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Enantiomeric recognition of chiral ammonium salts by chiral pyridino- and pyrimidino-18-crown-6 ligands: Effect of structure and solvents

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Abstract

Chiral pyridino-18-crown-6 ligands interact with chiral primary organic ammonium salts by hydrogen bonding from the ammonium cation to the pyridino nitrogen and two alternate ring oxygen atoms. Enantiomeric recognition in these interactions are caused by the steric bulk of the substituents at chiral macrocycle ring positions. Recognition is best for the interaction of chiral pyridino-18-crown-6 hosts with the enantiomers of α-(1-naphthylethyl)ammonium perchlorate ($NapEtHClO_4$) over (α-phenylethyl)ammonium perchlorate ($PhEtHClO_4$) possibly because of a greater π-π overlap between the naphthalene ring of the guest and pyridine ring of the host. Solvents play an important role in the degree of recognition. A binary solvent composed of 7/3 $C_2H_4Cl_2/CH_3OH$ (v/v) gave an enhanced degree of recognition. A new chiral pyrimidino-18-crown-6 ligand exhibited recognition for the enantiomers of $NapEtHClO_4$.

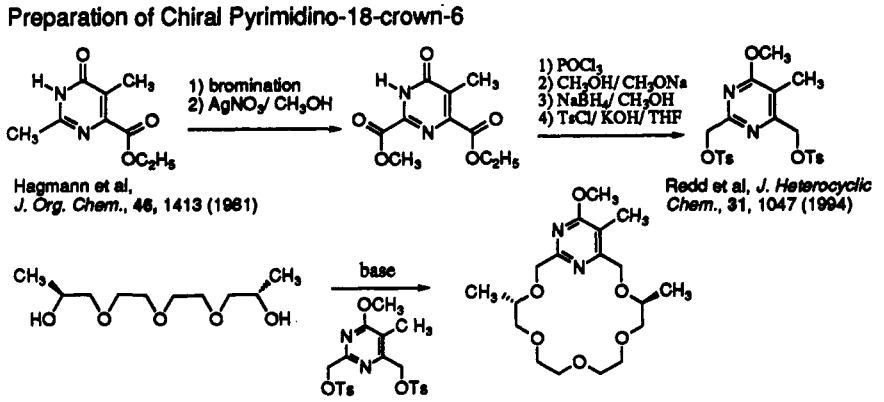
INTRODUCTION

There are numerous instances of molecular recognition in nature. Some examples are antibody-antigen interactions, biocatalysis reactions, DNA double helix and the use of single enantiomeric forms of amino acids and sugars in metabolic pathways. There are synthetic compounds which exhibit recognition for other molecules. For example, crown ethers exhibit excellent selectivity in their interactions with cations (ref. 1). Enantiomeric recognition of chiral organic ammonium salts by chiral crown ethers was first studied by Cram and coworkers (ref. 2). Many different chiral macrocyclic ligands have been prepared for recognition studies. Some of these ligands include those containing amino acid units (ref. 3), sugar molecules (ref. 4), diaza-crown units (ref. 5) and crown ethers containing the pyridine subcyclic unit (ref. 6-8).

In our laboratory, chiral pyridino-18-crown-6 ligand interactions with chiral organic ammonium salts have been characterized by ^1H NMR spectroscopy (ref. 6, 9-12), calorimetric titration (ref. 6,8,13), X-ray crystallography (ref 6,12,13), molecular mechanics calculations (ref. 7,10,11) and Fourier transform ion cyclotron resonance mass spectrometry (ref. 14). These studies have established a tripod hydrogen bonding involving the pyridine nitrogen and two alternate oxygen atoms of the macrocycle and three hydrogen atoms of the ammonium cation; secondary bonding of the pyridine ring of the crown ether and the aromatic group of the ammonium cation through π-π interaction sometimes occurs; and steric interactions between the alkyl groups on the chiral positions of the macrocycle and the bulky substituents on the chiral position of the organic ammonium salt. This short review summarizes recent work on the synthesis of new chiral pyridino- and pyrimidino-18-crown-6 ligands, the effect of solvents on the recognition process and recognition by the chiral pyridine-containing macrocycles for chiral ammonium cations other than (*R*)- and (*S*)-α-(1-naphthylethyl)ammonium perchlorate ($NapEtHClO_4$).

SYNTHESIS OF CHIRAL MACROCYCLES

The chiral pyridino-18-crown-6 ligands have been prepared by the interaction of chiral alkyl-substituted tetraethylene glycols with dimethyl pyridine-2,6-dicarboxylate for the diester crowns (ref. 6,10) and with pyridine-2,6-dimethyl ditosylate for the regular crown ethers (ref. 7,9-11). The chiral dimethyl-substituted pyrimidino-18-crown-6 ligand was prepared as shown below (ref. 15). The starting 4-methoxy-5-methyl-2,6-pyrimidinedimethyl ditosylate was prepared as shown below by modification of the procedure reported



by Hagmann and coworkers for the preparation of certain pyrimidine compounds (ref. 16). The methoxy group has been converted to a hydroxy unit making the pyrimidono-18-crown-6 (ref. 17). This chiral proton-ionizable macrocycle has a pK_a of about 8.5 and will react with chiral organic amines. These latter reactions have not yet been studied.

EFFECT OF CATION STRUCTURE ON ENANTIOMERIC RECOGNITION

The effect of the structure of the chiral organic ammonium cation was evaluated using the interaction of (*S,S*)-Me_2P18C6 (see Figure 1) with the enantiomeric forms of NapEtHClO$_4$, (α-phenylethyl)ammonium perchlorate (PhEtHClO$_4$), and the hydrogen perchlorate salts of methyl phenylalaninate (PheMeHClO$_4$) and 2-amino-2-phenylethanol [PhEt(OH)HClO$_4$]. NapEtHClO$_4$ has a more extended π system than PhEtHClO$_4$. PhEt(OH)HClO$_4$ was selected to study the effect of a hydroxy group in the guest molecule on enantiomeric recognition. PheMeHClO$_4$ has a larger CO_2CH_3 group at its chiral center. The log *K* values for these interactions was determined by a ^{1}H NMR titration technique as reported (ref. 18,19).

The results in Table 1 (ref. 19) show that the highest recognition factor as measured by a Δ log *K* value of 0.54 was for interaction with NapEtHClO$_4$. Interaction with PhEtClO$_4$ gave a Δ log *K* value of 0.33 indicating that π-π stacking of the host and guest aromatic systems may play an important role in enantiomeric recognition in these systems. Indeed, the presence of π-π stacking in these complexes was observed in the ^{1}H NMR NOESY spectra (ref. 20). Interaction with PhEt(OH)HClO$_4$ gave little or no recognition. It is possible that the hydroxy group of PhEt(OH)HClO$_4$ is hydrogen bonded to the pyridine nitrogen atom or a ring oxygen atom which could lead to poor recognition. Interaction of (*S,S*)-Me_2P18C6 with PheMeHClO$_4$ also gave little or no recognition probably because the chiral center of PheMeHClO$_4$ is one carbon atom away from the benzene ring resulting in poor or no π-π stacking.

TABLE 1. Log *K* values for the interactions of (*S,S*)-Me_2P18C6[a] with the enantiomers of several organic ammonium perchlorates in a 1M/1C[b] mixed solvent at 25°C as determined by a ^{1}H NMR method

Cation[c]	Salt Config.	log *K*	Δlog *K*	Ref.
NapEtHClO$_4$	*R*	3.96		
	S	3.42	0.54	19
PhEtHClO$_4$	*R*	3.62		
	S	3.29	0.33	8
PhEt(OH)HClO$_4$	*R*	3.21		
	S	3.27	-0.06	8
PheMeHClO$_4$	*R*	3.02		
	S	3.11	-0.09	8

[a] (*S,S*)-Me_2P18C6 = (*S,S*)-dimethylpyridino-18-crown-6. [b] M = CD_3OD, C = $CDCl_3$. [c] NapEtHClO$_4$ = α-(1-naphthylethyl)ammonium perchlorate; PhEtHClO$_4$ = α-phenylethylammonium perchlorate; PhEt(OH)HClO$_4$ = the hydrogen perchlorate salt of 2-amino-2-phenylethanol; PheMeHClO$_4$ = the hydrogen perchlorate salt of methyl phenylalaninate.

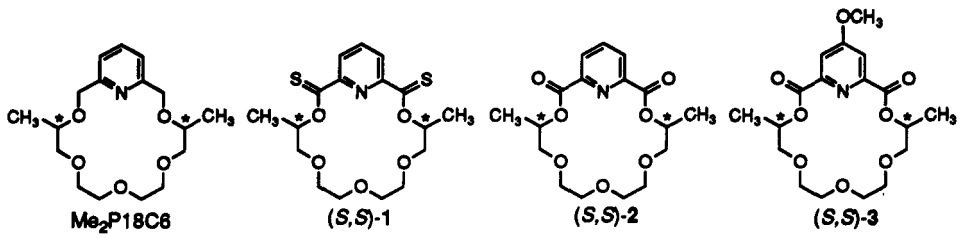


Figure 1. Chiral Pyridino-18-crown-6 Ligands Used in this Study

EFFECT OF SOLVENT ON ENANTIOMERIC RECOGNITION

Enantiomeric recognition in the interaction of NapEtHClO$_4$ with 3 chiral pyridino-18-crown-6 ligands in 1,2-dichloroethane/methanol ($C_2H_4Cl_2/CH_3OH$) and chloroform/methanol ($CDCl_3/CD_3OD$) solvent mixtures (from 100% to 10% methanol content) have been evaluated (ref. 21). The interactions in $C_2H_4Cl_2/CH_3OH$ were determined by a calorimetry technique while those in $CDCl_3/CD_3OD$ were determined by a ^{1}H NMR method. The data are given in Tables 2 and 3. In every case, (*R*)-NapEtHClO$_4$ formed a more stable complex with the (*S,S*)-ligand than did (*S*)-NapEtHClO$_4$. The log *K* values decreased as the dielectric constant increased. The thermodynamic quantities in Table 2 show that formation of the complexes is enthalpy driven. It is also evident in Tables 2 and 3 that best recognition, as determined by Δ log *K* values, occurred in solvent mixtures that had a moderate methanol component. The degree of recognition decreased in absolute methanol or in solvents with a very low methanol component.

There are different effects of chloroform and 1,2-dichloroethane solvent molecules on enantiomeric recognition for NapEtHClO$_4$. First, recognition in $C_2H_4Cl_2/CH_3OH$ (Table 2) is higher than that in $CDCl_3/CD_3OD$ (Table 3). Second, the increase in log *K* values with decreasing solvent polarity is larger for $C_2H_4Cl_2/CH_3OH$ than for $CDCl_3/CD_3OD$. The greater increase in log *K* values in $C_2H_4Cl_2/CH_3OH$ than in $CDCl_3/CD_3OD$ is unexpected. For the same ratios of $CDCl_3/CD_3OD$ and $C_2H_4Cl_2/CH_3OH$, each $CDCl_3/CD_3OD$ mixture has a lower dielectric constant value than that in $C_2H_4Cl_2/CH_3OH$ (see Tables 2 and 3). Therefore, the log *K* values in $CDCl_3/CD_3OD$ were expected to be larger than in the same ratio of $C_2H_4Cl_2/CH_3OH$. However, the opposite is true from the experimental results. Therefore, the greatly increased log *K* values in solvent mixtures $C_2H_4Cl_2/CH_3OH$ is not caused by the factor of dielectric constant. The $C_2H_4Cl_2$ solvent molecules must play a key role. The stronger host-guest interactions in $C_2H_4Cl_2/CH_3OH$ could be caused by modifying the complex conformation through the solvent molecules which could have an important effect on the formation of macrocycle complexes and on the thermodynamic parameters (ref. 22-24). Therefore, the $C_2H_4Cl_2$ molecules should have a more favorable effect in regulating the conformation of the host-guest complexes than the $CDCl_3$ molecules, resulting in a better recognition and larger log *K* values.

The greater degree of recognition demonstrated by **1** as compared with **2** in low polar solvents is probably related to its bulky sulfur atoms. When the naphthyl group of NapEtHClO$_4$ overlaps with the pyridine ring of the macrocycle through π-π interaction, the two bulky sulfur atoms act like two high energy barriers which further restrict movement of the naphthyl group of NapEtHClO$_4$. This effect is expected to increase the extent of recognition since the conformation of the host-guest complexes is more rigid.

ENANTIOMERIC RECOGNITION BY CHIRAL PYRIMIDINO-18-CROWN-6

Pyrimidino-18-crown-6 containing methyl groups on two chiral ring positions was prepared as shown above. The interaction of this chiral host with the enantiomers of chiral NapEtHClO$_4$ and PhEtHClO$_4$ in CD_3OD was determined by the ^{1}H NMR method. The preliminary log *K* value for the interaction of (*S,S*)-host with (*R*)-NapEtHClO$_4$ was 3.7 while that with (*S*)-NapEtHClO$_4$ was 3.4 giving a Δ log *K* of 0.4, while the log *K* value with (*R*)-PhEtHClO$_4$ was 3.51 and that with (*S*)-PhEtHClO$_4$ was 3.2 giving a Δ log *K* of 0.3 These recognition values compare favorably with those given above for (*S,S*)-**2**.

TABLE 2. Log K, ΔH (kJ/mol), $T\Delta S$ (kJ/mol) and Δ log K values determined by calorimetric titration for interactions of (*S,S*)-**1** and (*S,S*)-**2** with enantiomers of NapEtHClO$_4$ in different ratios (v/v) of 1,2-dichloroethane/methanol

$C_2H_4Cl_2/CH_3OH$ (ε^b)	log K	ΔH	$T\Delta S$	Δ log K	NapEtHClO$_4$
(*S,S*)-**1**					
0/10 (32.7)	1.72	-13.7	-3.8		(*R*)
	1.60			0.12	(*S*)
3/7 (26.0)	2.28	-16.0	-3.0		(*R*)
	-	-	-	-	(*S*)
5/5 (21.5)	2.69	-17.95	-2.57		(*R*)
	2.10	-12.4	-0.4	0.59	(*S*)
6/4 (19.3)	2.87	-20.5	-4.1		(*R*)
	2.25	-18.4	-5.5	0.62	(*S*)
7/3 (17.1)	3.08	-22.4	-4.8		(*R*)
	2.36	-21.1	-7.6	0.72	(*S*)
8/2 (14.8)	3.34	-25.3	-6.2		(*R*)
	2.74	-21.9	-6.3	0.60	(*S*)
9/1 (12.6)	3.86	-28.7	-6.7		(*R*)
	3.36	-23.5	-4.3	0.50	(*S*)
(*S,S*)-**2**					
0/10 (32.7)	2.47	-27.6	-13.5		(*R*)
	2.06	-26.4	-14.7	0.41	(*S*)
3/7 (26.0)	2.76	-29.0	-13.3		(*R*)
	2.26	-26.9	-14.0	0.50	(*S*)
5/5 (21.5)	3.14	-30.7	-12.8		(*R*)
	2.54	-27.5	-13.0	0.60	(*S*)
6/4 (19.3)	3.35	-28.5	-9.1		(*R*)
	2.70	-27.6	-12.2	0.65	(*S*)
7/3 (17.1)	3.62	-28.0	-7.3		(*R*)
	3.01	-27.1	-9.9	0.61	(*S*)
8/2 (14.8)	3.88	-29.3	-7.2		(*R*)
	3.38	-26.5	-7.2	0.50	(*S*)
9/1 (12.6)	4.47	-31.8	-6.3		(*R*)
	4.01	-28.6	-5.7	0.46	(*S*)

[a] Data taken from ref. 21. [b] ε is the dielectric constant.

TABLE 3. Log K and Δ log K values[a] determined by ^{1}H NMR method for interactions of (*S,S*)-**2** and (*S,S*)-**3** with enantiomers of NapEtHClO$_4$ in different ratios (v/v) of chloroform/methanol

$CDCl_3/CD_3OD$ (ε^b)	Log K	Δ log K	NapEtHClO$_4$	$CDCl_3/CD_3OD$ (ε^b)	Log K	Δ log K	NapEtHClO$_4$
(*S,S*)-**2**				(*S,S*)-**3**			
0/10 (32.7)	2.46		(*R*)	0/10 (32.7)	2.94		(*R*)
	2.06	0.40	(*S*)		2.53	0.41	(*S*)
3/7 (24.3)	2.75		(*R*)	3/7 (24.3)	3.19		(*R*)
	2.29	0.46	(*S*)		2.73	0.46	(*S*)
5/5 (18.8)	2.96		(*R*)	5/5 (18.8)	3.35		(*R*)
	2.43	0.53	(*S*)		2.85	0.50	(*S*)
6/4 (16.0)	3.09		(*R*)	6/4 (16.0)	3.52		(*R*)
	2.51	0.58	(*S*)		2.95	0.57	(*S*)
7/3 (13.2)	3.18		(*R*)	7/3 (13.2)	3.62		(*R*)
	2.70	0.48	(*S*)		3.11	0.51	(*S*)
9/10 (7.65)	3.41		(*R*)	9/1 (7.65)	3.82		(*R*)
	2.98	0.43	(*S*)		3.72	0.10	(*S*)

[a] Data taken from ref. 26. [b] ε = dielectric constant.

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REFERENCES

1. R.M. Izatt, K. Pawlak, J.S. Bradshaw and R.L. Bruening, *Chem. Rev.* **91**, 1721 (1991).
2. D.J. Cram, *Science*, **240**, 760 (1988).
3. S.D. Ericksen, J.A. Simon and W.C. Still, *J. Org. Chem.*, **58**, 1305 (1993).
4. J.F. Stoddard in *Progress in Macrocyclic Chemistry*, R.M. Izatt and J.J. Christensen, eds, Wiley-Interscience, New York, 1981, vol 2.
5. D.J. Chadwick, I.A. Cliffe and I.O. Sutherland, *J. Chem. Soc., Chem. Commun.*, 992 (1981).
6. R.B. Davidson, J.S. Bradshaw, B.A. Jones, N.K. Dalley, J.J. Christensen, R.M. Izatt, F.G. Morin and D.M. Grant, *J. Org. Chem.*, **49**, 353 (1984).
7. J.S. Bradshaw, P. Huszthy, C.W. McDaniel, M. Oue, C.-Y. Zhu, R.M. Izatt and S. Lifson, *J. Coordination Chem. Section B*, **27**, 105 (1992).
8. R.M. Izatt, T.-M. Wang, P. Huszthy, J.K. Hathaway, X.-X. Zhang, J.C. Curtis, J.S. Bradshaw and C. -Y. Zhu, *J. Incl. Phenom.*, **17**, 157 (1994).
9. J.S. Bradshaw, P. Huszthy, C.W. McDaniel, C.-Y. Zhu, N.K. Dalley and R.M. Izatt., *J. Org. Chem.* **55**, 3129 (1990).
10. P. Huszthy, J.S. Bradshaw, C.-Y. Zhu, R.M. Izatt and S. Lifson, *J. Org. Chem.*, **56**, 3330 (1991).
11. P. Huszthy, J.S. Bradshaw, C.-Y. Zhu, T.-M. Wang, N.K. Dalley, J.C. Curtis and R.M. Izatt, *J. Org. Chem.*, **57**, 3383 (1992).
12. R.M. Izatt, C.-Y. Zhu, N.K. Dalley, J.C. Curtis, X. Kou and J.S. Bradshaw, *J. Phys. Org. Chem.*, **5**, 656 (1992).
13. C.-Y. Zhu, R.M. Izatt, J.S. Bradshaw and N.K. Dalley, *J. Incl. Phenom.*, **13**, 17 (1992).
14. I.-H. Chu, D.V. Dearden, J.S. Bradshaw, P. Huszthy and R.M. Izatt, *J. Am. Chem. Soc.*, **115**, 4318 (1993).
15. J.T. Redd, J.S. Bradshaw, P. Huszthy and R.M. Izatt, *J. Heterocyclic Chem.*, **31**, 1047 (1994).
16. W.K. Hagmann, F.Z. Basha, M. Hashimoto, R.B. Frye, S. Kojo and S.M. Hecht, *J. Org. Chem.*, **46**, 1413 (1981).
17. J.T. Redd, J.S. Bradshaw and R.M. Izatt, unpublished observations.
18. C.-Y. Zhu, J.S. Bradshaw, J.L. Oscarson and R.M. Izatt, *J. Incl. Phenom.*, **12**, 275 (1992).
19. T.-M. Wang, J.S. Bradshaw, P. Huszthy, and R.M. Izatt, *Supramol. Chem.*, submitted.
20. T.-M. Wang, J.S. Bradshaw, J.C. Curtis, P. Huszthy, and R.M. Izatt, *J. Incl. Phenom.*, **13**, 113 (1993).
21. X.-X. Zhang, R.M. Izatt, C.-Y. Zhu and J.S. Bradshaw, *Supramol. Chem.*, submitted.
22. P.A. Mosier-Boss and A.I. Popov, *J. Am. Chem. Soc.*, **107**, 6168 (1985).
23. E.P. Hinz and D.W. Margenum, *J. Am. Chem. Soc.*, **96**, 4993 (1974).
24. M.H. Abraham, A.F. Danil de Namor and W.H. Lee, *J. Chem. Soc., Chem. Commun.* 893 (1977).