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A Structural Analysis of the Complexes of (*S*, *S*)-Dimethylpyridino-18-Crown-6 with (*R*) and (*S*)-[α-(1-Naphthyl)ethyl]ammonium Perchlorate by NMR Techniques and Molecular Modeling

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Abstract. Significant $\pi - \pi$ interaction is found in the complexes of (*S*, *S*)-dimethylpyridino-18-crown-6 with (*R*)- and (*S*)-[α-(1-naphthyl)ethyl]ammonium perchlorate. This finding is supported by the ^{1}H NOESY NMR spectral technique, greater chemical shift changes of aromatic protons in both host and guest molecules upon complexation, and by molecular mechanics calculations. Because of the flexibility of the ligand, the tripod hydrogen bonding causes ^{13}C relaxation times of all periphery carbons to decrease without significant selectivity. Rotational energy barrier calculations of the methyl groups of the complexed ligand also show that the (*S*, *S*)-host–(*R*)-guest is the more stable complex.

Key words: $\pi - \pi$ interaction, tripod hydrogen bonding, NOESY, relaxation time, chemical shift, molecular mechanics calculation.

1. Introduction

Since Cram first reported chiral macrocyclic compounds in 1973 [1, 2], hundreds of chiral macrocyclic compounds have been synthesized. Enantiomeric recognition of chiral organic ammonium salts by many of these chiral macrocyclic ligands has been studied by NMR spectroscopy, calorimetric titration, solvent extraction, liquid membrane transport and chromatography. Detailed discussions of the synthesis and characterization of chiral ligands are given in a few reviews [3–7]. Among the many chiral crown ethers, chiral pyridino-18-crown-6 ligands display moderate to significant recognition [6, 7]. However, interactions of most of the reported chiral ligands with enantiomeric guests have not been well characterized from either a thermodynamic or a kinetic standpoint [7]. Structural and conformational studies of complexes in solution could provide evidence for the basis of enantiomeric recognition.

In a previous paper [8], (*S*, *S*)-dimethylpyridino-18-crown-6 [(*S*, *S*)-Me_2Pl8C6; see Figure 1] was used as a probe to investigate the recognition behavior for sev-

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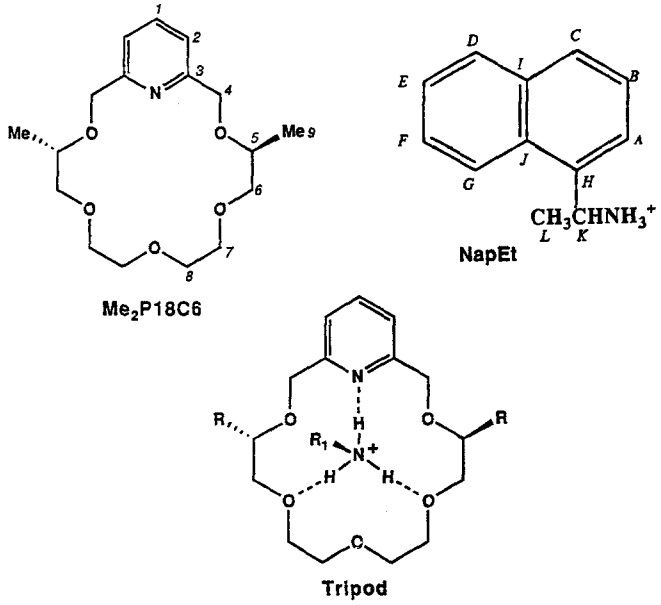


Fig. 1. Structures of compounds.

eral chiral ammonium salts in various solvent systems. Among the ammonium salts, (*R*)- and (*S*)-[α-(1-naphthyl)ethyl]ammonium perchlorate (NapEt; Figure 1) formed strong complexes with (*S*, *S*)-Me_2P18C6 in a mixed solvent of 50% CD_3OD and 50% $CDCl_3$ (v/v). The ligand exhibited good enantiomeric recognition with $\Delta \log K = 0.54$, $\Delta\Delta H = 3.91$ kcal/mol, $\Delta\Delta S = 10.86$ kcal/mol and $\Delta\Delta G^{\ddagger} = 0.74$ kcal/mol at 25°C.

The primary binding force between the ligand and the primary ammonium cation is that formed by the three hydrogen bonds as shown in Figure 1 [9, 10]. However, the $\pi - \pi$ interaction between the naphthalene group of NapEt and the pyridine ring of the chiral ligand is considered as one of the possible causes for enantiomeric recognition [7, 11, 12]. It is important to know if a $\pi - \pi$ interaction exists and if it plays a role in promoting enantiomeric recognition in these chiral complexes.

In this paper, we analyze the $\pi - \pi$ interaction in the complexes of (*S*, *S*)-Me_2P18C6 with (*R*)- and (*S*)-NapEt in a 50% CD_3OD and 50% $CDCl_3$ (v/v) solvent system by 2D ^{1}H NOESY spectroscopy, chemical shift changes, and molecular mechanics calculations. The effects of tripod hydrogen bonding on ^{13}C relaxation times in the complex are also discussed.

2. Experimental

2.1. Materials

(S, S)-Me_2Pl8C6 and (R)- and (S)-NapEt were prepared as reported [8, 13, 14]. Solvents CD_3OD and $CDCl_3$ were purchased from Aldrich and used without further purification.

2.2. NOESY Experiments

2D ^{1}H NOESY spectra of (S, S)-Me_2Pl8C6 complexes with (R)- and (S)-NapEt were taken on a Varian VXR-500 MHz NMR spectrometer at 25°C. Stoichiometric amounts of host and guest were weighed on a high precision balance and dissolved in a mixed solvent of 50% CD_3OD and 50% $CDCl_3$ (v/v) to give a concentration of 0.040 M. The 90 degree pulse width was always calibrated. Delay time was set to about 3 times the maximum $T1$ value.

2.3. ^{13}C $T1$ Measurements

All glassware was washed with a 0.1 M EDTA solution to remove paramagnetic metal impurities. The sample solutions were prepared as described above for the NOESY experiments to give a concentration of 0.20 M. Relaxation time measurements were performed at 125.67 MHz under proton-noise decoupling conditions by the inversion-recovery technique. Recovery delays were 30 seconds or longer. At least nine points were included for each $T1$ calculation. Usually, 150–200 scans were necessary for each recovery value in order to obtain an acceptable signal-to-noise ratio. All spectra were recorded at 25°C. The calculation of $T1$ values was performed using software supplied by the spectrometer manufacturer using direct least squares fitting to a multiparameter exponential equation. At least two runs were made for each system. The standard error was approximately 5% based on the values from all runs.

2.4. Molecular Mechanics Calculations

The conformational searches and comparisons of the lowest energy conformations of (S, S)-Me_2Pl8C6 complexes with (R)- and (S)-NapEt were performed on a Silicon Graphics Personal IRIS workstation using QUANTA/CHARMm software from Molecular Simulations, Inc.

3. Results and Discussion

During the determination of $\log K$ values for the complexation of (S, S)-Me_2Pl8C6 with several chiral organic ammonium salts in different solvent systems, the pyridine protons of the host molecules were found to have significant chemical shift changes upon complexation. A similar phenomenon has been observed in other

systems [12]. Table I lists the chemical shift values for free and complexed (S, S)-Me_2Pl8C6 with (R)-NapEt $[(S, S)$-$(R)]$ and (S)-NapEt $[(S, S)$-$(S)]$ as well as the differences between them. From these data, we can see that the pyridine proton in position 1 (Figure 1) has a 0.19 ppm upfield shift and a 0.01 ppm downfield shift on formation of complexes with (R)-NapEt and (S)-NapEt, respectively. Proton 2 has 0.35 ppm and 0.10 ppm upfield shifts for (S, S)-(R) and (S, S)-(S) complexes, respectively. Significant changes (0.33 and 0.12 ppm upfield shifts) also occurred at position 4 which is close to the pyridine ring. Chemical shift changes can be caused by many factors such as hydrogen bonding, conformation changes, shielding and deshielding effects of aromatic rings, and $\pi - \pi$ interactions. Hydrogen bonding and conformation changes should have little effect on the pyridine protons because the protons on the pyridine ring are not involved at the complexation site and the ring is a geometrically stable moiety. Deshielding and shielding effects of the $\pi - \pi$ interacting units are thus expected to play an important role in the chemical shift changes of the pyridine protons. The chemical shift changes shown in Table I suggest the presence of a strong $\pi - \pi$ interaction between the pyridine and naphthalene rings. This conclusion is supported by the chemical shift changes of guest molecule NapEt (Table II). The chemical shift assignments were made from an ^{1}H COSY spectrum. In this case, significant chemical shift changes occurred in positions A, C, E and F in the (S, S)-(R) complex and B, C and G in the (S, S)-(S) complex (see NapEt, Figure 1, for proton assignments). The relatively large chemical shift changes indicate that these positions are affected by the pyridine ring. The presence of positive and negative chemical shift changes results from shielding and deshielding effects of the pyridine ring depending on the relationship to the face or edge of the ring. Unlike a fixed structure in the crystalline state [10, 12], these data do not determine an absolute geometry for the interaction.

The data in Tables I and II also show that the protons in the (S, S)-(R) complex have a greater average chemical shift change than those in the (S, S)-(S) complex. Although the size of the absolute value of chemical shift change for a specific proton is not necessarily proportional to the stability of a complex [14], the greater overall changes in the (S, S)-(R) complex over those in the (S, S)-(S) complex indicate greater stability for the (S, S)-(R) complex.

The presence of a $\pi - \pi$ interaction is strongly supported by data from 2D ^{1}H NOESY spectra (Figure 2). In the NOESY spectra, there are strong off-diagonal signals in the 7.2–8.2 ppm range between the chemical shifts of the pyridine and naphthalene protons indicating that pyridine protons of the ligand and naphthalene protons of the ammonium salt are spatially close and that the complex is stable enough for NOE cross-relaxation to occur [15]. As shown in Figure 2, the π systems overlap spatially in both the (S, S)-(R) (Fig. 2a) and (S, S)-(S) (Fig. 2b) complexes. This $\pi - \pi$ interaction helps bind the two aromatic systems together, determines the steric environment for the methyl groups, and contributes to recognition.

TABLE I. ^{1}H NMR chemical shift values (ppm) for (S,S)-Me_2Pl8C6 and its complexes with (R) and (S)-NapEt in 1M/1C[a] mixed solvent system (v/v) at 25°C.

Proton[b]	(S,S)-Me_2Pl8C6 ppm	(S,S)-(R) Complex[c] ppm	Δppm	(S,S)-(S) Complex[d] ppm	Δppm
1	7.75	7.56	−0.19	7.76	+0.01
2	7.34	6.99	−0.35	7.24	−0.10
4	4.80	4.47	−0.33	4.68	−0.12
5	3.81	3.81	0.00	3.80	−0.01
6	3.47	3.54	+0.07	3.41	−0.06
7&8[e]	3.59–3.48	3.78–3.68		3.62–3.48	
9	1.19	1.25	+0.06	1.18	−0.01

[a] M = CD_3OD, C = $CDCl_3$.
[b] Numbers correspond to protons in (S,S)-Me_2Pl8C6 (see structure in Figure 1).
[c] (S,S)-(R) = Complex of (S,S)-Me_2Pl8C6 with (R)-NapEt.
[d] (S,S)-(S) = Complex of (S,S)-Me_2Pl8C6 with (S)-NapEt.
[e] Estimated values because of overlapping peaks.

TABLE II. ^{1}H NMR chemical shift values (ppm) for (R) and (S) NapEt and their complexes with (S,S)-Me_2Pl8C6 in 1M/1C[a] mixed solvent system (v/v) at 25°C.

Proton[b]	NapEt ppm	(S,S)-(R) Complex[c] ppm	Δppm	(S,S)-(S) Complex[d] ppm	Δppm
A	7.63	7.78	+0.15	7.66	+0.03
B	7.65	7.61	−0.04	7.49	−0.16
C	8.07	7.94	−0.13	7.91	−0.16
D	7.92	7.84	−0.08	7.94	+0.02
E or F	7.59	7.25	−0.34	7.57	−0.02
F or E	7.59	7.40	−0.19	7.57	−0.02
G	7.94	7.84	−0.10	8.06	+0.12
K	5.34	5.35	+0.01	5.30	−0.04
L	1.79	1.84	+0.05	1.83	+0.04

[a] See footnote a in Table I.
[b] Letters correspond to protons in NapEt (see structure in Figure 1).
[c] See footnote c in Table I.
[d] See footnote d in Table I.

The tripod hydrogen bonding shown in Figure 1 could also affect recognition in these systems. An attempt to determine the formation and location of these bonds was made by comparing the ^{13}C NMR relaxation times ($T1$) for host, guest and

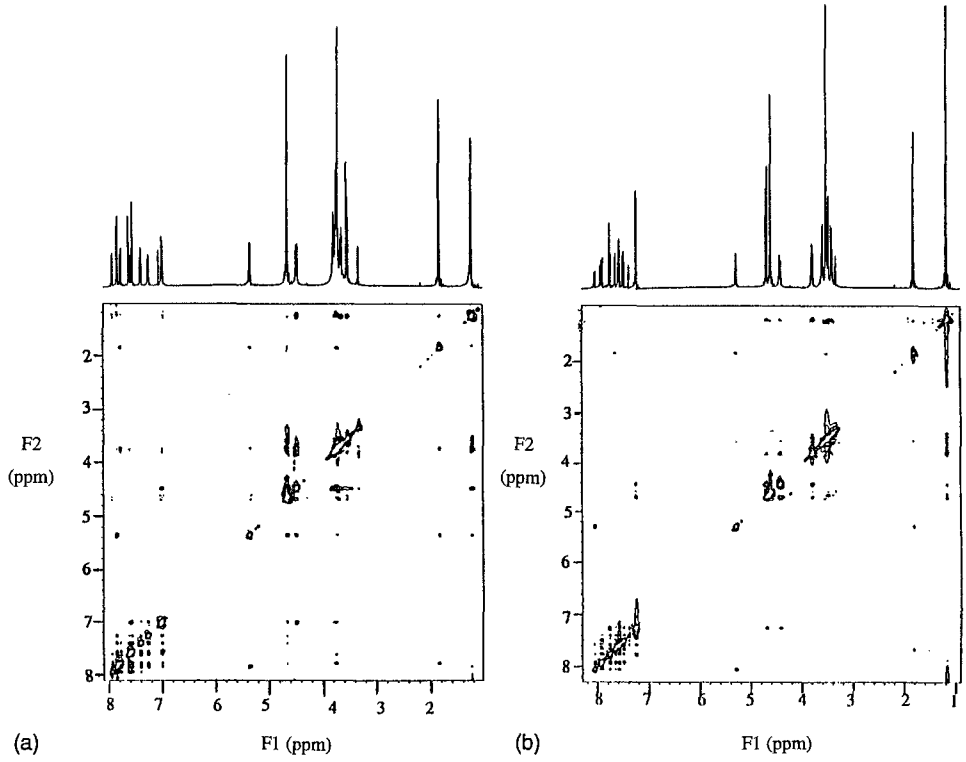


Fig. 2. ^{1}H NMR NOESY spectra of complexes of (S,S)-dimethylpyridino-18-crown-6 with (R)-[α-(1-naphthyl)ethyl]ammonium perchlorate (Fig. 2a) and (S)-perchlorate (Fig. 2b) in a mixed solvent of 50% CD_3OD + 50% $CDCl_3$ at 25°C.

complexes. The data are given in Tables III and IV. Individual carbon assignments were confirmed on the basis of chemical shifts and the 2D HETCOR spectra.

Generally speaking, in liquids, relaxation times ($T1$) for any given molecule reflect molecular mobility (tumbling) and specific internal motions determined by the internal degrees of freedom of the molecule [16]. The measurement and comparison of $T1$ values for the same carbon in each complex can give information about the relative stability of the complexes and an intramolecular $T1$ comparison can lead to estimates of the relative mobilities of the different parts of the macrocyclic ring framework in solution. Compounds with large molecular weights tumble more slowly than smaller molecules and thus exhibit shorter relaxation times than the smaller systems. The formation of a complex results in an increase in molecular weight, therefore, the complex should tumble more slowly than its components in the free state, resulting in a decrease in $T1$ values. A $T1$ comparison between (S,S)-(R) and (S,S)-(S) complexes can give information about their relative stabilities, i.e. a consistently larger $T1$ decrease is seen in the more stable complex. From Table III, carbons 1–8 show 6.4–51.1% decreases in $T1$ when the (S,S)-(R) complex is formed and 1.6–45.8% decreases in $T1$ when the (S,S)-(S)

TABLE III. ^{13}C relaxation times (seconds) for (S,S)-Me_2Pl8C6 and its complexes with (R) and (S)-NapEt in 1M/1C[a] mixed solvent system (v/v) at 25°C.

Carbon[b]	(S,S)-Me_2Pl8C6 $T1$	(S,S)-(R) Complex[c] $T1$	% $T1$ Decrease	(S,S)-(S) Complex[d] $T1$	% $T1$ Decrease
1	1.47	1.29	12.2	1.35	8.2
2	1.26	1.18	6.4	1.24	1.6
3	6.54	4.95	24.3	5.51	15.7
4	1.14	0.88	22.8	0.95	16.7
5	1.81	1.21	33.1	1.26	30.4
6	1.07	0.67	37.4	0.73	31.8
7 & 8	1.31	0.63 & 0.65	51.1	0.71	45.8
9	1.60	1.72	−7.5	1.76	−10.0

[a] See footnote a in Table I.

[b] Numbers correspond to carbons in (S,S)-Me_2Pl8C6 (see structure in Figure 1).

[c] See footnote c in Table I.

[d] See footnote d in Table I.

TABLE IV. ^{13}C relaxation times (seconds) for (R) and (S) NapEt and their complexes with (S,S)-Me_2Pl8C6 in 1M/1C[a] mixed solvent system (v/v) at 25°C.

Carbon[b]	NapEt $T1$	(S,S)-(R) Complex[c] $T1$	% $T1$ Decrease	(S,S)-(S) Complex[d] $T1$	% $T1$ Decrease
A	1.93	1.10	43.0	1.27	34.2
B	2.06	1.21	41.3	1.36	34.0
C	1.75	1.12	36.0	1.23	29.7
D or G	1.75	1.10	26.7	1.23	29.7
E or F	1.81	1.20	33.7	1.28	29.3
F or E	2.14	1.18	44.9	1.41	34.1
G or D	1.78	1.12	37.1	1.25	29.8
H	8.22	4.80	41.6	5.32	35.3
I	7.60	4.45	41.4	5.48	27.9
J	7.70	5.24	31.9	4.65	39.6
K	2.34	1.37	41.4	1.65	29.5
L	1.41	0.90	36.2	0.95	32.6

[a] See footnote a in Table I.

[b] Numbers correspond to carbons in NapEt (see structure in Figure 1).

[c] See footnote c in Table I.

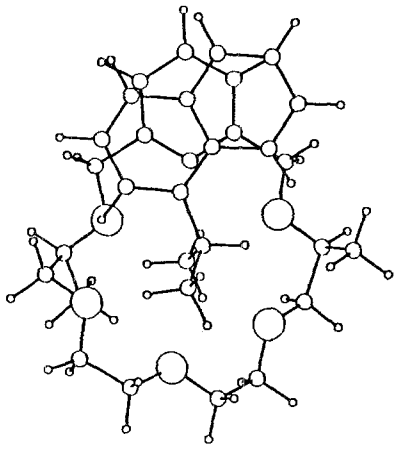
[d] See footnote d in Table I.

complex is formed. From the above arguments we conclude that the (S,S)-(R) complex is more stable than the (S,S)-(S) complex, as already proved by the $\log K$ values [8].

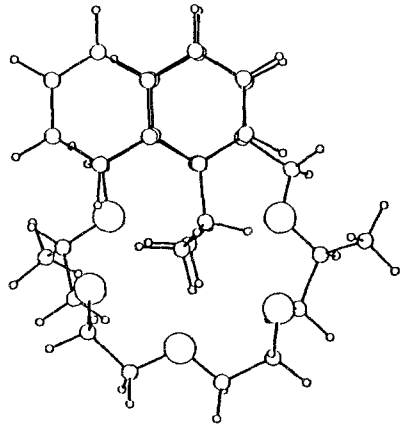
It is also sometimes possible to compare $T1$ values for specific sites within a molecule to understand changes to internal mobility that occur selectively at particular locations, thus giving information about how the complex binds. We had hoped to find greater decreases in $T1$ for C3, C6, and C7 than for the other periphery carbon atoms upon complexation because they are closer to the proposed tripod hydrogen bonds. The $T1$ data in Table III, unfortunately, do not provide conclusive evidence for the specific location of the tripod hydrogen bonds. The $T1$ data are consistent, however, with the conclusion that hydrogen bonding greatly reduces the flexibility of the macrocycle. As expected, the loss of flexibility increases with increasing distance from the already semi-rigid pyridine ring. Note that in either tripod hydrogen-bonding scheme, the only large scale intramolecular freedom of motion would be concerted rotation about the C-C macrocycle single bonds causing motion of the non-hydrogen-bonded oxygens but not causing motion to any of the macrocycle carbons.

Molecular mechanics conformational searches on (S,S)-Me_2Pl8C6 complexes with (R)- and (S)-NapEt in the gas phase yielded the lowest energy conformation, which exhibits $\pi - \pi$ stacking as shown in Figure 3. The (S,S)-(R) complex was 1.73 kcal/mol more stable than the (S,S)-(S) complex. The results of molecular mechanics calculations for the rotational energy barriers of the methyl groups in these low energy conformations of the complexes and in the free crown ether are summarized in Table V. The rotational energy barriers of the methyl groups in both complexes are greater than they are in the free crown ether except Me(A) in the (S,S)-(S) complex, which is still larger than the average for the free ether, predicting a decrease in relaxation times instead of the increase as observed. It is important to note that the data in Table 5 again confirm that the (S,S)-(R) complex is more stable than the (S,S)-(S) complex. There is a much greater energy barrier in the most stable (S,S)-(R) complex indicating a more firmly bound system.

The reasons for the observed increase in $T1$ for the methyl carbons in both complexes (carbon 9 in Table III) is not immediately apparent. The increase would normally suggest that the methyl groups have greater mobility in the complex than in the free state. However, as stated in the previous paragraph, the rotational energy barriers of the methyl groups are greater in the complexed form than in the free crown. In liquids, normally extreme narrowing conditions prevail and spin-rotation is the dominant relaxation method so that $T1$ values correlate with mobility [18]. However, in the case of these methyl groups, a combination of slow tumbling and slow rotation of the methyl groups could cause the dipole-dipole relaxation mechanism to become important. The effect on $T1$ of the dipole-dipole mechanism is opposite to the normal spin-rotation mechanism and could cause the observed increase in $T1$.



(a)



(b)

Fig. 3. Computer-generated views obtained from molecular mechanics calculations of the complexes of the (S,S)-dimethylpyridino-18-crown-6 with (R)-[α-(1-naphthyl) ethyl]ammonium perchlorate (view a) and with (S)-perchlorate (view b).

Acknowledgements

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TABLE V. The rotational energy barriers (kcal/mol) of methyl groups in the free and complexed (S, S)-Me_2Pl8C6 from molecular mechanics calculations.

	Free crown ether		(S, S)-(R) complex		(S, S)-(S) complex	
	Me(1)	Me(2)	Me(A)[a]	Me(T)[b]	Me(A)[a]	Me(T)[b]
	3.359	3.444	6.777	9.258	3.409	3.529
Average[c]	3.402		8.018		3.469	

[a] Methyl group away from salt.

[b] Methyl group toward salt.

[c] The average is the only meaningful number as applied to NMR measurements since the molecular mechanics calculations apply to the 'lowest' energy conformation. Due to the C_2 symmetry of the ether, and the dynamic equilibria in solution, the methyls are not distinguishable by NMR measurement at room temperature.

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