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Molecular Recognition as Shown by the Solvent Extraction of (*R*)- and (*S*)-[α-(1-Naphthyl)ethyl] ammonium Picrate or Orange 2 by Chiral Pyridino-Crown Ethers

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Abstract. A solvent extraction technique was used to determine equilibrium constants for the reactions occurring when an aqueous phase containing [α-(1-naphthyl)ethyl]ammonium ions [(*R*)- and (*S*-isomers] is equilibrated with a chloroform phase containing chiral substituted pyridino-18-crown-6 ligands. Selectivity coefficients and equilibrium constants for the interactions in chloroform solutions were calculated. The existence of two different types of ion pairs separated by the macrocycle molecule was detected from the UV spectra. One ion pair has a nearly complete separation of the picrate anion from the protonated amine by the ligand. The other has the picrate ion only partly separated from the cation by the macrocycle.

Key words: Pyridino-18-crown-6, chiral recognition, solvent extraction equilibrium constants.

1. Introduction

Although solvent extraction of metal ions with crown ethers has been studied extensively, few investigations involving the solvent extraction of organic cations with crown compounds have been reported. Amines and amino acids have been extracted into dichloroethane or chloroform as protonated cations using picrate [1, 2], Methanil Yellow [3, 4] or Orange 2 [2, 5] as counter-ions. The selectivity of crown ethers for various types of amines could be improved by making use of results obtained by the solvent extraction method [1, 5].

We report here the solvent extraction of (*R*)- and (*S*)-[α-(1-naphthyl)ethyl] ammonium picrate (NapEtHPic) from water to chloroform with several chiral

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pyridino-crown ether ligands. Picrate ion was selected as the counter ion because of its absorptivity in the near UV region and also because it is convenient to compare the results with data from many other picrate salts studied earlier. For ligands with a large absorbance in the near UV region, the Orange 2 anion was used instead of picrate.

2. Experimental Section

Crown ethers **1–9** were synthesized and purified as described previously [6, 7]. (*R*)- and (*S*)-isomers of [α-(1-naphthyl)ethyl]ammonium ion ($NapEtH^+$) were used as the perchlorate salts. Standard solutions of macrocycles in chloroform and $NapEtHClO_4$ in water were used. A phosphate buffer [8] at a pH of 5.8 and with total phosphate concentration of 0.05 mol/L was used in all experiments. Orange 2 [4-(2-hydroxy-1-naphthylazo)benzenesulfonic acid, sodium salt] was recrystallized from ethanol before use.

A typical extraction procedure was as follows: 2 mL of an aqueous solution containing 0.5–3 $\times$ 10^{-4} M sodium picrate (or Orange 2), 1–3 $\times$ 10^{-4} M $NapEtHC1O_4$ and buffer solution was mixed with 2 mL of chloroform containing 1–5 $\times$ 10^{-4} M of the crown compound. After equilibrium had been reached (about 5 min), the absorbance in the organic phase at 320–460 nm was measured. This value was corrected in all cases by a blank experiment involving the absorbance of the same solutions, but without crown compound or ammonium salt (NapEtHPic). The amine-containing macrocycles form very weak complexes with the alkali metal ions so that ammonium salt extractions can be studied in sodium-containing solution. This extraction process was carried out 6–10 times for the determination of each equilibrium constant. The experiment was carried out with both (*R*)- and (*S*)-isomers of NapEtHPic simultaneously at nearly the same concentrations to reduce possible errors in selectivity coefficients. The temperature at each experimental point was measured with a precision of $\pm$0.2 K.

3. Results and Discussion

3.1. Equilibria in the Two-Phase System

When an aqueous phase of $NapEtHClO_4$ and picrate ion (R^-) is equilibrated with a chloroform phase containing crown ether (L), the equilibrium constants may be defined by the following equations

$$K_1 = [\text{NapEtHLR}]_o/[\text{NapEtH}^+]_{aq}[\text{L}]_o[\text{R}^-]_{aq} \quad (1)$$

$$P_1 = [\text{NapEt}]_o/[\text{NapEt}]_{aq} \quad (2)$$

$$P_2 = [\text{L}]_o/[\text{L}]_{aq} \quad (3)$$

$$P_3 = [\text{HR}]_o/[\text{HR}]_{aq} \quad (4)$$

$$K_5 = [H^+]_{aq}[R^-]_{aq}/[HR]_{aq} \tag{5}$$

$$K_6 = [H^+]_{aq}[L]_{aq}/[HL^+]_{aq} \tag{6}$$

$$K_7 = [H^+]_{aq}[NapEt]_{aq}/[NapEtH^+]_{aq}. \tag{7}$$

Where K_1 is the overall extraction constant, P_1–P_3 are the corresponding partition constants, and K_5–K_7 are acid dissociation constants. The subscripts 'o' and 'aq' refer to the organic and aqueous phases, respectively.

The extraction of NapEtHR may be described by the following

$$K_2 = [NapEtHR]_o/[NapEtH^+]_{aq}[R^-]_{aq} \tag{8}$$

and the reaction for complex formation in chloroform solution may be written

$$NapEtHR_o + L_o = NapEtHLR_o.$$

It is important to emphasize that this latter equilibrium does not depend on processes in the aqueous phase. The equilibrium constant corresponding to complex formation in the organic phase is as follows

$$K_3 = [NapEtHLR]_o/[NapEtHR]_o[L]_o \tag{9}$$

$$K_3 = K_1/K_2. \tag{10}$$

At the conditions of our experiment (pH = 5.8), the concentrations of HL^+ and HR in the aqueous phase can be neglected. As a result, only equations (1), (2), (7) and (9) are significant for further consideration. The following expression is valid for the protonated amine concentration

$$[NapEtH^+]_{aq} = C_{NapEt}[H^+]/(K_7P_1 + [H^+])$$

where C is the total concentration of uncomplexed NapEt.

The conditional extraction constants K_{c1} and K_{c2}

$$K_{c1} = [NapEtHLR]_o/C_{NapEt}[L]_o[R^-]_{aq} = K_1[H^+]/(K_7P_1 + [H^+]) + [H^+])$$

$$K_{c2} = [NapEtHR]_o/C_{NapEt}[R^-]_{aq} = K_2[H^+]/(K_7P_1 + [H^+]) + [H^+])$$

can be used instead of K_1 and K_2 at constant pH. The equilibrium constant for complex formation in the organic phase is also the ratio of these constants

$$K_3 = K_{c1}/K_{c2}$$

TABLE I. Extraction constants K_2 for NapEtHR complexes, at 25 °C (standard deviation in parentheses).

Anion, R	pH	I	Log K_{c2}	2 × Log f[a]	Log (K_2/K_{c2})[b]	log K_2 [c]
Picrate	3.0	0.001	2.03(3)	0.03	0.00	2.06
	5.8	0.05	1.80(4)	0.16	0.17	2.13
Orange 2	3.0	0.001	3.07(10)	0.03	0.00	3.10
	5.8	0.02	2.84(4)	0.11	0.17	3.08

[a]Activity coefficient from the Davies equation.
[b]Correction term on unprotonated form of NapEt.
[c]Corrected using activity coefficients.

The selectivity of the solvent extraction process can be described by the selectivity coefficient

$$k_{R/S} = K_1(R)/K_1(S) = K_{c1}(R)/K_{c1}(S) = K_3(R)/K_3(S)$$

where (R) and (S) designate the constants for the R- and S-isomers of NapEt, respectively (The dissociation constant K_7 and partition constant P_1 are assumed to be the same for both isomers).

The resulting K_1 and K_2 values must also be corrected for the activity coefficients of $NapEtH^+$ and R^- ions in the aqueous phase at a given ionic strength. For the comparatively low $I = 0.05$ used herein, one can calculate activity coefficients using the Davies equation.

The corrections for the free amine formation and for the activity coefficients are the same for both K_1 and K_2. In order to check the correction terms, K_2 was measured directly at low ionic strength conditions ($I = 0.001$) at a pH of 3.0 where no significant amount of deprotonated amine was present. The results of these experiments are presented in Table I. The agreement of the log K_{c2} and log K_2 values at pH 3.0 confirms that both approaches yield similar K values within a reasonable standard deviation.

The conditional equilibrium constants and selectivity coefficients obtained for reaction (1) as well as log K_1 and log K_3 values are given in Table II.

The log K_1 values for complexes of tetramethyl-substituted **1** with (R)- and (S)-$NapEtH^+$ were the same within a narrow standard deviation. Dimethyl-substituted chiral diester crown **3** exhibited recognition for the R enantiomer over the L enantiomer of $NapEtH^+$ as shown by the log $k_{R/S}$ value of 0.47 (Table II). This value is very near the Δ log K value (0.42 in CD_3OD and 0.44 in $CD_3OD/CDCl_3$:1/9) determined by the ^{1}H-NMR technique [7]. Substitution of sulfur atoms for the carbonyl oxygens of **3** to form **2** gave a slight decrease in log K_1 as well as in selectivity (log $k_{R/S}$ = 0.38). Chiral ligands **4** and **7** exhibited no extractive selectivity for the enantiomers of $NapEtH^+$ as was also observed by the ^{1}H-NMR technique [6d, 7]. Chiral ligands **5**, **6** and **8** exhibited the largest log K_1 values and

TABLE II. Equilibrium constants for the reaction $NapEtH^+_{(aq)} + R^-_{(aq)} = NapEtHL^+R^-$ in a water–chloroform system at 25 °C (pH = 5.8, I = 0.05)[a]

Ligand	Log K^c_{c1}	Log K^c_{c1}	Log $k_{R/S}$	Log K^d_1	Log K^d_1	Log K^e_3	Log K^e_3
	(*R*)-	(*S*)-		(*R*)-	(*S*)-	(*R*)-	(*S*)-
1	6.39(5)	6.39(5)	0.00(7)	6.7	6.7	4.6	4.6
2	5.80(6)	5.42(5)	0.38(8)	6.1	5.7	4.0	3.6
3	6.13(3)	5.65(3)	0.47(5)	6.5	6.0	4.3	3.8
4	5.60(3)	5.59(4)	0.01(5)	5.9	5.9	3.8	3.8
4[b]	5.42(3)	5.41(5)	0.01(7)	5.7	5.7	2.6	2.6
5	7.64(4)	7.33(5)	0.31(7)	8.0	7.7	5.8	5.5
6	7.72(4)	7.30(6)	0.42(7)	8.1	7.6	5.9	5.5
7	4.48(3)	4.48(3)	0.00(4)	4.8	4.8	2.6	2.6
8	6.97(4)	6.50(5)	0.47(7)	7.3	6.8	5.2	4.7
8[b]	6.55(3)	6.14(9)	0.41(10)	6.8	6.4	3.7	3.3
9[b]	5.16(5)	4.9(1)	0.2(1)	5.4	5.2	2.3	2.1

[a]Standard deviation in parentheses.
[b]Value for Orange 2 complex, otherwise R = picrate ion.
[c]K_{c1} is a condition-specific equilibrium constant.
[d]Log K_1 values are corrected for ionic strength using the Davies equation.
[e]Log K_3 values are for chloroform saturated with water during the extraction process.

were selective with log $k_{R/S}$ values of 0.31, 0.42 and 0.47, respectively. These selectivity coefficients compare favorably with Δ log K values for single phase systems calculated from ^{1}H-NMR data i.e., for **5** the Δ log K value obtained in CH_3OH is 0.24 [7], and for **6** the Δ log K value obtained in $CD_3OD/CDCl_3$ (1/1, v/v) is 0.35 [7]. Chiral ligand **9** was intermediate, with a log $k_{R/S}$ value of 0.2. The large size of the S atoms in **9** compared to the O atoms in **7** may account for the small selectivity observed.

The use of Orange 2 instead of picrate increased log K_2 (Table I) but slightly decreased log K_1 (Table II). The reason for this latter decrease may be steric repulsion between the comparatively large sulfonate group of the anion and the macrocycle molecule or, perhaps, from a greater stability of the ion pair. The selectivity coefficients when using Orange 2 (Table II) are similar to those with picrate.

3.2. UV Spectra

The UV spectra of NapEtH–picrate in chloroform exhibited two maxima at 344 and 403 nm. One can see more details from the second derivative spectra (see Figure 2a, curve 1). Two minima, 345 and 415 nm (not shown), correspond to a maxima in the usual UV spectrum, and belong to the contact ion pair (CIP) of [NapEtH–picrate]. The band at 345 nm, see Figure 2a, curve 1, was used for the discussion of the structure of the ion pair. Interaction of this contact ion pair with

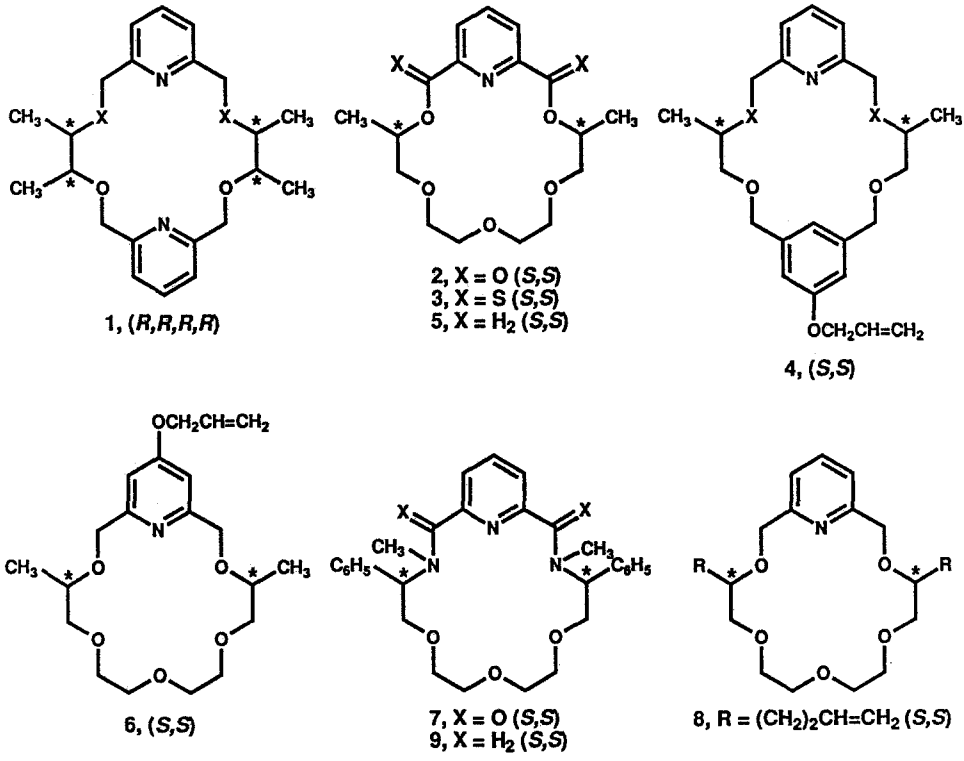

Fig. 1. Chiral macrocyclic ligands used in this study.

the macrocycle leads to significant changes in the spectrum. These changes are sensitive to the structure of the macrocycle-amine cation complex.

The existence of two different types of ion pairs separated by macrocycle molecules was detected from the UV spectrum (Figure 2a,b). The first ion pair type is a nearly complete separation of the picrate anion from the protonated amine by the ligand (Ligand Separated Ion Pair, LSIP). In the other, the picrate ion is only partly separated from the cation by the macrocycle (Partly Separated Ion Pair, PSIP). In the spectrum of the complex, one can find a band at 378–380 nm which corresponds to an LSIP ion pair [NapEtH$^+$L–picrate] (Figure 2a, curves 2–4). The equilibrium constant was not dependent on complex concentration, which confirms the absence of dissociation of the ion pairs under these conditions. The other band at 363 nm may be caused by another ion pair (perhaps the PSIP), as well as the band at 356 nm (for **7**, see Figure 2a, curve 4). These 356 and 363 nm bands are weaker for complexes which exhibited good recognition (e.g., **5** and **6** compared to **7** – see Figure 2a). This is not a general rule. For complexes with **1**, these bands are weak but there is no enantiomer recognition. Similar ion pairs were observed

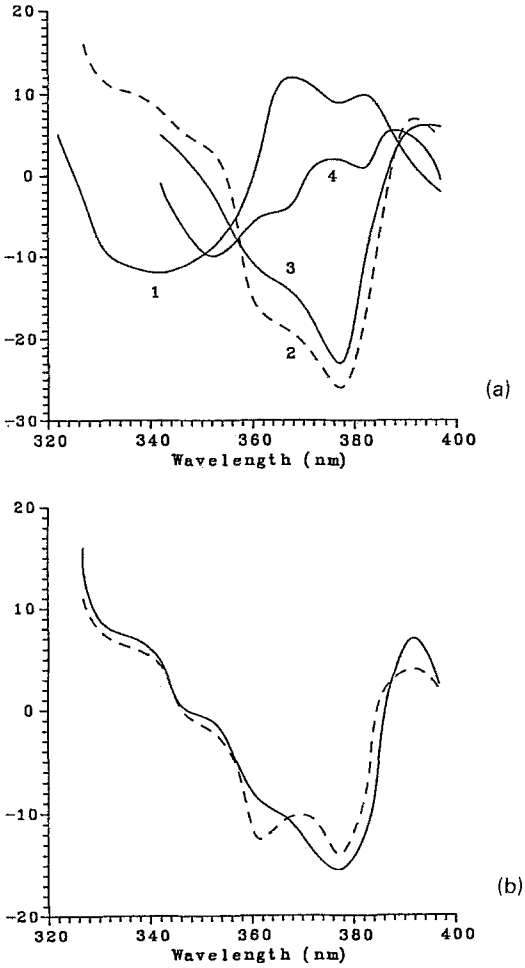

Fig. 2. Second derivative spectra of picrate ion in ion pairs in chloroform saturated with water. (a) 1 = [NapEtH–picrate]; 2 = [(*R*)-NapEtyH–**5**–picrate]; 3 = [(*R*)-NapEtH–**6**–picrate]; and 4 = [(*S*)-NapEtH–**7**–picrate]. (b) solid line = [(*R*)-NapEtH–**8**–picrate] and dashed line = [(*S*)-NapEtH–**8**–picrate].

for the metal picrate and amine picrate complexes with non-chiral crown ethers in chloroform [2].

Interaction of the chiral macrocycles with the $NapEtH^+$ cation is different for the (*R*)- and (*S*)-enantiomers so small changes in the picrate ion spectrum were observed. For example, one can see differences between (*R*)- and (*S*)-isomer complexes with **8** (Figure 2b). The intensity of the PSIP band at 363 nm is slightly higher for the NapEtH-(S) complex. This is in good agreement with a weaker interaction of the macrocycle with (*S*)-$NapEtH^+$ cation and, as a result, a lower K_3 value (Table II).

In general, the best recognition was obtained for complexes which are mainly LSIP ion pairs. Those complexes which are characterized by PSIP complexes (**4** and **7**) exhibited no resolution of the (*R*)- and (*S*)-isomers. In these cases, the macrocycle molecule only solvated the existing CIP pair [NapEtHR] forming PSIP and the interaction of macrocycle asymmetric fragments with the amine was weak. The requirement of complete separation is necessary but not enough for chiral recognition. In the [NapEtH–**1**–picrate] spectrum, we observed a strong band at 370 nm for the LSIP but no chiral recognition (see Table II). In this case, there are two possible orientations for the chiral ammonium ion which causes a loss in recognition.

The Orange 2 anion is coordinated to cations by the sulfonate group, resulting in separation of the dye chromophore and cationic complex. Therefore, the macrocycle did not influence the spectra of Orange 2 compounds.

3.3. Temperature Effects on Equilibria

Neglecting the temperature dependence of the reaction enthalpy, one can estimate the ΔH values from the van't Hoff plot of log K vs T^{-1} (see Figure 3). The measurements of such dependencies for picrate complexes gave enthalpy changes of -6 ± 1 kcal mol^{-1} from log K_{c2} and -20 ± 2 kcal mol^{-1} [NapEt–(*R*)–**8**] and -18 ± 2 kcal mol^{-1}[NapEt–(*S*)–**8**] from log K_{c1}. The values obtained for macrocyclic cation extraction are similar to those observed for the extraction of alkali metal cations in chloroform with 18-crown-6 [9] using a similar procedure. The standard deviation of the ΔH calculated by this procedure is comparatively high but the precision is enough to estimate that the effect on recognition is mostly enthalpic.

4. Conclusion

In the ligand separated ion pair [NapEtH$^+$ *L*-*R*$^-$], a protonated amine cation is bonded to the macrocycle with three hydrogen bonds, one of which is directed to the pyridine nitrogen atom [6c]. These bonds fix the geometry of the complexed cation, and they are nearly the same for both enantiomers. As a result, the weak van der Waals interactions remain the main source of chiral recognition. The low total energy of recognition which was observed in the present study (Δ (log $k_{R/S}$) $\sim$ 0.4 to *0.5* and ΔH about 1 kcal mol^{-1}) confirms this explanation. In general, it is difficult to expect a much higher recognition for chiral amines without the substitution of functional groups on the macrocycle.

In the case of two pyridine groups (macrocycle **1**), there are two possible orientations of the chiral ammonium ion leading to a loss in recognition. In partly separated ion pairs, the direct interaction of the protonated amine with the anion makes the contact between chiral species weak, resulting in poor recognition. The

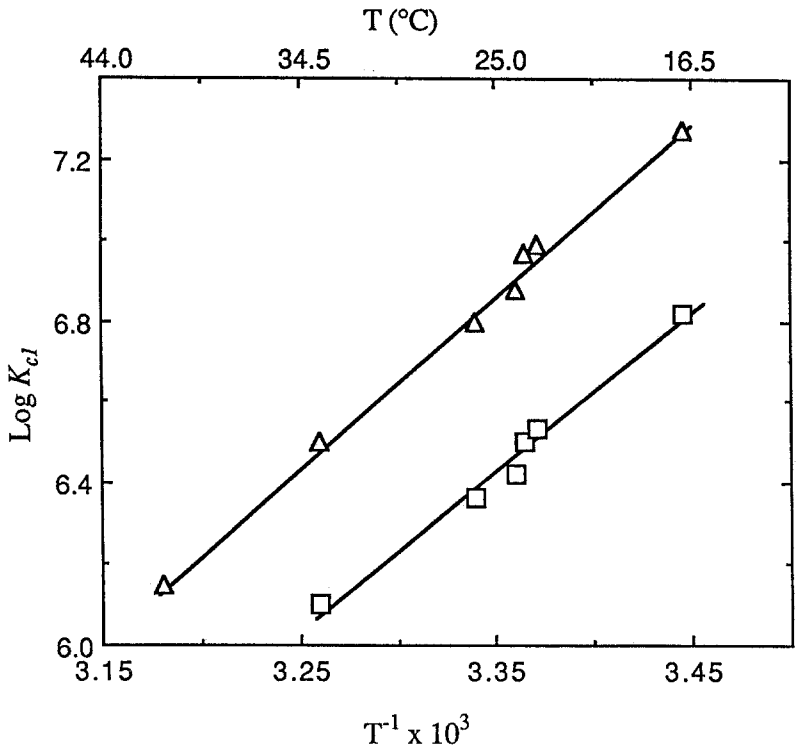

Fig. 3. Plot of log K_1 vs. $T^{-1} \times 10^3$, for the reaction: $NapEtH^+_{(aq)} + L_{(o)} + R^-_{(aq)} = NapEtHLR_{(o)}$, Equation 1. Δ = R-$NapEtH^+$, □= S-$NapEtH^+$.

procedure used in this study appears to be a convenient and simple technique to study chiral recognition using small amounts (ca. 1–3 mg) of ligand.

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