus on the effect of solvent on the extent of chiral recognition (Δ log K) and on the interaction strength (log K), respectively.

3.1. Effect of Ligand Structures

Although **1–16** are similar in that each of them has at least one pyridine (or a closely related derivative) subunit incorporated into the macrocyclic ring, they differ systematically in the following aspects: (a) the substituent at the chiral centers (**1** compared to **2** and **3**, **4** compared to **5** and **6**); (b) the presence or absence of two carbonyl oxygens next to the pyridine subunit (**1** compared to **4**, **2** to **5** and **3** to **6**); (c) the locations of the chiral centers and the substituents in the macrocyclic ring (**1** compared to **7**, **5** compared to **8**); (d) the number and location of the oxygen donor atoms substituted by nitrogen or carbon in the macrocyclic ring (**1** compared to **9** and **11**, **5** compared to **10**); (e) the presence or absence of sulfur atoms in place of the carbonyl oxygen atoms in the ligand molecule (**4** compared to **12**); (f) the presence or absence of a substituent at the 4-position of the pyridine ring (**1** compared to **14**, **4** compared to **13**); and (g) the number of chiral centers and molecular symmetry of the ligand (**1** compared to **15** and **16**). The data in Table I show that each type of ligand structural variation affects the complex stability (log K) and enantiomeric recognition (Δ log K) for the chiral ammonium salt-ligand interactions.

3.1.1. *Effect of the substituent at the chiral center*

Ligands **2** and **3** differ from **1** in that the two methyl substituents in **1** are replaced by two phenyl groups in **2** and two tert-butyl groups in **3**, respectively. The same variation also appears in **4–6** where **5** and **6** differ from **4** in the same way. Since

TABLE I. Log K, ΔH, and ΔS values[a] for the interactions of the macrocyclic ligands with enantiomers of several primary ammonium cations at 25°C

Ligand	Cation[b]	Solvt[c]	Meth[d]	Log K	ΔH[e]	ΔS[e]	ΔLog K	Ref.
(S,S)-**1**	(R)-NapEt	M	Cal.	3.00(2)	–29.1(1)	–40.3		
	(S)-NapEt	M	Cal.	2.76(2)	–22.3(1)	–21.8	0.24(4)	
	(R)-PhEt	1M/1C	NMR	3.62(5)				
	(S)-PhEt	1M/1C	NMR	3.29(5)			0.33(10)	
	(R)-PhEtOH	1M/1C	NMR	3.21(5)				
	(S)-PhEtOH	1M/1C	NMR	3.27(5)			–0.06(10)	
	(R)-PheOMe	1M/1C	NMR	3.02(5)				
	(S)-PheOMe	1M/1C	NMR	3.11(5)			–0.09(10)	
(R,R)-**2**	(R)-NapEt	M	NMR	2.92(5)				
	(S)-NapEt	M	NMR	3.10(5)			0.18(10)	11
	(R)-PhEt	M	NMR	2.91(5)				
	(S)-PhEt	M	NMR	3.10(5)			0.14(10)	11
(S,S)-**3**	(R)-NapEt	1M/9C	NMR	1.33(5)				
	(S)-NapEt	1M/9C	NMR	0.62(8)			0.71(13)	11
(S,S)-**4**	(R)-NapEt	M	Cal.	2.47(2)	–27.6(1)	–45.2		
	(S)-NapEt	M	Cal.	2.06(2)	–26.4(1)	–49.3	0.41(4)	9
	(R)-PhEt	M	NMR	2.33(5)				
	(S)-PhEt	M	NMR	2.11(5)			0.22(10)	
(S,S)-**5**	(R)-NapEt	7M/3C	NMR	2.15(6)				
	(S)-NapEt	7M/3C	NMR	<1.30			>0.85	11
	(R)-PhEt	1M/1C	NMR	2.62(5)				
	(S)-PhEt	1M/1C	NMR	2.06(5)			0.56(10)	11
	(R)-PhEtOH	1M/1C	NMR	2.24(5)				
	(S)-PhEtOH	1M/1C	NMR	2.95(6)			–0.71(11)	11
	(R)-BzEtOH	1M/1C	NMR	2.18(5)				
	(S)-BzEtOH	1M/1C	NMR	1.76(5)			0.42(10)	11
	(R)-PheOMe	1M/1C	NMR	1.60(7)				
	(S)-PheOMe	1M/1C	NMR	1.28(7)			0.32(14)	11
(S,S)-**6**	(R)-NapEt	1M/9C	NMR	ND				
	(S)-NapEt	1M/9C	NMR	ND				11
(R,R)-**7**	(R)-NapEt	M	NMR	3.00(5)				
	(S)-NapEt	M	NMR	2.94(4)			–0.06(9)	11
(S,S)-**8**	(R)-NapEt	1M/1C	Cal.	2.57(3)	–29.7(2)	–50.6		
	(S)-NapEt	1M/1C	Cal.	2.35(3)	–44.4(4)	–104	0.22(6)	
	(R)-PhEt	M	Cal.	2.58(3)	–17.3(2)	–8.6		
	(S)-PhEt	M	Cal.	2.44(3)	–17.7(2)	–12.8	0.14(6)	
(S,S)-**9**	(R)-NapEt	M	NMR	1.51(6)				
	(S)-NapEt	M	NMR	1.49(7)			0.02(13)	13
(S,S)-**10**	(R)-NapEt	1M/1C	NMR	ND				
	(S)-NapEt	1M/1C	NMR	ND				13

TABLE I. (continued)

Ligand	Cation[b]	Solvt[c]	Meth[d]	Log K	ΔH^e	ΔS^e	ΔLog K	Ref.
(S, S)-**11**	(R)-NapEt	1M/1C	Cal.	ND				
	(S)-NapEt	1M/1C	Cal.	ND				
(S, S)-**12**	(R)-NapEt	1M/1C	Cal.	2.34(5)	–26.4(2)	–43.5		
	(S)-NapEt	1M/1C	Cal.	2.43(4)	–12.6(4)	4.14	–0.09(9)	
	(R)-NapEt	1M/1C	NMR	2.45(6)				
	(S)-NapEt	1M/1C	NMR	2.45(7)			0.00(13)	
(S, S)-**13**	(R)-NapEt	M	Cal.	2.71(2)	–35.6(2)	–67.8		
	(S)-NapEt	M	Cal.	2.26(3)	–38.5(3)	–86.2	0.45(5)	
	(R)-PhEt	M	Cal.	2.85(3)	–25.6(3)	–31.3		
	(S)-PhEt	M	Cal.	2.66(3)	–21.6(2)	–21.5	0.19(6)	
	(R)-PhEtOH	M	Cal.	2.70(3)	–23.0(3)	–25.4		
	(S)-PhEtOH	M	Cal.	2.88(2)	–25.8(2)	–31.3	–0.18(5)	
	(R)-PhEtOH	1M/1C	Cal.	2.69(4)	–31.0(3)	–52.3		
	(S)-PhEtOH	1M/1C	Cal.	3.04(3)	–44.4(4)	–90.8	–0.35(7)	
(S, S)-**14**	(R)-NapEt	1M/1C	NMR	3.89(6)				
	(S)-NapEt	1M/1C	NMR	3.54(5)			0.35(11)	
(R, R, R, R)-**15**	(R)-NapEt	1M/1C	NMR	3.00(5)				
	(S)-NapEt	1M/1C	NMR	3.05(4)			0.05(9)	
	(R)-PhEt	1M/9C	NMR	3.58(6)				
	(S)-PhEt	1M/9C	NMR	3.31(5)			–0.27(11)	
(R, R, R, R)-**16**	(R)-NapEt	M	NMR	1.55(6)				
	(S)-NapEt	M	NMR	1.56(6)			0.01(12)	
	(R)-PhEt	1M/9C	NMR	2.98(6)				
	(S)-PhEt	1M/9C	NMR	2.87(7)			–0.11(13)	

[a] Uncertainties are indicated in parentheses following each value. ND indicates not determined because no significant amount of heat (or chemical shift change, in the case of NMR) is observed.

[b] Perchlorate salts of the ammonium cations were used. The notations for the ammonium cations are defined with the structures.

[c] M = methanol, C = chloroform, 1M/1C = 50% methanol-50% chloroform (v/v). For NMR experiments, 100% deuterated solvents were used. For calorimetric measurements, non-deuterated solvents were used.

[d] NMR = ^{1}H NMR method, Cal. = titration calorimetry.

[e] ΔH and ΔS values are in the units of kJ mol^{-1} and J · K^{-1} · mol^{-1}, respectively.

one of the origins for enantiomeric recognition was expected to be the steric repulsion between the substituents at the chiral centers and the alkyl group of the ammonium cation [9], it is expected that the extent of enantiomeric recognition could be improved as the bulkiness of the substituents at the chiral centers increases. The data in Table I confirm this expectation. Ligand **3** displayed much improved enantiomeric recognition toward chiral NapEt over **1** in terms of Δ log K (0.71 in 10%CD_3OD-90%$CDCl_3$ (1M/9C) for **3** to 0.24 in MeOH (M) for **1**). Although the Δ log K value for the **1**-NapEt system is not directly comparable to that for the **3**-NapEt system because the solvents are different, the Δ log K increase from 0.24

to 0.71 can still be partly attributed to the effect of substituent size increase since the effect of solvent on enantiomeric recognition is not significant enough to cause this much $\Delta \log K$ increase, as will be discussed later. The effect of the substituent size increase from the methyl group to the tert-butyl group is that the log K values decrease sharply. The log K values for **3**-NapEt interaction in 1M/9C are almost two log K units smaller than those for **1**-NapEt in pure MeOH. Since the change of solvent from pure MeOH to 1M/9C (v/v) is expected to enhance the complex stabilities due to the decreased solvent polarity, the actual log K difference between **3**-NapEt and **1**-NapEt could be even greater than 2.

Similarly, it is expected that **6** should show enhanced enantiomeric recognition and decreased complex stabilities when compared to **4** in reacting with the enantiomers of NapEt. We did see the decreased complex stabilities, but unfortunately, the decrease of complex stability was too large to allow accurate measurement of log K values. Therefore, the extent of enantiomeric recognition by **6** toward NapEt could not be evaluated. In summary, the increase in ligand substituent size improves the extent of enantiomeric recognition but decreases complex stability. Steric contact between the substituents at the chiral centers in the ligand and the alkyl group or the naphthyl group of NapEt does exist in the complexes of ligands **1**–**6** with NapEt.

Changing the substituent from methyl to phenyl does not improve enantiomeric recognition or decrease complex stabilities in **2**, but does bring improved enantiomeric recognition in **5** at the cost of decreased complex stability, as is seen in Table I. Since the size difference between the phenyl group and the methyl group is not as large as that between the tert-butyl group and the methyl group, a possible explanation is that the replacement of the methyl by a phenyl should bring less stability drop than that seen when a methyl is replaced by a tert-butyl group. Ligands **1** and **2** are apparently more flexible than **4** and **5** because of the presence of carbonyl oxygen atoms in the latter two. Therefore, in reacting with NapEt, the size difference between the phenyl group and the methyl group in **1** and **2** can be less significant than that in **4** and **5** because the more flexible ligands can adjust their conformations to minimize steric strains caused by contact between the ligand and the guest substituents.

3.1.2. *Effect of the carbonyl groups*

Ligands **4**–**6** differ from **1**–**3** by having two carbonyl oxygen atoms between the pyridine ring and the chiral centers in each molecule. The addition of the two carbonyl oxygen atoms results in significant improvement in the enantiomeric recognition. Ligand **4** shows much improved chiral recognition over **1** toward enantiomers of NapEt, $\Delta \log K$ (0.41 vs. 0.24 in M). Ligand **5** shows excellent enantiomeric recognition toward NapEt ($\Delta \log K > 0.85$ in 7M/3C), PhEt ($\Delta \log K = 0.56$ in 1M/1C), and PhEtOH ($\Delta \log K = 0.71$ in 1M/1C), while **2**

displays little recognition toward enantiomers of NapEt ($\Delta \log K = 0.18$ in M) and PhEt ($\Delta \log K = 0.14$ in M).

Compared to **1**, **4** forms less stable complexes by ca. 0.5 log K unit with enantiomers of NapEt in MeOH. Since the solvent change from pure M to 1M/1C brings only about 0.3 log K unit stability increase (see Table III), it is clear that **4** also forms less stable complexes than **1** with PhEt enantiomers. Likewise, **5** forms less stable complexes than **2** with NapEt and PhEt enantiomers. Therefore, the addition of two carbonyl oxygen atoms seems to improve the enantiomeric recognition toward NapEt and PhEt at the cost of complex stability.

One likely reason for the improved enantiomeric recognition by **4** and **5** is the reduced ligand flexibility as a result of the addition of two carbonyl oxygen atoms. A less flexible ligand cannot adjust its conformation well enough to accommodate both enantiomers of a guest molecule. If a less flexible ligand is pre-organized to fit one enantiomer, it will not fit the other enantiomer well. Hence, the less flexible ligand will display better chiral recognition. Another possible reason for the improved enantiomeric recognition by **4** and **5** is the enhanced π-π interaction as the result of the addition of two carbonyl oxygen atoms. The presence of two carbonyl oxygen atoms conjugated with the pyridine ring makes the π area of the ligand larger. The carbonyl oxygen atoms can also make the pyridine ring more electron deficient through the inductive effect. The increased π-area and the decreased π-electron density for the ligand are expected to enhance the π-π interaction with the aromatic group of the ammonium cation. The reason for the reduced stabilities in complexes of **4–6** may be the electron withdrawing effect of the two carbonyl oxygen atoms which weakens the strength of the N^+-H$\cdots$N hydrogen bond. The decreased ligand flexibility may also have an effect on the reduced complex stability.

3.1.3. *Effect of the chiral center positions*

Ligand **7** differs from **1** in that the two chiral centers are located on the same side of the pyridine ring. No enantiomeric recognition by **7** towards NapEt (Table I) is found, probably because the bulky group of each NapEt enantiomer can find open space on the other side of the pyridine ring where no methyl substituents are present and, thus, avoid steric contact with the ligand. Ligand **8** differs from **5** by having two chiral centers one carbon position farther away from the pyridine ring. The chiral recognition displayed by **8** is much smaller than that by **5** toward both NapEt and PhEt enantiomers. A molecular modeling study using modified MM2 force field ($CHARM_m$ [25]) and random sampling with minimization to investigate the conformational space of ligand **8** and NapEt, found that in the lowest energy **8**-NapEt complex the naphthyl group of NapEt does not overlap with the pyridine ring. Nevertheless, it is evident that the position of chiral centers in the ligand molecule plays a key role in causing enantiomeric recognition.

3.1.4. *Effect of donor atom substitution*

Ligands **9** and **11** differ from **1** in that one of the oxygen donor atoms in the macrocyclic ring is replaced by a nitrogen (**9**) or a carbon (**11**) atom. Compared to **1**, **9** shows no enantiomeric recognition toward NapEt and forms much less stable complexes with NapEt enantiomers in CD_3OD. Ligand **11** has one oxygen donor atom replaced by a benzene carbon atom. No observable reaction was found for **11** with NapEt enantiomers. Ligand **10** differs from **5** in that two oxygen atoms are replaced by nitrogen atoms. Ligand **10** shows no interactions with NapEt enantiomers.

There are two possible reasons for **9** not showing enantiomeric recognition toward NapEt. First, the secondary amine NH group at position 10 is a strong competitor of the pyridine N for hydrogen bonding with the ammonium cation. Since a secondary amine group has stronger basicity than pyridine, the three point hydrogen bond pattern may very likely be the NH-O-O triangle instead of the (Py)N-O-O triangle. If the NH-O-O pattern is assumed, the chiral centers of the ligand may thus become one carbon unit too far away to provide the steric interaction between the ligand and the ammonium cation substituents which is necessary for enantiomeric recognition. Second, the replacement of an oxygen donor atom by NH may change the conformation of the free ligand in such a way as to make the formation of the ideal three point hydrogen bond difficult. The decreased complex stabilities shown by **9** compared to those by **1** could be the result of this different ligand conformation.

The two amide NH groups in **10** are weaker bases than pyridine and are not in competition with the pyridine nitrogen for hydrogen bonding. However, their poor location may pose serious steric hindrance (through the hydrogen atoms of the NH groups) for the ammonium cation to approach the pyridine nitrogen to form a hydrogen bond. Also, an amide NH group takes a much different local conformation (because of the presence of H) than that of an ether oxygen atom. Therefore, the two amide NH groups alter the general conformation of the ligand significantly. Apparently, the much altered ligand conformation causes the lack of interaction of **10** with NapEt. The lack of interaction between **11** and NapEt may also be attributed to the poor ligand conformation caused by the replacement of the oxygen donor atom by a benzene group.

3.1.5. *Effect of the substitution of carbonyl oxygens by sulfur*

Ligand **12** differs from **4** in that the two carbonyl oxygen atoms are replaced by sulfur atoms. Because a sulfur atom is less electronegative than an oxygen atom, it is expected that the replacement of oxygen by sulfur would enhance the hydrogen bond strength between the pyridine nitrogen and the ammonium cation. On the other hand, since a sulfur atom is much larger than an oxygen atom, it is also expected that bulky sulfur atoms may cause increased steric hindrance for the

aromatic group of the ammonium cation as this cation approaches the pyridine ring of the ligand to participate in π-π interaction. It was found that the stabilities of the complexes formed by **12** with NapEt were similar to those of **4** with these guests. The log K values listed in Table I for **12** were determined calorimetrically. These values were also verified using the NMR method. The Δ log K value of 0.09 for the interactions of **12** with NapEt enantiomers indicates a much weaker enantiomeric recognition than that displayed by **4**. However, the poor chiral recognition is not caused by the lack of π-π interaction as we expected. ^{1}H NMR spectra of the **12**-NapEt complexes showed significant upfield chemical shift changes for the ligand pyridine signals compared to the chemical shifts for the free ligand signals. This indicates the presence of π-π interaction between the naphthyl group of the ammonium cation and the pyridine ring of the ligand. The actual cause for the poor chiral recognition by **12** toward NapEt enantiomers in CD_3OD is not understood. However, our unpublished calorimetric results [26] show that **12** displays excellent enantiomeric recognition for NapEt in 1:4 methanol-dichloroethane mixture with Δ log K values being 0.6.

3.1.6. *Effect of substitution on the pyridine ring*

Ligands **13** and **14** each have a substituent in the *para* position of the pyridine ring. As expected, the addition of the electron donor groups OMe and $OCH_2CH{=}CH_2$ enhance the complex stability. Ligand **13** forms more stable complexes than **4** with NapEt and PhEt by about 0.2–0.6 log K unit. Ligand **14** also forms more stable complexes than **1** with NapEt by about 0.85 log K unit. The introduction of the $OCH_2CH{=}CH_2$ group makes another application possible since the molecule can be chemically bonded to silica gel. The silica gel bound ligand can then be used in the chromatographic separation of enantiomers. The silica gel bound **14** has been synthesized and a preliminary test of the silica gel bound **14** in batch mode chromatographic separation of NapEt enantiomers has been done [17].

3.1.7. *Effect of the increased number of chiral centers*

Ligands **15** and **16** each have four chiral centers. Ligand **16** has two pyridine subrings which seems to bring C_i symmetry to the ligand molecule. It was expected that the increased number of chiral centers and enhanced ligand symmetry would benefit enantiomeric recognition because of the reduced chances for the ammonium cations to avoid necessary steric contacts with the ligand. It was found that neither ligand displayed recognition toward NapEt enantiomers and little recognition toward PhEt enantiomers. Both ligands, especially **16**, form much weaker complexes than **1** with the ammonium cations. The lowered extent of enantiomeric recognition and complex stability may be due to the distorted conformations of the ligands. The crystal structure of **16** was found to be distorted and strained and possessed no C_i symmetry [10]. Molecular modeling of the **16**-NapEt complexes

also indicates no C_i or pseudo C_i symmetry. It is possible that four chiral centers and four methyl substituents in one ligand molecule may be too crowded to allow the incoming ammonium cation to find a position for ideal three point hydrogen bonding with the ligand.

3.2. Effect of ammonium cation structures

The variation of ligand structure significantly affects the ligand's ability to recognize guest enantiomers and to form stable complexes with the guests, as we have seen from the above discussion. It should be equally true that the variation of guest structure will also affect the extent of enantiomeric recognition displayed by a given ligand and the stability of the complex formed between the guest and the given ligand. Five ammonium cations have been studied. Three of these, NapEt, PhEt, and PhEtOH, have an α-aromatic (either naphthyl or phenyl) group one carbon unit away from the ammonium group. The other two ammonium cations, BzEtOH and PheOMe, have a phenyl group two carbon units away from the ammonium group.

Both NapEt and PhEt form stable complexes with **1** and **4**. PheOMe and PhEtOH form stable complexes with **1**. NapEt has a larger π-group than PhEt, hence a better chance to form a π-π bond with the pyridine ring of the ligand. The π-π overlap between the naphthyl group of NapEt and the pyridine group of the ligand (average distance between the two aromatic planes being 3 Å) has been found to exist in NapEt complexes with most of the ligands studied. The π-π interaction between the phenyl group of PhEt and PhEtOH and the pyridine ring of the ligand was found to occur only in complexes with ligands not containing carbonyl groups. PhEt with **4** and **5** and PhEtOH with **5** form complexes but no π-π interaction was found in these complexes in solution [27].

Despite the difference between NapEt and PhEt or PhEtOH in π-π interaction, **5** displays excellent enantiomeric recognition not only for NapEt, but also for PhEt and PhEtOH. It is evident that π-π overlap is not absolutely necessary to cause good chiral recognition, but π-π interactions may contribute to enantiomeric recognition when present.

3.3. Effect of solvent

The effect of solvent on macrocycle-metal ion interactions has been investigated [28–30]. However, few studies have been reported on macrocycle-ammonium salt interactions in different solvents. It is of interest to see how different solvents affect hydrogen bonding and ion-dipole interactions. It is of particular interest to learn how solvents will affect the enantiomeric recognition in the systems studied.

Solvent can play an important role in host-guest interactions because both the reactant and product species are solvated in solution. The formation of a host-guest complex in solution can be considered as a four step process: (1) desolvation of

the host and guest molecules, (2) conformational reorganization of the host and guest molecules, (3) host-guest interaction through hydrogen bonding or ion-dipole interaction or both, and (4) solvation of the complex. Solvent is involved in steps 1 and 4. Other than solvation, solvent as a neutral medium can also affect interaction strength through its dielectric constant. If the host-guest interaction is electrostatic in nature, and the solvent is a weak solvating agent toward both the host and the guest molecules, the strength of the host-guest interaction should be inversely related to the dielectric constant of the solvent.

Although achiral solvents such as those we have been using are supposed to solvate each of the two enantiomers equally, they should solvate the complex of each enantiomer differently since the conformations of the two diastereomeric complexes are different. Therefore, it is likely that change of solvent will have a certain impact on the extent of enantiomeric recognition. Tables II and III list $\log K$ and $\Delta \log K$ values for the interactions of **1** and **4** with NapEt enantiomers in various solvents and solvent mixtures.

It is seen from Table II that the value of $\Delta \log K$ for the interaction of **1** with NapEt enantiomers varies as the solvent changes. As the solvent changes from pure methanol to 2-butanone and acetonitrile, the $\Delta \log K$ value increases from 0.24 to 0.41 and 0.54, respectively. Although the uncertainties associated with the $\Delta \log K$ values are large compared to the magnitudes of $\Delta \log K$, this trend of $\Delta \log K$ differences is significant. It is also seen from Table II that the value of $\Delta \log K$ for the interaction of (R, R)-**4** with NapEt enantiomers remains nearly unchanged at 0.42 in most of the solvents and solvent mixtures studied except in 1:1 (v/v) methanol-chloroform, ethanol-chloroform, and isopropyl alcohol- chloroform mixtures. In the latter three solvent mixtures, the $\Delta \log K$ values are equal to or greater than 0.6. It is of interest to note that the change of solvent from methanol to any other solvent studied (except DMSO) does not decrease the $\Delta \log K$ value. Instead, it apparently increases the $\Delta \log K$ value in some solvents. The maximum $\Delta \log K$ increase observed so far is 0.3 (M to 1E/1C).

With the uncertainties in the data obtained so far, it is difficult to correlate $\Delta \log K$ changes with solvent properties. As a trend, it is observed that a greater $\Delta \log K$ value (compared to that in methanol) is likely to occur in a solvent which has less solvating power toward cations than methanol. Among the systems studied, the largest $\Delta \log K$ value for **1**-NapEt complexes occurs in acetonitrile and 2-butanone whose dielectric constants and Gutmann donor and acceptor numbers are all smaller than those of methanol (Table III).

The change of solvent alters the absolute complex stabilities ($\log K$) to a great extent. One striking example is that the change of solvent from methanol to DMSO brings the complex stabilities to zero. In DMSO, no interaction between **1** (or **4**) and NapEt could be observed either by NMR or by calorimetry. The change of complex stability as a result of the change of solvent could be as large as several $\log K$ units. It is evident from Table III that the stabilities of the **4**-NapEt complexes are inversely related to the Gutmann donor number [31] with no apparent

TABLE II. Log K, ΔH, and ΔS values[a] for chiral macrocycle-ammonium cation interactions at 25°C in various solvents

Ligand	Cation[b]	Solvt[c]	Meth[d]	Log K	ΔH[e]	ΔS[e]	ΔLog K
(S,S)-**1**	(R)-NapEt	M	Cal.	3.00(2)	−29.1(1)	−40.3	
	(S)-NapEt	M	Cal.	2.76(2)	−22.3(1)	−21.8	0.24(4)
	(R)-NapEt	BT	Cal.	4.71(6)	−44.4(4)	−58.6	
	(S)-NapEt	BT	Cal.	4.30(5)	−38.9(4)	−48.1	0.41(11)
	(R)-NapEt	AN	NMR	4.64(8)			
	(S)-NapEt	AN	NMR	4.10(7)			0.54(15)
	(R)-NapEt	DMSO	NMR	ND			
	(S)-NapEt	DMSO	NMR	ND			
(S,S)-**4**	(R)-NapEt	M	Cal.	2.47(2)	−27.6(1)	−10.8	
	(S)-NapEt	M	Cal.	2.06(2)	−26.4(1)	−11.8	0.41(4)
	(R)-NapEt	E	Cal.	2.37(3)	−29.1(2)	−52.3	
	(S)-NapEt	E	Cal.	1.93(5)	−31.9(3)	−70.0	0.44(8)
(R,R)-**4**	(R)-NapEt	M	NMR	2.08(4)			
	(S)-NapEt	M	NMR	2.50(3)			0.42(7)
	(R)-NapEt	1M/1C	NMR	2.20(5)			
	(S)-NapEt	1M/1C	NMR	2.80(4)			0.60(9)
	(R)-NapEt	1M/9C	NMR	2.97(7)			
	(S)-NapEt	1M/9C	NMR	3.41(7)			0.44(14)
	(R)-NapEt	A	NMR	2.98(5)			
	(S)-NapEt	A	NMR	3.40(5)			0.42(10)
	(R)-NapEt	AN	NMR	3.80(5)			
	(S)-NapEt	AN	NMR	4.27(7)			0.44(12)
	(R)-NapEt	DMSO	NMR	ND			
	(S)-NapEt	DMSO	NMR	ND			
	(R)-NapEt	NM	NMR	5.5(1)			
	(S)-NapEt	NM	NMR	>6			>0.5
	(R)-NapEt	1M/1B	NMR	2.55(5)			
	(S)-NapEt	1M/1B	NMR	2.99(6)			0.44(11)
	(R)-NapEt	1E/1C	NMR	2.08(5)			
	(S)-NapEt	1E/1C	NMR	2.78(5)			0.70(10)
	(R)-NapEt	1iPr/1C	NMR	2.17(6)			
	(S)-NapEt	1iPr/1C	NMR	2.77(5)			0.60(11)

[a] See note a of Table I.

[b] See note b of Table I.

[c] M = methanol, C = chloroform, 1M/1C = 50% methanol-50% chloroform (v/v), BT = 2-butanone, A = acetone, AN = acetonitrile, DMSO = dimethylsulfoxide, NM = nitromethane, E = ethanol, B = benzene, iPr = isopropyl alcohol. For NMR experiments, 100% deuterated solvents were used. For calorimetric measurements, non-deuterated solvents were used.

[d] See note d of Table I.

[e] See note e of Table I.

TABLE III. Log K values for the interaction of (R, R)-**4** with (S)- and (R)-NapEt in various deuterated solvents and solvent mixtures at 25°C

Solvent[a]	log K[b]				Solvent parameters[c]	
	(S)	(R)	ε_r	E_T	DN	AN
DMSO	N/O	N/O	46.45	0.444	29.8	19.3
M	2.50	2.08	32.66	0.762	19.0	41.5
1M/1C	2.80	2.20				
1M/9C	3.41	2.97				
C			4.81	0.259	4.0	23.1
A	3.40	2.98	20.56	0.355	17.0	12.5
AN	4.24	3.80	35.94	0.460	14.1	18.9
NM	>6.0	5.5	35.94	0.481	2.7	20.5

[a] See note c of Table II for solvent notations.

[b] N/O = no observable interaction.

[c] ε_r = dielectric constant, E_T = empirical polarity, DN Gutmann donor number, and AN = Gutmann acceptor number. The values ε_r, E_T, DN, and AN are cited from ref. 33.

correlation to the dielectric constant or empirical polarity [32] of the solvent. The inverse correlation of complex stability with solvent donor number indicates that (1) solvation and desolvation play important roles in the complex formation, and (2) the formation of the complexes is mainly the result of the hydrogen bonding and ion-dipole interaction. Electrostatic interaction plays a less important role in the complex formation.

3.4. ENTHALPY AND ENTROPY CHANGES IN CHIRAL LIGAND-AMMONIUM SALT INTERACTIONS

Because of the limitation in sample amounts, the number of calorimetrically determined ΔH and ΔS values for the chiral ligand-ammonium salt interactions is limited. From the available ΔH and ΔS values in Tables I and II, the formation of all the complexes studied is driven by favorable enthalpy changes. An average of -25 to -30 kJ mole^{-1} enthalpy change is observed in the formation of each complex. In most cases, the entropic changes for the formation of the complexes are negative, indicating unfavorable entropic contribution to the formation of complexes. The negative enthalpic change and negative entropic change for the formation of an ammonium cation-ligand complex is in agreement with the "rule of compensation" observed in crown ether-metal ion complexes [33]. As for enantiomeric recognition, both enthalpic and entropic changes contribute. In some cases, the more stable complex of the two is enthalpy favored. But in other cases, the opposite is true.

Two observations can be drawn from the ΔH and ΔS values in Tables I and II. First, PhEt complexes with **8** and **13** have less negative ΔH and less negative ΔS values than the NapEt complexes with the same ligands, indicating that PhEt complexes are less enthalpy favored and more entropy favored. This may be partly

attributed to the difference in the size of the aromatic group between NapEt and PhEt and the difference in the ability of π-π interaction with the ligand between NapEt and PhEt. Second, the enthalpy changes for **12** complexes with NapEt enantiomers are much smaller than those for the **4** complexes. The replacement of two carbonyl oxygen atoms by sulfur atoms reduces the interaction enthalpy significantly. This reduced interaction may be partly attributed to the size of the sulfur atoms which would prevent good π-π interactions between the aromatic groups and result in longer hydrogen bond lengths between the ligand and the ammonium cation.

4. Conclusions

In general, our knowledge about the achievement of enantiomeric recognition in systems involving chiral crown ethers and primary ammonium cations is as follows. First, the ligand should be able to form reasonably stable complexes with the chiral guests. If the conformation of a chiral ligand is twisted such that the three point hydrogen bond cannot form between the primary ammonium cation and the ligand, the ability of the ligand to recognize guest enantiomers will be poor. Second, bulkiness of the substituents at the chiral center is correlated with enantiomeric recognition. Third, the ligand molecule should be rather rigid. If the ligand is too flexible, it will be able to match both enantiomers of a guest equally well by adjusting its conformation. Fourth, the chiral center must be positioned to influence the R group on the ammonium cation, but not the three point hydrogen bonding. Fifth, the substitution of nitrogen for oxygen at various parts of the ring disrupts the binding of the cation to the ligand. Sixth, when thiocarbonyl instead of carbonyl groups are used to increase rigidity, recognition is usually decreased. Seventh, the solvent appears to affect $\Delta \log K$ values, but attempting to correlate these effects with specific properties of the solvent is difficult. The role of solvent and other weak interactions such as anion effects on complex formation remains inconclusive.

For the specific systems discussed in this paper, the pyridino-18-crown-6 ligands generally form more stable complexes with ammonium cations than do the diesterpyridino-18-crown-6 ligands. However, the latter display much improved enantiomeric recognition toward chiral primary ammonium cations. The origin of the improved chiral recognition is probably associated with the increased rigidity of the diester-pyridino-18-crown-6 ligands. Chiral crown ethers with one or more ether oxygen(s) replaced by nitrogen(s) have much decreased interactions with primary ammonium cations.

In the systems reported in this paper, the two major factors influencing recognition are steric hindrance and π-π overlap between the aromatic substituents of the ammonium salts and the pyridine ring. π-π overlap does not occur in all systems, such as some PhEt systems, so recognition, in these cases, results mainly from steric hindrance. In systems where π-π overlap occurs, the aromatic substituent on the

ammonium salt and the pyridine ring are positioned to optimize the overlap. The steric hindrance provided by bulky side groups attached to the ligand may interfere with these π-π interactions. Usually the interference is greater for one of the enantiomers. However, without the π-π overlap, the aromatic group can be positioned such that the difference in steric hindrance for the two enantiomer complexes decreases, resulting in less enantiomeric recognition. Therefore, the combination of these two factors has the most influence on the degree of recognition found in these systems.

Acknowledgement

Appreciation for financial support of this research is expressed to the Office of Naval Research.

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