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Synthesis of chiral monoaza-15-crown-5 ethers from L-valinol and the enantiomeric recognition of chiral amines and their perchlorates salts

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Abstract—A practical synthesis of chiral monoaza-15-crown-5 ethers **1** and **2** has been achieved from L-valinol. The molecular recognition by these chiral crown ethers for (*RS*)-α-phenylethylamine, (*RS*)-α-(1-naphthyl)ethylamine and their perchlorate salts has been characterized by UV–vis.

1. Introduction

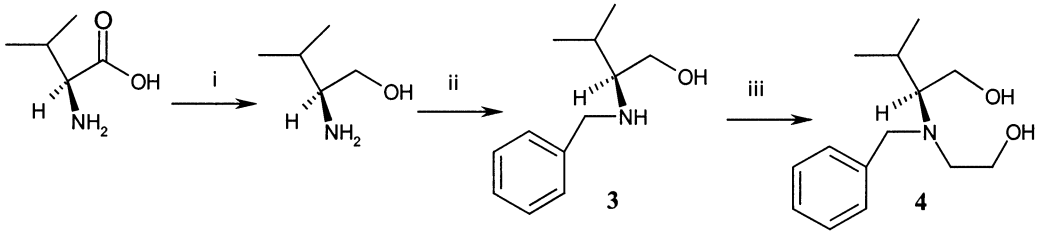
The design, synthesis, and use of macrocycles capable of selective recognition of other molecules is of great interest in a variety of fields. Various types natural and synthetic chiral compounds have been used as chiral subunits for constructing optically active crown ethers, and continuing development of chiral building blocks has resulted in the production of a wide variety of optically active crown ethers exhibiting characteristic chiral recognition behavior.[1] Cram et al. first described in 1973 the syntheses and characterization of a number of chiral crown ethers capable of enantiomeric recognition towards primary ammonium salts.[2,3] Since then, the study of enantiomeric recognition by crown ethers and other molecules blossomed.

There has been continuing interest in the molecular recognition of amino acids esters, amino acids potassium and sodium salts and ammonium perchlorate salt[4] by NMR, UV–vis, extraction and transport experiments.[5–7] Here, we report a practical synthesis of chiral amino alcohol precursors, two chiral monoaza crown ethers, their enantiomeric recognition, the binding constants (K_a) and free-energy chances ($-\Delta G°$) for the enantiomers of (*RS*)-phenylethylamine, (*RS*)-α-(1-naphthyl)ethylamine and their perchlorate salts determined by UV–vis titration method in $CHCI_3$.

2. Results and discussion

2.1. Synthesis

The synthesis of L-valinol was accomplished in one step from L-valine according to procedures described in the literature.[8] The conversion of L-valinol to *N*-benzyl amino alcohol derivatives was carried out by our previ-



Scheme 1. *Reagents and conditions*: (i) $NaBH_4$–I_2, THF; (ii) $PhCH_2CI$, Na_2CO_3, 110°C, (iii) ethylene oxide, MeOH, –20°C.

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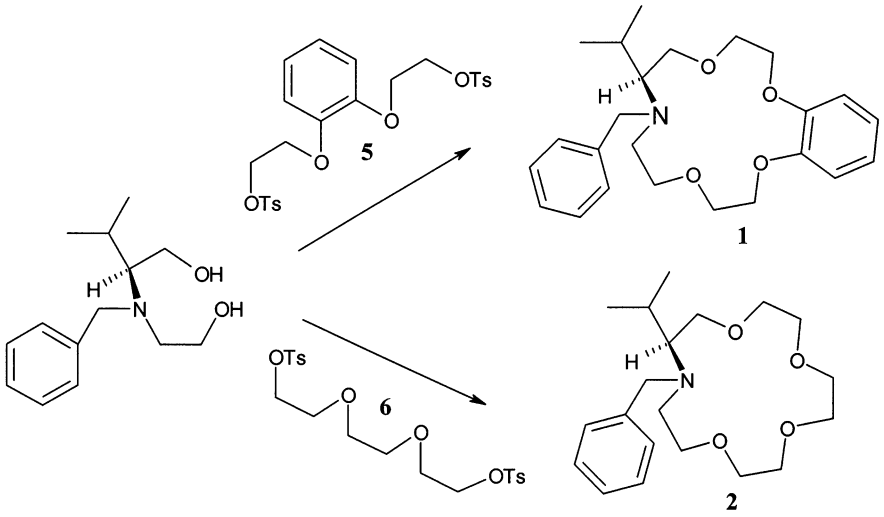


Scheme 2. *Reagents and conditions*: NaH, THF, reflux, 50 h.

ous method.[9] The conversion of **3** to **4** was carried out at −20°C, as shown in Scheme 1. Chiral macrocycles **1** and **2** were prepared in the 47, 33% yields, respectively, as shown in Scheme 2. Tosylates **5** and **6** were prepared according to the reported procedure.[9,10] Crown ether **1** was obtained as white solid (mp 81–82°C) and crown **2** was isolated as a yellow oil. The structures proposed for these new chiral macrocycles and amino alcohols are consistent with data obtained from ^{1}H, ^{13}C NMR, IR spectra and elemental analyses.

2.2. UV–vis

UV–vis spectroscopy is a convenient and widely used method for the study of binding phenomena. When the receptor (or substrate) absorbs light at different wavelengths in free and complexed states, the differences in ultraviolet spectrophotometry may suffice for estimation of molecular recognition. In the UV spectroscopic titration experiments, addition of varying concentrations of guests molecules resulted in gradual increase or decrease of characteristic absorptions of the host molecules. The typical UV spectral changes upon the addition of (*R*)-NapEtHClO$_4$ to **1** are shown in Figure 1.

The association constant of supramolecular system formed were calculated according to the modified Benesi–Hildebrand equation, Eq. (1),[11] where $[H]_o$ and $[G]_o$ refer to the total concentration of crown ether and free chiral amine or their perchlorate salt, respectively, $\Delta\varepsilon$ is the change in molar extinction coefficient between the free and complexed crown ether and ΔA denotes the absorption changes of crown ether on addition of free amine or perchlorate salts (Scheme 3).

$$[H]_o[G]_o/\Delta A = 1/K_a\Delta\varepsilon + [G]_o/\Delta\varepsilon \quad (1)$$

The binding constants (K_a) and free-energy changes ($-\Delta G°$) of these hosts with guest molecules obtained from usual curve fitting analyses (R>0.9651) of observed K_a values and $-\Delta G°$ changes are summarized in Table 1. Typical plots are shown for the complexation of **1** with (*R*)-PhEtHClO$_4$ in Figure 2.

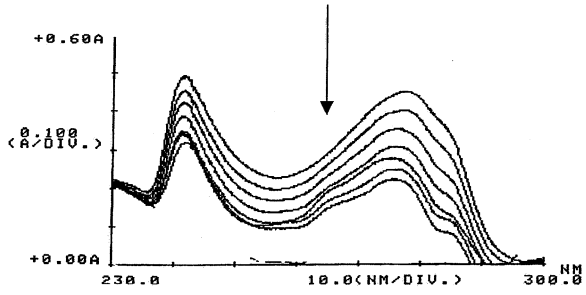


Figure 1. UV–vis spectra of **1** (1.4×10^{-4} mol dm^{-3}) in the presence of (*R*)-NapEtHClO$_4$ (5.0×10^{-5}–1.1×10^{-3} mol dm^{-3}).

It should be equally true that the variation of guest structure will also affect the extent of enantiomeric recognition displayed by a given ligand and stability of the complex formed between the guest and the given ligand.

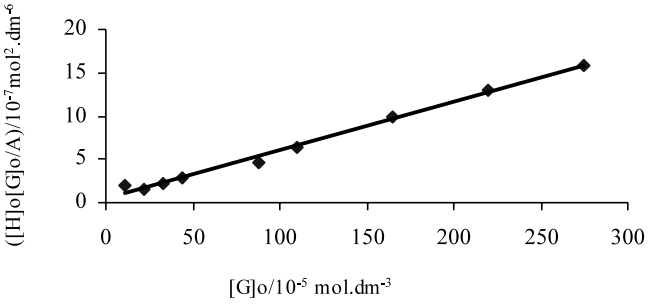
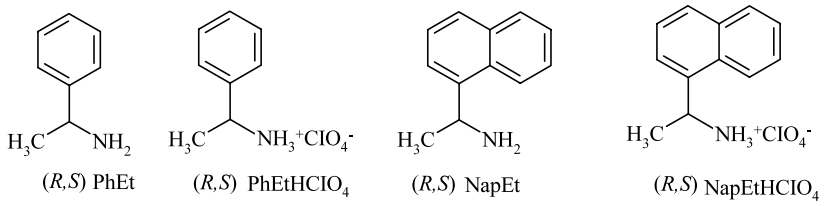


Figure 2. Typical plot of $[H]_o[G]_o/\Delta A$ versus $[G]_o$ for the host–guest complexation of **1** and (*R*)-PhEtHClO$_4$ in CHCl$_3$.

The data in Table 1 show that important differences were not observed in the K_a values for **1** in the enantiomeric recognition of (*R*)-PhEt and (*S*)-PhEt. On the other hand, the K_a values for its perchlorate salt were found to be significantly different. It can be concluded that **1** has a greater recognition ability against (*R*)-PhEtHClO$_4$, also in the case of (*R*)- and (*S*)-



Scheme 3. Chiral amine and their perchlorate salts.

Table 1. Binding constants (K_a) and free energy of complexation ($-\Delta G^o$) for 1:1 complexes between **1**, **2** and chiral amines and their perchlorate salts

Host	Guest	K_a (dm^3 mol^{-1})	$-\Delta G°$ (kJ mol^{-1})
1	(*R*)-PhEt	$(6.5\pm0.022)\times10^3$	5.29×10^3
	(*S*)-PhEt	$(7.0\pm0.042)\times10^3$	5.33×10^3
	(*R*)-PhEtHClO$_4$	$(1.2\pm0.050)\times10^4$	5.65×10^3
	(*S*)-PhEtHClO$_4$	$(6.6\pm0.043)\times10^3$	5.30×10^3
	(*R*)-NapEt	$(1.0\pm0.038)\times10^3$	4.16×10^3
	(*S*)-NapEt	$(5.0\pm0.065)\times10^3$	5.13×10^3
	(*R*)-NapEtHClO$_4$	$(3.0\pm0.054)\times10^3$	6.21×10^3
	(*S*)-NapEtHClO$_4$	$(3.3\pm0.054)\times10^4$	6.27×10^3
2	(*R*)-PhEt	$(2.7\pm0.052)\times10^3$	4.77×10^3
	(*S*)-PhEt	$(3.0\pm0.010)\times10^3$	4.82×10^3
	(*R*)-PhEtHClO$_4$	$(4.5\pm0.070)\times10^3$	5.06×10^3
	(*S*)-PhEtHClO$_4$	$(1.4\pm0.033)\times10^3$	4.36×10^3
	(*R*)-NapEt	$(1.1\pm0.07)\times10^3$	4.25×10^3
	(*S*)-NapEt	$(1.0\pm0.054)\times10^3$	4.16×10^3
	(*R*)-NapEtHClO$_4$	$(1.6\pm0.034)\times10^2$	3.06×10^3
	(*S*)-NapEtHClO$_4$	$(5.0\pm0.014)\times10^3$	5.13×10^3

NapEtHClO$_4$ salts, the (*S*) forms are recognized more than the (*R*) forms. Enantiomeric recognition for the homochiral forms of (*R*)-PhEtHClO$_4$ and (*S*)-NapEtHClO$_4$ free energy values are greater than other measured forms values. Thus, as predicted, phenyl substituent provides sufficient steric hindrance that one of the enantiomeric guest is recognized over the other form.

By comparison with the binding constant for **2**, it can be seen that recognition against (*R*)-PhEtHClO$_4$ is much better than (*S*)-form of its salts. However, the binding constant for (*R*)-NapEtHClO$_4$ is quite small relative to (*S*)-NapEtHClO$_4$.

In conclusion, by comparison of **1** and **2** in the ring of **1**, the π–π interaction overlap between the naphthyl and phenyl group of (*S*)-NapEtHClO$_4$ and (R)-PhEtHClO$_4$ respectively, and benzo unit of **1** is evidently not absolutely necessary to cause good chiral recognition, but π–π interactions may contribute to enantiomeric recognition when present.

3. Experimental

3.1. General information

All chemicals were reagent grade unless otherwise specified. L-Valine was purchased from Fluka chemical company. Silica gel 60 (Merck, 0.040–0.063 mm) and silica gel/TLC- cards (F254) were used for flash column chromatography and TLC. Melting points were determined with a Gallenkamp Model apparatus with open capillaries. Infrared Spectra were recorded on a Mattson 1000 FTIR model spectrometer. Elemental analyses were performed with a Carlo-Erba 1108 model apparatus. Optical rotations were taken on a Perkin–Elmer 341 model polarimeter. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker DPX-400 High Performance Digital FT-NMR Spectrometer.

3.2. UV spectral measurements

The abilities of crown ethers to coordinate to free amines and their perchlorate salts were investigated using UV spectroscopic titration.[12] The UV–vis spectra were measured at 30±0.1°C with thermostated cell compartment by Shimadzu 160 UV spectrometer. The same concentration of guest solution were added to the sample cell and reference cell. The maximum wavelengths are 241.5 and 277.4 nm for **1,** 242.8 nm for **2**. $CHCl_3$ was used as the solvent. The concentration of the hosts are 5.0×10^{-5}–1.1×10^{-3} mol dm^{-3} with the increasing concentration of the added guest.

3.3. (*S*)-*N*-Benzyl-2-amino-3-methyl-1-butanol 3

S-Valinol (33 g, 0.32 mol), benzyl chloride (10.13 g, 0.08 mol) and anhydrous Na_2CO_3 (8.48 g, 0.08 mol) were placed in a 250 mL two-necked round bottomed flask equipped. The mixture was stirred at 110°C for 12 h under dry N_2. Then the mixture was cooled and $CHCl_3$ (150 mL) was added to the mixture and refluxed for 2 h. The $CHCl_3$ layer was separated from the solid phase. The solid phase was re-extracted with $CHCl_3$ (3×150 mL). The combined organic phase were dried over anhydrous $MgSO_4$, filtered and evaporated, The product was then distilled under reduced pressure to give 12 g (78%); bp 110–112°C/0.8 mmHg, $[\alpha]_D^{20}$ −10.5 (*c* 1, MeOH), IR: *ν* 3397, 3095, 3070, 3024, 2960, 2877, 1612, 1503, 1464, 1406, 1375, 1162, 1060, 918, 874, 739 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 0.87–1.02 (m, 6H), 1.86–1.91 (m, 1H), 2.44–2.48 (m, 1H), 3.39–3.44 and 3.62–3.65 (dd, 2H), 3.74–3.81(dd, 2H), 7.23–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) *δ* 18.86, 19.84, 29.09, 52.04, 60.98, 64.29, 127.42, 128.84, 140.97. Anal. calcd for $C_{12}H_{19}NO$: C,70,61; H, 9.84; N, 7.25. found: C, 70.50; H, 9.80; N, 7.00.

3.4. (*S*)-*N*-Benzyl-4-hydroxymethyl-3-aza-5-methyl-hexane-1-ol 4

A solution of **3** (20 g, 0.01 mol) in 250 mL methanol was cooled to −20°C in a 100 mL flask. Ethylene oxide (3.8 mL, 0.1 mol) in 10 mL of methanol was added to the solution drop wise at −20°C. The mixture was kept at −20°C during addition in deepfreeze. After addition the mixture was stirred for 24 h at −20°C and 24 h at +4°C. The mixture was kept for one day at rt in a closed flask. Methanol was evaporated in rotary evaporator. The product was purified by distillation under reduced pressure to give 21 g (89%); bp 160–162°C/0.8 mmHg; $[\alpha]_D^{20}$ −14.9 (*c* 1, MeOH), IR: *v* 3352, 3070, 3024, 2973, 1956, 1599, 1490, 1464, 1375, 1157, 1053, 913, 746, 701 cm^{-1}; ^1H NMR ($CDCI_3$) δ 0.86–1.07 (m, 6H), 1.85–1.91 (m, 1H), 2.50–2.56 (m, 1H), 2.80–2.92 (m, 2H), 3.55–3.44 and 3.63–3.69 (m, 4H), 3.37–3.91 (dd, 2H) 7.20–7.36 (m, 5H); ^{13}C NMR ($CDCI_3$) δ 22.45, 29.18, 55.90, 60.89, 61.14, 68.89, 77.38, 77.70, 127.44, 128.83, 129.23, 141.14. Anal. calcd for $C_{14}H_{23}NO_2$: C, 70.89; H, 9.70; N, 5.91, found: C, 70.95; H, 9.70; N, 5.95.

3.5. (*S*)-2-Isopropyl-*N*-benzyl-4,7,10,13-tetraoxa-8,9-benzo-1-azacyclopentadec-8-ene 1

To a suspension of NaH (2.52 g, 0.084 mol, % 80 in mineral oil) in 100 mL dry THF at 0°C was added a solution of diol **4** (5 g, 0.021 mol) in 250 mL of THF. The reaction mixture was refluxed for 2 h. The reaction after cooling to 0°C, a solution of **5** (10.67 g, 0.021 mol) in 250 mL of THF slowly added. The suspension was refluxed for 50 h. The solvent was evaporated and 100 mL of water was added to the residue. The mixture was extracted with CH_2CI_2 (3×150). The combined organic layers were washed with 100 mL water again, dried on anhydrous Na_2SO_4 and the solvent was evaporated. The crude product was purified by flash column chromatography on silica gel (eluent: triethylamine/ethyl acetate/petroleum ether 60–80 = 3/17/80) to give 4 g (47%); mp 81–82°C, $[\alpha]_D^{20}$ −26.3 (*c* 1, $CHCI_3$), IR: *v* 3070, 3037, 2960, 1606, 1503, 1458, 1368, 1323, 1259, 1208, 1118, 1047, 938, 790, 758, 732, 701,617 cm^{-1}; ^1H NMR ($CDCI_3$) δ 0.90–1.02 (dd, 6H), 1.97–2.38 (m, 2H), 3.01–3.07 (m, 2H), 3.70–4.17 (m, 14H), 6.89–6.92 (m, 4H), 7.23–7.35 (m, 5H); ^{13}C NMR ($CDCI_3$) δ 20.92, 21.61, 28.66, 50.94, 56.87, 67.04, 68.85, 61.61, 69.85, 69.96, 70.80, 71.45, 113.27, 113.40, 121.37, 121.42, 126.88, 128.38, 141,84. Anal. calcd for $C_{24}H_{33}NO_4$: C, 72.89; H, 8.88; N, 3.2, found: C, 72.18; H, 8.27; N, 3.51.

3.6. (*S*)-2-Isopropyl-*N*-benzyl-4,7,10,13-tetraoxa-1-azacyclopentadecane 2

This compound was prepared in similar manner **1**. Using NaH (2.52 g, 0.084 mol), **4** (5 g, 0.021 mol) and **6** (9.66 g, 0.021 mol). The crude product was purified by flash column chromatography on silica gel (eluent: triethylamine/ethyl acetate/petroleum ether 60–80 = 3/17/80), yield was obtained as yellow oil 2.5 g (33%); $[\alpha]_D^{20}$ −16.4 (*c* 1, $CHCI_3$), IR: *v* 3089, 3070, 3024, 2954, 1439, 1343, 1297, 1246, 1119, 1027, 932, 732, 701 cm^{-1}; ^1H NMR ($CDCI_3$) δ 0.84–1.02 (m, 8H), 1.28–2.09 (m, 4H), 3.58–3.90 (m, 16H), 7.20–7.37 (m, 5H); ^{13}C NMR ($CDCI_3$) δ 20.93; 21.54; 29.11, 51.39; 56.36; 66.99; 70.69; 70.79; 70.89; 71.03; 71.13; 71.62; 126.88; 128.41; 128.93; 141.84. Anal. calcd for $C_{20}H_{33}NO_4$: C, 68.37; H, 9.47; N, 3.99, found: C, 68.30; H, 9.50; N, 3.38.

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