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Jon K. Hathaway[a]; Reed M. Izatt[a]; Cheng Y. Zhu[b]; Peter Huszthy[c]; Jerald S. Bradshaw[a]
[a] Department of Chemistry, Brigham Young University, Provo, Utah, U.S.A. [b] Marion Merrell Dow, Inc., Analytical Chemistry, Kansas City, MO [c] Institute of Organic Chemistry, Technical University, Budapest, Hungary

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Enantiomeric recognition by chiral pyridino-18-crown-6 for 1-naphthylethylamine. The effect of alkyl substituents on the macrocycle ring.

JON K. HATHAWAY, REED M. IZATT, CHENG Y. ZHU[a], PETER HUSZTHY[b] and JERALD S. BRADSHAW*

Department of Chemistry, Brigham Young University, Provo, Utah 84602, U.S.A., [a]Marion Merrell Dow, Inc., Analytical Chemistry, Kansas City, MO. and [b]Institute of Organic Chemistry, Technical University, Budapest, Hungary

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Molecular recognition of three chiral pyridino-18-crown-6 macrocycles with various dialkyl substituents for (R)- and (S)-[α-(1-naphthyl)ethyl]ammonium perchlorate (NapEt) has been determined by isoperibol titration calorimetry and compared to values already determined for the chiral di-methyl- and di-*tert*-butyl-substituted crowns. Possible mechanisms of recognition for these systems are discussed using the thermodynamic values log *K*, ΔH, and $T\Delta S$. Macrocycles with the bulky substituents *tert*-butyl, isobutyl, and sec-butyl showed better recognition than those with the less bulky isopropyl and methyl substituents. In the case of macrocycles with bulky substituents, recognition of the enantiomers of NapEt was mainly the result of differences in entropy value changes. With macrocycles having less bulky substituents, reognition was mainly the result of differences in enthalpy value changes.

INTRODUCTION

Molecules which have the ability to selectively recognize enantiomers are of great interest to researchers in analytical, biological, organic, and pharmaceutical chemistry.[1] In fact, macrocycles with specific, tailored properties are widely used by researchers in these fields. Enantiomers can be separated in chromatographic columns containing chiral macrocyclic ligands.[2] Enzyme and receptor protein analogues can be used to understand enzyme functionality in cells and membranes. For example, Kikuchi and coworkers have recently reported molecular recognition of anionic guests using host macrocycles imbedded into multi-walled bilayer membranes, thus simulating natural biological receptors.[3] One of the major focal points in our research is the design of novel ligands capable of molecular recognition. Characterization of the interactions of these ligands with chiral organic ammonium salts is done by calorimetric titrations, ^{1}H NMR spectroscopy, X-ray crystallography and most recently, Fourier transform ion cyclotron resonance mass spectrometry.[4]

Pirkle has postulated that chiral recognition follows a three-point rule: "Chiral recognition requires a minimum of three simultaneous [points of] interaction between the [chiral crown ether] and at least one of the enantiomers, with at least one of these interactions being stereochemically dependent."[5] Three main interactions have been identified, two positive and one negative, between chiral crown ethers and organic ammonium perchlorates.[6] Hydrogen bonding occurs between the three protons of the ammonium ion and the nitrogen and two oxygen atoms of the ring as shown in Figure 1.[7] We have shown that hydrogen bonding is the strongest interaction in the complex.[4c] However, none of these bonds are stereospecific. It is well known that π-π interactions influence recognition.[1c,1d,4e,8] We have shown that π-π interactions of the pyridino-crown with α-(1-naphthyl)ethylammonium perchlorate (NapEt) are attractive.[4c,4e,9] When π-π interactions are stronger, the ΔH and ΔS values are lower due to an increase in the number of solvent molecules released and more conformational changes imposed on the macrocycle. Steric hindrance may occur between various substituents attached to the host ring and the substituents on the chiral carbon of the guest organic ammonium cation which weakens the overall complex. The chiral crowns studied here have alkyl substituents attached to two chiral positions on the ring. The steric hindrance caused by the host alkyl side chains is the stereospecific interaction required for recognition.

*To whom correspondence should be addressed.

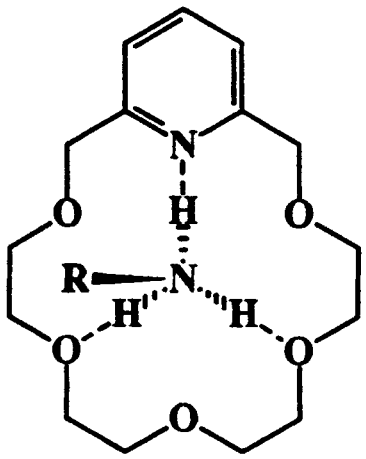

Figure 1 Hydrogen bonding of a primary ammonium ion to pyridino-18-crown-6.

We have reported recognition by dimethyl-substituted (**1**) and di-*t*-butyl-substituted pyridino-18-crown-6 (**5**) (Figure 2) for the enantiomers of various chiral organic ammonium salts.[4b,6,8b]

The recognition, as measured by the Δlog *K* values, is greater for **5** than for **1**, although the absolute log *K* values are less for **5** (Table 1). Both effects, greater recognition and smaller log *K* values, are thought to be a result of the steric hindrance provided by the bulky *t*-butyl substituent of **5**. Since the recognition difference between **1** and **5** was large, the next logical step was to determine if chiral pyridino-18-crown-6 ligands containing dialkyl

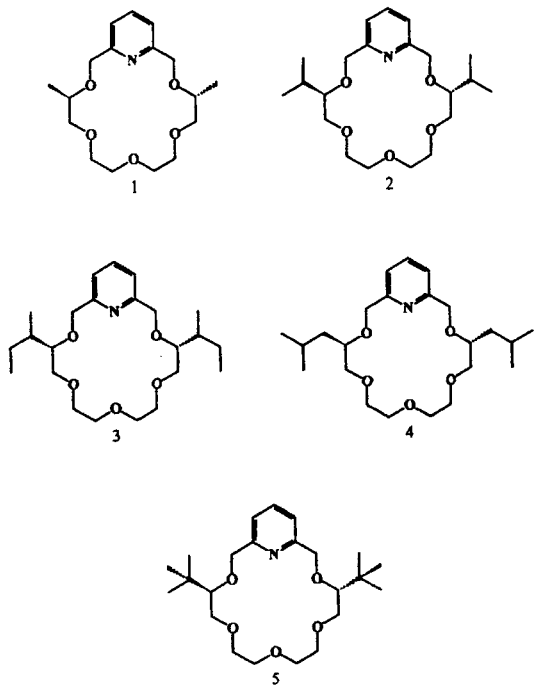

Figure 2 Chiral pyridino-18-crown-6 ligands.

Table 1 Log *K*, Δ*H*, Δ*S*, and Δlog *K* values for the interactions of chiral crown ethers with chiral α-(1-naphthyl)ethylammonium perchlorate (NapEt) in methanol at 25°C

Ligand	*Isomer*	*Log* K	Δ*H* *kJ/mol)*	*TΔS* *kJ/mol)*	*Δlog* K Δ*log* K
(*S,S*)-**1**	*S*	2.76	-22.3	-6.5	0.24
	R	3.00	-29.1	-12.0	
(*R,R*)-**2**	*R*	2.18±0.03	-7.8±0.6	4.6	0.18±0.07
	S	2.36±0.06	-18.8±2.2	-5.4	
(*R,R*)-**3**	*R*	2.05±0.03	-7.2±0.6	4.5	0.42±0.08
	S	2.47±0.07	-7.5±0.8	6.6	
(*R,R*)-**4**	*R*	2.22±0.03	-9.3±0.6	3.3	0.51±0.06
	S	2.73±0.05	-10.0±0.7	5.6	
(*S,S*)-**5**	*S*	0.62	ND[a]	ND[a]	0.71
	R	1.33	ND[a]	ND[a]	

[a]The heat of reaction for 5 with NapEt is too small to be measured accurately in the calorimeter used. The log K values were determined using ^{1}H NMR spectroscopy.

substituents larger than methyl but smaller than *tert*-butyl would exhibit intermediate recognition. The following crown ethers were studied: (4*R*,14*R*)-4,14-di-isopropyl-3,6,9,12,15-pentoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (**2**), (4*R*,14*R*)-4,14-di-*sec*-butyl-3,6,9,12,15-pentoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (**3**), and (4*R*,14*R*)-4,14-di-isobutyl-3,6,9,12,15-pentoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (**4**). This paper discusses the enantiomeric recognition of these chiral dialkyl-substituted pyridino-18-crown-6 ligands (**2–4**) for (*R*)- and (*S*)-NapEt and compares the results with the reported recognition by the dimethyl-substituted (**1**) and di-*tert*-butyl (**5**) analogues. The discussion centers on the log *K*, Δ*H*, and Δ*S* values for these interactions and explores reasons for recognition in terms of solvent and steric interactions.

RESULTS AND DISCUSSION

All of the chiral crowns studied exhibited the typical hydrogen bonding behavior shown in Figure 1.[4e,6,9,10] The N-H···N hydrogen bond is stronger than the N-H···O hydrogen bond, so ammonium ion bonding to the ligand always includes the nitrogen atom of the pyridine ring.[11] Since both enantiomers of NapEt exhibit the same hydrogen bonding pattern, recognition must come from more stereospecific interactions.

The naphthalene group of the ammonium ion and the pyridine group of the crown ether interact by π-π bonding. The optimum orientation of the naphthalene group is directly over the pyridine group, which allows the strongest π-π interaction between the aromatic rings.[4b,4e] For each NapEt enantiomer, there are two possible orientations of the three substituents on NapEt that allow the optimum π-π interaction. For the complex of (*R*)-NapEt with these (*R,R*)-crowns, the guest naphthyl substituent and/or the methyl substituent is directed, in both orienta-

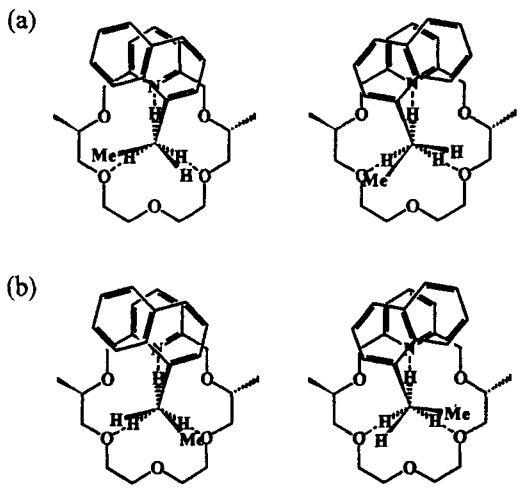

Figure 3 (a) The two possible orientations of (*R*)-NapEt with disubstituted (*R,R*)-pyridino-18-crown-6 which have optimal π-π bonding between the cation and the ligand. (b) The two possible orientations of (*S*)-NapEt with disubstituted (*R,R*)-pyridino-18-crown-6 which have optimal π-π bonding between the cation and the ligand.

tions, toward the host alkyl substituent that lies above the plane of the pyridino-crown as shown in Figure 3(a). For (*S*)-NapEt, the guest naphthyl substituent and/or the hydrogen atom is directed, in both orientations, toward the alkyl substituent that lies above the plane of the macrocycle as shown in Figure 3(b). Since the hydrogen atom on the guest has a smaller van der Waals radius than the methyl substituent, steric hindrance of the alkyl substituent on the (*R,R*)-macrocycle discriminates against (*R*)-NapEt more than (*S*)-NapEt.

The more the host alkyl substituent interferes with the binding of the ammonium ion, specifically by sterically hindering the π-π interaction, the more selectivity the chiral host macrocycle will exhibit toward NapEt as shown by the Δlog *K* values. The order of selectivity provided by the two host alkyl substituents, based on this hypothesis, should be isobutyl (**4**) > *sec*-butyl (**3**) > isopropyl (**2**). This assumes that solvation effects, π-π interaction strengths, hydrogen bond energies, etc. are similar for each enantiomer of the NapEt-macrocycle complex. Table 1 shows that the Δlog *K* values for the crown ethers follow the predicted order. Ligand **4** has two methyl substituents extending from a two-carbon arm. These two methyl substituents are better able to sterically hinder the binding of the (*R*)-NapEt enantiomer than the substituents on **2** and **3**. For the interactions of **4** with NapEt, recognition is mainly due to differences in entropy values (entropy driven). Figure 4 provides a comparison of ΔH and $T\Delta S$ values for these interactions. The ability of the host alkyl substituent to rotate freely even after (*S*)-NapEt is bound increases the ΔS value. When (*R*)-NapEt is bound, the movement of the host alkyl substituent is hindered by the guest naphthyl substituent. The host alkyl substituent cannot come closer than van der Waals distances to the guest naphthyl substituent.[8b] This restriction of rotation is shown by a decrease in the ΔS value, thus decreasing the log *K* value.

Ligand **3**, in comparison, has one ethyl and one methyl substituent extending from a one-carbon arm. Although the ethyl substituent on **3** extends as far as the methyl substituents on **4**, there is only one on **3**. Again, the Δlog *K* value is a result of entropy value differences. The selectivity of these chiral pyridino-crown compounds is directly related to the steric hindrance caused by the host alkyl substituent as measured by the ΔS values. It may

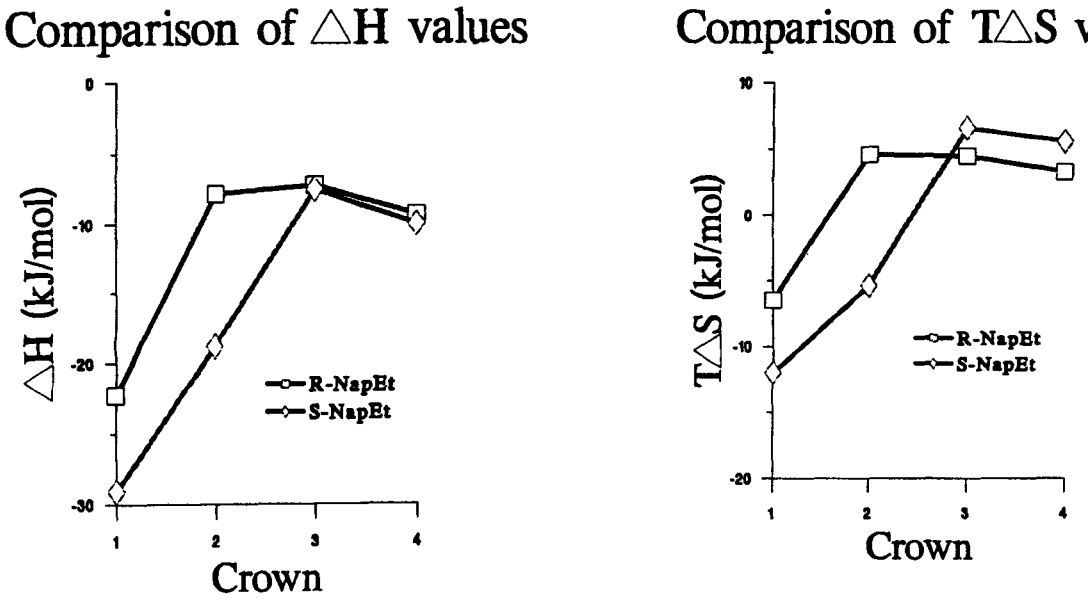

Figure 4 (a) A comparison of the ΔH values for each host/guest interaction. (b) A comparison of the TΔS values for each host/guest interaction.

seem that **5** should have less recognition than **3** and **4** because of the shorter length of the *tert*-butyl substituent. However, **5** has three methyl substituents and no hydrogen atoms attached to its one-carbon arm. The alkyl substituent of **5** may not extend as far as those on **3** or **4**, but the *tert*-butyl substituent will always hinder binding with at least one methyl substituent in any orientation.

We expected **4** to have a much higher $\Delta\log K$ than **3** (Figure 5). Ligand **4** should be able to hinder more since it is bulkier at the end of the chain. However, **4** has two hydrogen substituents on the first carbon attached to the crown, so the steric hindrance is more like the methyl substituent of **1**. Therefore, NapEt is able to bind closer, thus displacing more solvent molecules from the host macrocycle. This explains the slightly larger difference in ΔH values for the interaction of each ammonium ion enantiomer with **4** compared with the difference in ΔH values for those interactions with **3**. The alkyl substituent on **3** has one hydrogen substituent on its first carbon attached to the crown. Thus, it cannot bind NapEt as close as **4** and displace as many solvent molecules, so the ΔH values for the interactions of the (*R*) and (*S*) enantiomers with **3** are more equivalent than those for **4**. This steric effect accounts for the similar $\Delta\log K$ values for these two systems.

Ligand **2** has two methyl substituents extending from a one-carbon arm. Recognition of the enantiomers of NapEt by **2** is due to the large difference in ΔH values (enthalpy driven). Even though the ΔS value for the binding of (*S*)-NapEt to **2** is negative, the ΔH value is negative enough to overcome this decrease in entropy.

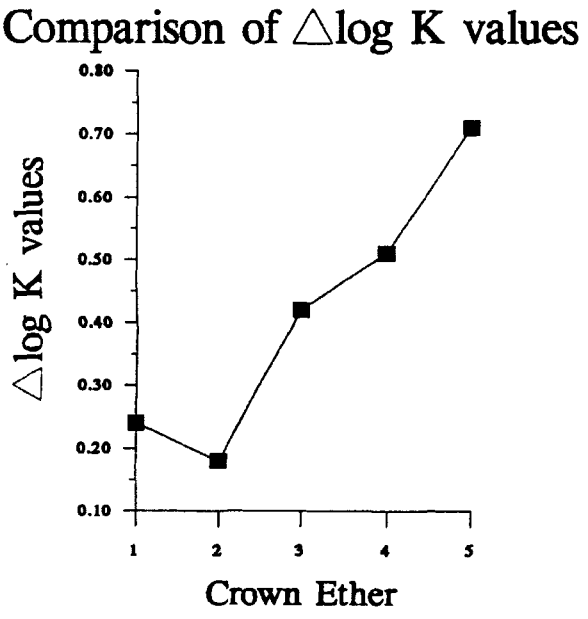

Figure 5 A comparison of molecular recognition ability for each macrocycle as measured by $\Delta\log K$.

This is similar to the interactions of **1** which are also enthalpy driven. NapEt is probably able to bind closer to these less bulky macrocyclic hosts, thereby more effectively removing solvent molecules which is consistent with the decreased ΔS and ΔH values.

CONCLUSIONS

The more bulky alkyl substituents on the crown cause greater recognition by the crown for one enantiomer of NapEt. The selectivity shown by the bulkier dialkyl-substituted crowns arises from the differences in entropy values whereas selectivity by the less bulky dialkyl-substituted crowns is derived from the differences in enthalpy values. NapEt is not able to bind as close when the macrocyclic host contains bulky side chains. This reduces the enthalpy value difference between the enantiomer interactions and the selectivity is based on entropy value differences. The smaller dialkyl-substituted host selectivity is a result of enthalpy differences. This is due to the ability of the enantiomers of guest NapEt to bind closer to the less bulky crown ethers, thus removing more solvent molecules from the host. By studying ΔH and ΔS values in addition to log K values, the processes that occur during complexation can be better understood. This allows for the design and synthesis of ligands which may display superior recognition.

EXPERIMENTAL

The synthesis and purification of chiral macrocycles **2–4** have been reported.[12] (*R*)- and (*S*)-NapEtClO_4 salts were made by treating the free amines (Aldrich) with dilute aqueous perchloric acid (Aldrich) followed by recrystallization from chloroform/acetonitrile mixtures.

The thermodynamic measurements were done using a Tronac model 450 isoperibol calorimeter. The measurements were made in methanol (Aldrich, HPLC) which was used as obtained. The heat of dilution of the ammonium salt into the solvent was substracted from the total heat to determine the reaction heat. The volume of the titrate was 20 mL. The volume of titrant was 1.75 ML. The final molar ratio of ammonium salt to macrocycle was a minimum of 2:1. For each titration, 20 lead points, 100 titration points and 20 trail points were taken. Due to limited amounts of ligands **2** and **4**, only one titration was possible. The calculation of log K, ΔH, and ΔS values was done on a VAX 11/780 computer using programs developed earlier.[13] The greatest error in titration calorimetry involving crown ethers comes from impure crowns. Purities of the macrocycles were determined using a Varian Gemini 200MHz NMR spectrometer. The errors

in the thermodynamic quantities for **2** and **4** were determined by assuming the purity of the macrocycles was accurate to ±5% which is approximately the limit detectable by NMR spectroscopy. The only NMR active impurity detected was the protonated macrocycle, which does not complex or interfere with the unprotonated ligand.

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