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Recognition by New Pyridino-18-crown-6 Ligands Containing Two Methyl, Two *t*-Butyl or Two Allyl Substituents on Chiral Positions Next to the Pyridine Ring for the Enantiomers of Chiral Organic Ammonium Perchlorates

by

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### Abstract

The log  $K$  values for the interaction of new chiral pyridino-18-crown-6 ligands containing two substituents on chiral positions next to the pyridine ring with the enantiomers of  $\alpha$ -phenylethylammonium perchlorate (PhEt) and  $\alpha$ -(1-naphthyl)ethylammonium perchlorate (NapEt) were measured using a  $^1\text{H}$  NMR titration method in a  $\text{CDCl}_3/\text{CD}_3\text{OD}$  (1/1) solvent mixture. The log  $K$  values indicate that these chiral pyridino-18-crown-6 ligands have high complexing abilities and good enantiomeric recognition for the chiral organic ammonium perchlorates. The  $^1\text{H}$  NMR titration experiments also show that the phenyl ring of the guest PhEt is almost parallel to the pyridine ring in the chiral diallyl- and dimethyl-substituted ligand complexes with chiral PhEt, and the phenyl ring is perpendicular to the pyridine ring in the chiral di-*t*-butyl-substituted ligand complex with PhEt. These results were supported by MM2 calculations.

### Introduction

Since the pioneering work of Cram and his co-workers on chiral crown ethers based on the "naphthalene wall",<sup>1</sup> enantiomeric recognition of optically active amino acids and organic ammonium ions by chiral crowns and their analogues has received much attention.<sup>2</sup> In order to develop qualitative and quantitative relationships between molecular structural features of chiral crown ether hosts and chiral organic ammonium ion guests, we have prepared a series of chiral crown ethers, azacrown ethers and crown ether-diesters having pyridine, triazole and pyrimidine subcyclic units.<sup>3-14</sup> Thermodynamic and kinetic parameters for chiral host - chiral guest interactions have been determined using <sup>1</sup>H NMR spectroscopy, titration calorimetry and Fourier transform ion cyclotron resonance mass spectrometry techniques.<sup>4, 7, 8, 10-12, 14, 15-18</sup> To expand our research on the chiral host - chiral guest interactions by the pyridino-crown ethers, we have prepared new pyridino-18-crown-6 ligands containing substituents on chiral positions next to the pyridine ring (in positions 2 and 16). Computer and CPK modeling shows that introduction of allyl or alkyl groups at the 2- and 16-positions in pyridino-18-crown-6 gives an effective chiral barrier in the crown ring and increases the rigidity around the chiral barrier.<sup>19</sup> The rigidity may prevent a "splaying motion"<sup>20</sup> in the molecule which would greatly reduce enantiomeric recognition. Therefore, it is expected that the 2,16-disubstituted pyridino-18-crown-6 derivatives would exhibit high enantiomeric recognition for chiral organic ammonium ions. Li et al. reported that chiral 2,16-dimethyl-substituted triazolo-18-crown-6 having cholesteryl or *n*-dodecyl groups as lipophilic side arms exhibited high chiral recognition for the enantiomers of several organic ammonium ions.<sup>21</sup> Those results also support our supposition.

## Results and Discussion

**Enantiomeric Recognition of Chiral Ammonium Perchlorates.** Enantiomeric recognition of PhEt and NapEt with the chiral 2,16-disubstituted pyridino-18-crown-6 ligands and dimers (see Figure 1) in a  $\text{CDCl}_3/\text{CD}_3\text{OD}$  (1/1) solvent mixture has been evaluated using the  $^1\text{H}$  NMR titration method<sup>2,16</sup> (Table 1). These chiral ligands exhibited good chiral recognition toward the enantiomers of PhEt. (-)-**4a**, having allyl groups, favored the (*R*)-form of PhEt and NapEt over the (*S*)-forms by 0.22 and 0.08 log *K* units, respectively, while (*S,S*)-(-)-**5a** and (*S,S*)-(-)-**6a**, having methyl and *t*-butyl groups as chiral barriers, formed more stable complexes with (*S*)-PhEt than (*R*)-PhEt ( $\Delta \log K$  of (*S,S*)-(-)-**5a** and (*S,S*)-(-)-**6a** complexes were 0.24 and 0.34, respectively). In previous systems where the alkyl groups are attached to chiral carbon positions next to the 1st ether oxygens, the (*S,S*)-ligands formed stronger complexes with the (*R*)-forms of the ammonium salts.<sup>16</sup> It is important to note that the spatial arrangement of the similar groups in (*S,S*)-(-)-**5a** and (*S,S*)-(-)-**6a** are the same as in the (*R,R*)-forms of the previous systems. The  $^1\text{H}$  NMR spectra for the (*S,S*)-(-)-**6a** complexes with (*R*)- and (*S*)- NapEt were very complicated because of the overlap of signals from the pyridine and naphthalene rings. This prevented a determination of log *K* values.

Figure 2 shows the results of the computer modeling of (*S,S*)-**4a**-(*R*)-PhEt, (*S,S*)-**5a**-(*S*)-PhEt and (*S,S*)-**6a**-(*S*)-PhEt systems.<sup>19</sup> The models show that the crown rings are twisted with the ethyleneoxy groups forced in a direction opposite from the substituent. This forms a chiral wall or barrier on the side of the macroring opposite to the substituent. When the substituents are effective chiral barriers such as methyl and *t*-butyl groups, the hosts recognize the guests by the chiral substituent barriers (Figure 3). On the other hand, when the substituent is an ineffective barrier such as the allyl group, the ethyleneoxy wall in the crown ring acts as the chiral barrier. Thus, (*S,S*)-**4a** may exhibit recognition towards the opposite guest enantiomers than do ligands

(*S,S*)-(-)-**5a** and (*S,S*)-(-)-**6a**. The dimers did not interact with the ammonium salts because the large and flexible rings do not allow the formation of tripod-type hydrogen bonds with the ammonium salts.

The  $^1\text{H}$  NMR titration experiments for  $\log K$  measurements also offered some information on structures of the complexes. When (*S*)- and (*R*)-PhEt were added to the crown ethers, the signals for the protons in position 4 of the pyridine ring shifted to the higher field for (-)-**4a** and (*S,S*)-(-)-**5a** and lower field for (*S,S*)-(-)-**6a**. These differences in the chemical shifts can be explained by the ring current effects of the phenyl ring of PhEt. When the pyridine ring of the crown ether is placed in the shielding zone of the phenyl ring of the guest (the pyridine ring is parallel to the phenyl ring), the pyridine ring protons shift to higher field. On the other hand, when the pyridine ring is placed in the deshielding zone of the phenyl ring (the pyridine ring is perpendicular to the phenyl ring), pyridine ring protons shift to lower field. Therefore, the  $^1\text{H}$  NMR spectral data suggest that the aromatic rings of the host and guest may be overlapped parallel in (-)-**4a**-(*R*)-PhEt and (*S,S*)-(-)-**5a**-(*S*)-PhEt systems, and perpendicular in (*S,S*)-(-)-**6a**-(*S*)-PhEt system. We suspect that the large *t*-butyl substituent is not allowing the two aromatic rings to become parallel in the (*S,S*)-**6a**-(*S*)-PhEt complex. Figure 2 shows the molecular model with the phenyl ring of PhEt parallel to the pyridine ring in the (*S,S*)-**4a**-(*R*)-PhEt and (*S,S*)-**5a**-(*S*)-PhEt systems, and the phenyl ring perpendicular to the pyridine ring in the (*S,S*)-**6a**-(*S*)-PhEt system. MM2 calculations support the presumed structures of (-)-**4a**-(*R*)-PhEt, (*S,S*)-(-)-**5a**-(*S*)-PhEt and (*S,S*)-(-)-**6a**-(*S*)-PhEt complexes.

### Experimental

**Determination of  $\log K$  values.** The  $\log K$  values were determined by the  $^1\text{H}$  NMR titration method as reported.<sup>2,16</sup>

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**Figure captions.**

Figure 1. Structures of ligands.

Figure 2. One of the lowest energy structures of (*S,S*)-**4a**, (*S,S*)-**5a**, (*S,S*)-**6a**, (*S,S*)-**4a**-(*R*)-PhEt, (*S,S*)-**5a**-(*S*)-PhEt and (*S,S*)-**6a**-(*S*)-PhEt.

Figure 3. Schematic drawing of the chiral pyridino-18-crown-6 ligand-enantiomeric PhEt complexes.

Table 1. The log *K* values for the complexation of chiral macrocyclic compounds with (*R*)- and (*S*)-forms of  $\alpha$ -phenylethylammonium perchlorate (PhEt) and  $\alpha$ -(1-naphthyl)ethylammonium perchlorate (NapEt) in CDCl<sub>3</sub>/CD<sub>3</sub>OD (1/1) solution.

Table 1. The log *K* values for the complexation of chiral macrocyclic compounds with (*R*)- and (*S*)-forms of  $\alpha$ -phenylethylammonium perchlorate (PhEt) and  $\alpha$ -(1-naphthyl)ethylammonium perchlorate (NapEt) in CDCl<sub>3</sub>/CD<sub>3</sub>OD (1/1) solution.

Compound	Substituent	log <i>K</i> values			
		( <i>S</i> )-PhEt	( <i>R</i> )-PhEt	( <i>S</i> )-NapEt	( <i>R</i> )-NapEt
meso-4a	allyl	3.67 <sup>a</sup>			
(-)-4a	allyl	3.62 <sup>a</sup>	3.84 <sup>a</sup>	3.84	3.92
meso-5a	methyl	3.74			
( <i>S,S</i> )-(-)-5a	methyl	3.69	3.45		
( <i>S,S</i> )-(-)-6a	<i>t</i> -butyl	2.25	1.91	b	b
meso-4b	allyl	c			
(-)-4b	allyl	c			
(+)-4b	allyl	c			

<sup>a</sup> At 26 °C. All others at 25 °C.

<sup>b</sup> Values could not be determined because of overlap between the signals corresponding to the pyridine and naphthalene rings.

<sup>c</sup> Did not show complexation.

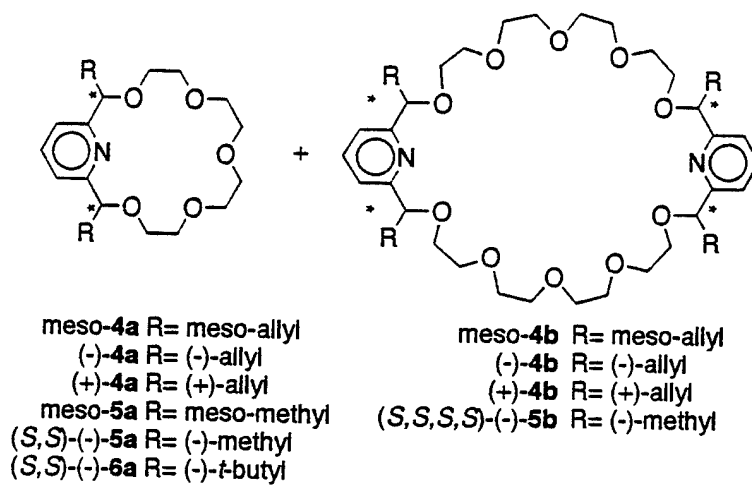
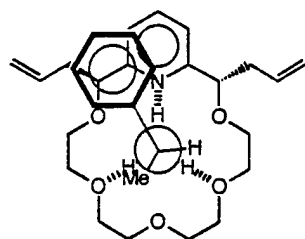
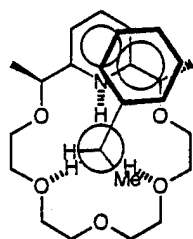


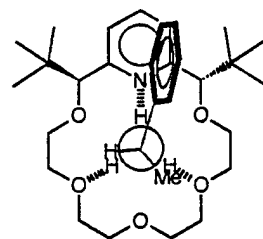
Figure 1. Structures of ligands.



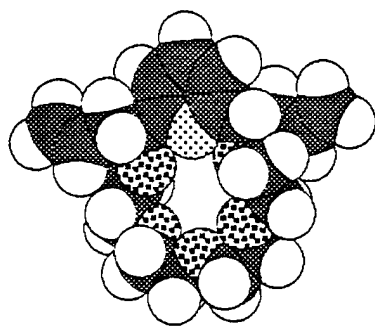
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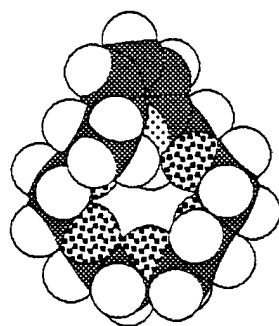
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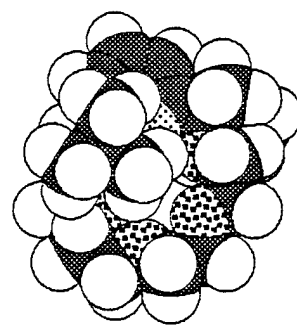
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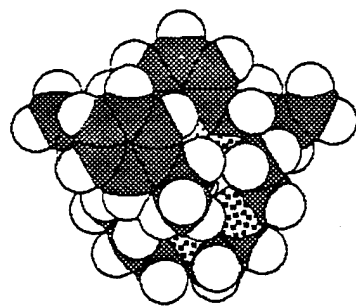
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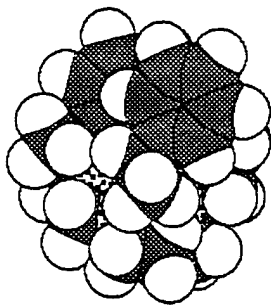
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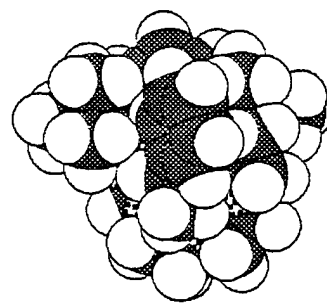
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(*S,S*)-4a-(*R*)-PhEt



(*S,S*)-5a-(*S*)-PhEt



(*S,S*)-6a-(*S*)-PhEt

Figure 2. One of the lowest energy structures of (*S,S*)-4a, (*S,S*)-5a, (*S,S*)-6a, (*S,S*)-4a-(*R*)-PhEt, (*S,S*)-5a-(*S*)-PhEt and (*S,S*)-6a-(*S*)-PhEt.

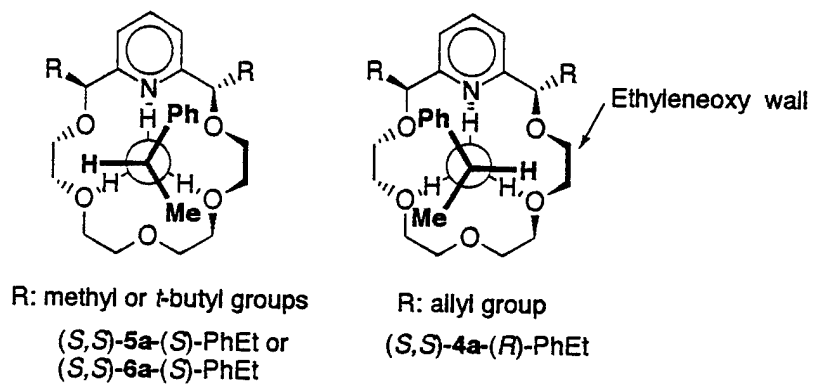


Figure 3. Schematic drawing of the chiral pyridino-18-crown-6 ligand-enantiomeric PhEt complexes.