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Enantiomeric Recognition of Organic Ammonium Salts by Chiral Dialkyl-, Dialkenyl- and Tetramethyl-Substituted Pyridino-18-Crown-6 Ligands

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Complexation of the enantiomeric forms of various organic ammonium salts by chiral pyridino-18-crown-6 ligands 1-8 (Figure 1) has been studied by the temperature dependent ^1H NMR technique.[1,2] At low temperatures, the peaks in the ^1H NMR spectra of the complexes attributable to the hydrogen atoms on the CH_2 groups attached to the pyridine rings (centered at about δ 4.5), or the methyl hydrogens in the cases of 7 and 8, separated into two peaks of equal intensities. The low temperature peak separations were 40-140 Hz. At high temperatures, the appearance of a single peak is caused by a fast intermolecular or intramolecular face to face guest exchange. The kinetic parameters for the dissociation of these complexes were calculated as reported.[1,2] Table I shows the coalescence temperatures (T_c) and $\Delta G_c^{\ddagger}$ for the

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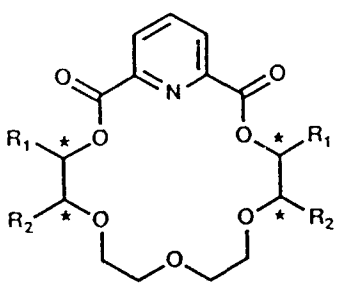
dissociation of the complexes of 1-8 with various chiral organic ammonium salts. The majority of the data are for complexes of these chiral ligands with the hydrogen perchlorate salts of (R)- and (S)-α-(1-naphthyl)ethylamine (A).

It is evident from these differences in the $\Delta G_c^{\ddagger}$ values in Table I that these chiral ligands exhibit enantiomeric recognition for chiral-forms of various organic ammonium salts. All the (S,S)-ligands formed kinetically more stable complexes with the (R) than with the (S)- form of A. As expected, complexes of the (R,R)- and (R,R,R,R)-ligands with the (S)- form of A were more stable kinetically than those with the (R)- form. The degree of recognition was similar in all ligand-A complexes as shown by the $\Delta\Delta G_c^{\ddagger}$ values being 0.7 to 0.9 kcal/mol except for 1, 2 and 4 where $\Delta\Delta G_c^{\ddagger}$ values were 1.1, 1.3 and 1.6 kcal/mole, respectively. An X-ray crystal study of the complexes of (S,S)-1- with both (R) and (S)-A showed that the methyl groups on the chiral carbons of (S,S)-1 interact sterically with one of the naphthylene hydrogens of A in the (S,S)-1-(R)-A complex.[1] We had hoped that larger alkyl groups attached to the chiral centers, such as the sec-butyl groups of 5, would cause even greater enantiomeric recognition. This was not the case. It is possible that the larger substituents cause steric interactions in both sets of complexes.

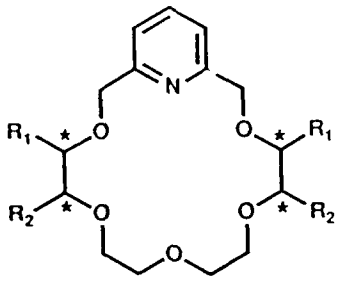
The reasons for the observed enantiomeric recognition by these ligands for the other chiral salts are not so clear. Ligand 7 showed excellent recognition of the (S)-form of the hydrogen perchlorate salt of α-phenylethylamine (B) over the (R)-form by 2.2 kcal/mol. Even though high recognition values were not evident for the complexes of 5 with the enantiomers of A, ligand 7 did show good recognition for the (R)-form of the hydrogen perchlorate salt of 2-amino-2-phenylethanol (D) over the (S)-form by 1.6 kcal/mol.

1. Davidson, R. B.; Bradshaw, J. S.; Jones, B. A.; Dalley, N. K.; Christensen, J. J.; Izatt, R. M. Izatt, R. M.; Morin, F. G.; Grant, D. M. J. Org. Chem. 1984, 49, 353.
2. Bradshaw, J. S.; Thompson, P. K.; Izatt, R. M.; Morin, F. G.; Grant, D. M. J. Heterocyclic Chem. 1984, 21, 897.

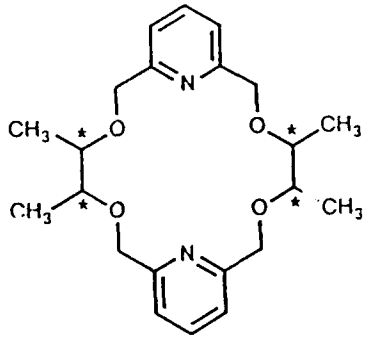
Figure 1. Chiral Pyridino-18-Crown-6 Ligands



1, $R_1 = CH_3$; $R_2 = H$ (S,S) & (R,R)
2, $R_1 = C_6H_5$; $R_2 = H$ (S,S)
3, $R_1 = H$; $R_2 = C_6H_5$ (S,S)



4, $R_1 = CH_3$; $R_2 = H$ (S,S)
5, $R_1 = CH(CH_3)CH_2CH_3$; $R_2 = H$ (R,R)
6, $R_1 = CH_2CH_2CH{=}CH_2$; $R_2 = H$ (S,S)
7, $R_1, R_2 = CH_3$; (R,R,R,R)



8, (R,R,R,R)

Table I. Free Energies of Activation, $\Delta G_c^{\ddagger}$ values (kcal/mole) in CD_2Cl_2[a] for the Interaction of Chiral Macrocyclic Ligands with Chiral Alkyl Ammonium Salts

Ligand	value[a]	(R)-A[b]	(S)-A[b]	(R)-B[b]	(S)-B[b]	(R)-C[b]	(S)-C[b]	(R)-D[b]	(S)-D[b]
(S,S)-1[c]	Tc, °C	12	-19			-25	-36		
	$\Delta G_c^{\ddagger}$	13.4	12.3			12.1	11.8		
(S,S)-2[d]	Tc, °C	11	-35			-21	-45		
	$\Delta G_c^{\ddagger}$	13.3	12.0			11.9	10.8		
(S,S)-3[c]	Tc, °C					-33	-28		
	$\Delta G_c^{\ddagger}$					11.5	11.6		
(S,S)-4[c]	Tc, °C	-56	-86			-40	-73		
	$\Delta G_c^{\ddagger}$	10.3	8.7			11.3	10.0		
(R,R)-5	Tc, °C	-20	5	-50	-15	-42	-48	-30	-39
	$\Delta G_c^{\ddagger}$	12.5	11.3	10.8	12.1	11.3	10.9	12.6	11.0
(S,S)-6	Tc, °C	29	10						
	$\Delta G_c^{\ddagger}$	14.2	13.3						
(R,R,R,R)-7	Tc, °C	3	27	-21	25				
	$\Delta G_c^{\ddagger}$	13.4	14.3	12.1	14.3				
(R,R,R,R)-8	Tc, °C	-52	-43	-38	-46				
	$\Delta G_c^{\ddagger}$	10.5	11.2	11.2	10.6				

[a]A Varian Gemini-200 spectrometer was used to record all ^1H NMR spectra. Equimolar amounts of ligand and salt were dissolved in CD_2Cl_2. The hydrogens on the CH_2 next to the pyridine ring were used as the ^1H NMR probe for all complexes of 5 and 6 and the methyl hydrogen atoms for 7 and 8. T_c = coalescence temperature. $\Delta G_c^{\ddagger}$ values were ±0.2. [b]A = the hydrogen perchlorate salt of (R)- or (S)-α-(1-naphthyl)ethylamine; B = hydrogen perchlorate salt of (R)- or (S)-α-phenylethylamine; C = the hydrogen perchlorate salt of methyl phenylalaninate; D = the hydrogen perchlorate salt of (R) or (S)-2-amino-2-phenylethanol. [c]Data for 1, 3, 4 are taken from reference 1. [d]Data for 2 were 13 and 12.3 kcal/mole in Reference 2. The measurements were repeated on the Gemini 200 to give the values shown.