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Synthesis of chiral diaza 18-crown-6 ethers from chiral amines and molecular recognition of potassium and sodium salts of amino acids

N. Demirel* and Y. Bulut

University of Dicle, Faculty of Science, Department of Chemistry, 21280 Diyarbakır, Turkey

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Abstract—A practical synthesis of chiral amine precursors **3** and **4** and chiral diaza 18-crown-6 ethers **5**, **6** and **7** starting from chiral amines are reported. The molecular recognition of these chiral crown ethers for amino acids potassium and sodium salts has been characterized by UV–vis. The selectivity order is Phe>Thr>Ala. In the case of **6** the cavity of the macrocycle plays an important role in recognition.

1. Introduction

Molecular recognition has been the focus of supramolecular chemistry as one of fundamental processes in biochemical systems.[1] Recent successes in imitating the natural phenomena using synthetic artificial receptors have shown that biological behavior can be engineered into relatively simple molecules.[2] Crown ethers, first introduced in 1967 by Pedersen[3,4] are macrocyclic polyethers which are able to form stable and selective complexes with alkali, alkaline-earth, and primary ammonium cations. Following this fascinating discovery, chemists realized that asymmetric derivatives of these molecules could serve as models for the study of chiral recognition in enzymatic and other reactions. Among the artificial carriers previously developed, macrocyclic polyethers and crown ethers have been well-recognized as potential carrier models for selective transport of cations. Gokel et al.[5] described the first enantioselective transport of Z-amino acids and dipeptide K^+ carboxylates through a bulky chloroform membrane by two lariat ethers bearing *N*-pivot dipeptide arms. There has been continuing interest for molecular recognition of amino acids esters and amino acids potassium and sodium salts by NMR, UV–vis, extraction and transport experiment.[6–8] Herein we report a practical synthesis of chiral amine precursors and three chiral lariat type ethers and molecular recognition of amino acids potassium and sodium salts.

* Corresponding author. E-mail: demireln@dicle.edu.tr

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2. Results and discussion

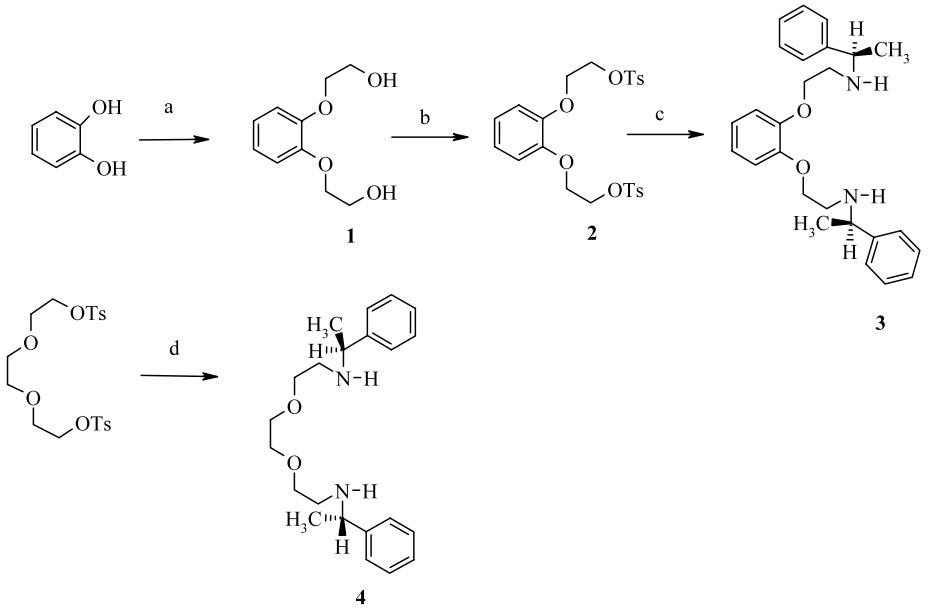
2.1. Synthesis

The versatile building block, **1**, for crown ether synthesis was prepared as shown in Scheme 1. A single step reaction of catechol with ethylene oxide in the presence of a catalyst at mild temperature gave **1** in high yield. In the reaction two catalyst were used, diethylamine hydrochloride and piperidine hydrochloride, but the yield of product was similar.[11,12]

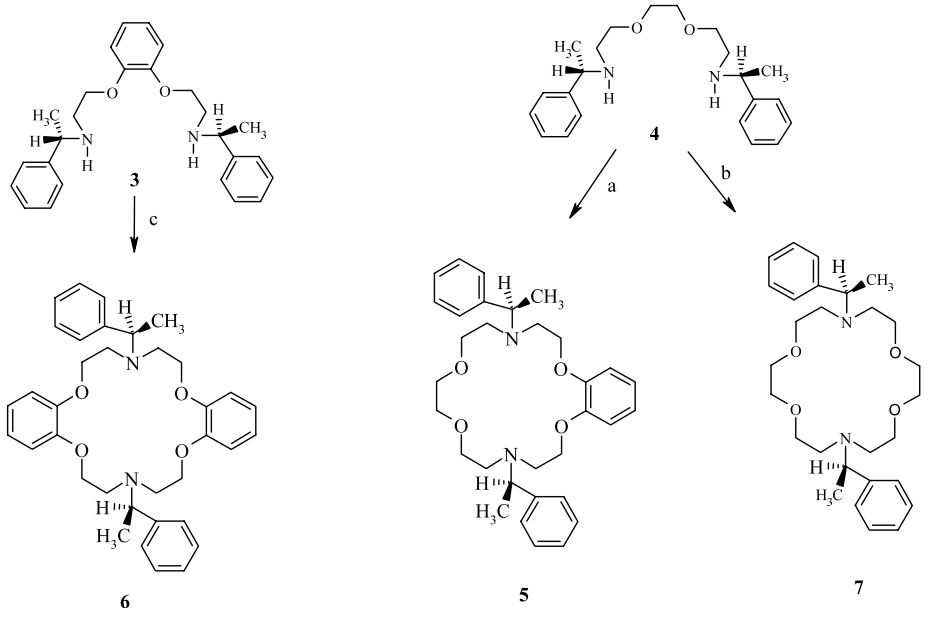
Compound **2** (1 mol equiv.) was allowed to react with (*R*)-(+)-1-phenylethylamine (10 mol equiv.) to afford **3** and triethylene glycol ditosylate was allowed to react with (*R*)-(+)-1-phenylethylamine (10 mol equiv.) to afford **4**. In the cyclization reaction, although sodium perchlorate ($NaClO_4 \cdot H_2O$) was added to reaction medium to promote cyclization, the product analysis revealed that macrocycle **6** existed as the free ligand, no complexation being observed. On the other hand macrocycles **5** and **7** were isolated as $NaClO_4$ complexes. This may be attributed to steric hindrance of the arene units on the ring of **6** preventing complex formation (Scheme 2).

2.2. UV–vis

UV–vis spectroscopy is a convenient and widely used method for the study of binding phenomena. When the



Scheme 1. *Reagents and conditions*: (a) ethylene oxide, piperidine hydrochloride, MeOH, 40°C; (b) TsCl, pyridine, −10°C; (c) (*R*)-(+)-1-phenylethylamine (10 equiv.), xylene, 120°C; (d) (*R*)-(+)-1-phenylethylamine (10 equiv.), xylene, 120°C.



Scheme 2. *Reagents and conditions*: (a) tripropylamine (10 equiv.), **2**, xylene, 120°C, 48 h; (b) tripropylamine (10 equiv.), triethylene glycol ditosylate, xylene, 120°C, 48 h; (c) tripropylamine (10 equiv.), **2**, xylene, 120°C, 48 h.

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 guest molecules resulted in gradual increase or decrease of characteristic absorptions of the host molecules. The typical UV spectral changes upon the addition of ThrNa to **5** are shown in Figure 1.

The association constants of the supramolecular system formed were calculated according to the modified Benesi–Hildebrand equation (Eq. (1))[10] where $[H]_o$ and $[G]_o$ refer to the total concentration of crown ether and amino acid potassium or sodium 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 amino acid salt.

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

The binding constants (K_a) and free-energy changes ($-\Delta G^o$) of these hosts with guest molecules obtained from usual curve fitting analyses (R>0.9851) of

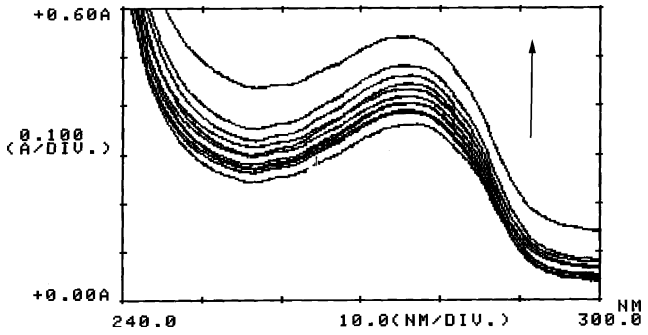


Figure 1. UV–vis spectra of **5** (1.33×10^{-4}) in the presence of ThrNa (4×10^{-5}–14×10^{-4}).

observed absorbance changes are summarized in Table 1. Typical plots are shown for the complexation of **5** with ThrNa in Figure 2.

Amino acids may interact in four ways to form stable complexes. In neutral solution the amino acid may be complexed in its neutral form[13] (coordination of the amino group and hydrogen bonding of the acid part) or more generally in its zwitterionic form for which thermodynamic studies have been undertaken,[14] complexation being weak; in acidic medium the amino acid is bound through the ammonium ion.[15] In basic medium it is complexed through the carboxylate function.[16]

Table 1. Binding constants (K_a) and free energy of complexation ($-\Delta G^\circ$) for 1:1 complexes between **5**, **6** and amino acids potassium and sodium salts

Host	Guest	K_a (dm^3 mol^{-1})	$-\Delta G^\circ$ (kJ mol^{-1})
	L-PheNa	$(1\pm0.06)\times10^4$	5.45×10^3
	L-PheK	$(4\pm0.042)\times10^4$	6.27×10^3
	L-ThrNa	$(1.86\pm0.05)\times10^4$	5.82×10^3
5	L-ThrK	$(9.33\pm0.043)\times10^3$	5.41×10^3
	L-AlaNa	$(1.6\pm0.038)\times10^3$	4.37×10^3
	L-AlaK	$(5.67\pm0.054)\times10^3$	5.12×10^3
	L-PheNa	$(1.14\pm0.048)\times10^3$	4.17×10^3
	L-PheK	$(1.33\pm0.042)\times10^4$	5.62×10^3
	L-ThrNa	No recognition	
6	L-ThrK	No recognition	
	L-AlaNa	No recognition	
	L-AlaK	No recognition	

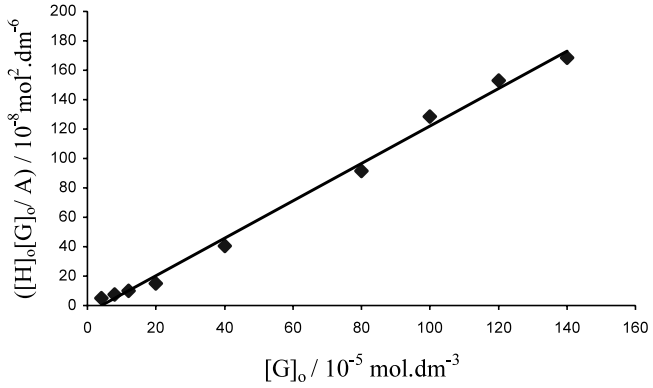


Figure 2. Typical plot of $[H]_o[G]_o/\Delta A$ versus $[G]_o$ for the host–guest complexation of **5** and ThrNa in (H_2O/CH_3CN = 1:50).

UV–vis spectroscopic studies indicate that π-stacking interactions between the aromatic moiety and aromatic part of the amino acid may contribute further to the overall binding strength of receptor. Although the potassium ion forms a stronger complex with 18-crown-6 than its sodium counterpart, it is very unlikely to find a correlation between the cation size and selectivity. ThrNa is recognized better than the respective potassium salt. The situation is reversed for other amino acids. In the case of Thr, additional hydrogen bonding between the OH group and the macrocycle is highly probable. Macrocycle **6** recognizes only PheNa and PheK, which deserves special attention. This result may be attributed to the strong π-stacking interaction between the four aromatic moieties on macrocycle and aromatic part of the amino acid. The reverse effect may result from the cavity of **6**. The dibenzo substitution on the diaza crown ether, due to steric hindrance of the arene units on the ring and π–π interaction between aromatic moieties on the ring and aromatic moieties on the side chains may close the cavity. Also the properties of macrocycle **7** deserve special interest. Macrocycle **7** did not give an absorbance in a mixture of CH_3CN–H_2O, it gives good absorbance in $CHCI_3$ at 244.2 nm but in this case solubility problem of amino acids salts arise. In MeOH, it gives absorbance at 207.4 nm but, here MeOH compete with amino acids; so the binding studies of **7** could not be performed.

3. Experimental

3.1. General information

All chemicals were grade reagent unless otherwise specified. Melting points were determined with a GALLENKAMP Model apparatus with open capillaries. Infrared spectra were recorded on a MIDAC-FTIR Model 1700 spectrophotometer. The elemental analysis were obtained with CARLO-ERBA Model 1108 apparatus. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a BRUKER DPX-400 High Performance Digital FT-NMR spectrometer, with tetramethylsilane as internal standard for solutions in deuteriochloroform. *J* values are given in hertz. Optical rotations were recorded using a ATAGO DR Model 21949 polarimeter, and $[\alpha]_D$ values are in units of 10^{-1} deg cm^2 g^{-1}.

3.2. Spectra measurement

The abilities of crown ethers to coordinate to amino acids salts were investigated using UV spectroscopic titration.[9] The UV–vis spectra were measured at 25± 0.3°C with Shimadzu 160 UV spectrometer. The maximum wavelengths are 276.4 and 274.2 nm for **5** and **6**, respectively. A solution of CH_3CN(HPLC grade)–H_2O (50:1) was used as the solvent. The concentrations of the hosts are 3.5×10^{-5}–1.33×10^{-4} M with the increasing concentration of the added guest.

3.3. 1,10-Di-(*R*)-(+)-1-phenylethyl-4,7-dioxa-1,10-diazadecane 4

Triethylene glycol ditosylate (11.45 g, 25 mmol) and (*R*)-(+)-1-phenylethylamine (30.25 g, 250 mmol) was stirred at 120°C under dry nitrogen for 16 h in xylene (400 ml). The mixture was cooled to the rt and then white precipitate filtered off and xylene evaporated. The product distilled under reduced pressure to afford **4** (7.65 g) in yield 86% as yellow oil had a bp 176–178°C/0.2 mmHg. $[\alpha]_D^{20}$ +25.5 (*c* 1, EtOH); IR: *v* 3330, 3084, 3061, 3023, 2953, 2865, 1600, 1492, 1446, 1372, 1349, 1303, 1123, 1029, 757, 702, 589; ^{1}H NMR: δ 1.34 (d, *J* 6.60, 6H, CH_3); 1.67 (bs, 2H, NH); 2.56–2.69 (m, 4H, NCH_2); 3.50–3.56 (m, 8H, OCH_2CH_2O, OCH_2); 3.74–3.76 (q, *J* 6.57, 2H, NCH); 7.18–7.33 (m, 10H, Ar-H); ^{13}C NMR: δ 24.94, 47.61, 58.69, 70.62, 71.09, 127.05, 127.27, 128.81, 146.03. Anal. calcd for: $C_{22}H_{32}N_2O_2$: C, 74.12; H, 9.05; N, 7.86. Found: C, 74.23; H, 9.12; N, 7.76.

3.4. (*R*)-(+)-1,2-Bis-[2-(*N*-1-phenylethylamino)-ethoxy]benzene 3

1,2-Bis-(2-*p*-tolylsulphonylethoxy)benzene (12.65 g, 25 mmol) and (*R*)-(+)-1-phenyl-ethylamine (30.25 g, 250 mmol) was stirred at 120°C under dry nitrogen for 16 h in xylene (400 ml). The mixture was cooled to rt and then white precipitate filtered off and xylene evaporated. The product distilled under reduced pressure to afford **3** (6.36 g) in yield 63% as yellow oil had a bp. 191–193°C at 0.2 mmHg. $[\alpha]_D^{20}$ +42.6 (*c* 1, EtOH); IR: *v* 3328, 3066, 3027, 2963, 2933, 2871, 2831, 1591, 1499, 1452, 1398, 1367, 1252, 1221, 1120, 1042, 759, 744, 704; ^{1}H NMR: δ 1.14–1.16 (d, *J* 6.59, 6H, CH_3); 2.2 (bs, 2H, NH); 2.6–2.67 (m, 4H, NCH_2); 3.61–3.62 (q, *J* 6.58, 2H, NCH); 3.82–3.86 (m, 4H, OCH_2); 6.66–6.67 (s, 4H, Ar-H); 6.99–7.14 (m, 10H, Ar-H); ^{13}C NMR: δ 25.00, 47.16, 58.52, 69.32, 115.03, 122.09, 127.18, 127.50, 128.99, 145.76, 149.45. Anal. calcd for: $C_{26}H_{32}N_2O_2$: C, 77.19; H, 7.92; N, 6.93. Found: C, 77.06; H, 7.86; N,6.95.

3.5. *N*,*N*′-Di-(*R*)-(+)-1-phenylethyl-7,16-diaza-1,4,10,13-tetraoxa-2,3-benzo-cyclooctadec-2-ene 5

To a mixture of tripropylamine (14.3 g, 100 mmol) in xylene (500 ml) 1,2-bis-(2-*p*-tolylsulphonylethoxy)-benzene **2** (5.06 g, 10 mmol) and 1,10-di-(*R*)-(+)-1-phenylethyl-4,7-dioxa-1,10-diazadecane **4** (3.56 g, 10 mmol) was added simultaneously. The mixture was stirred for 2 days at 120°C. The mixture was then cooled to the rt. The xylene was evaporated. The concentrated crude product was washed with hot water then extracted with $CHCI_3$ (3×50 ml) and dried (Na_2SO_4). The chloroform was then evaporated and the residue purified by column chromatography (200 mesh Si-gel, ethyl acetate:petroleum ether:triethylamine 17:80:3) to afford **5** (2.80 g) in 54% yield as a yellow oil. $[\alpha]_D^{20}$ +27.4 (*c* 0.05, CH_2CI_2), IR: *v* 3068, 3029, 2974, 2926, 2872, 1597, 1496, 1441, 1371, 1348, 1325, 1261, 1215, 1122, 1053, 1029, 776, 745, 699; ^{1}H NMR: δ 1.17–1.19 (d, *J* 6.70, 6H, CH_3); 2.68–2.72 (m, 4H, $ArOCH_2\underline{CH_2}N$); 2.84–2.87 (t, *J* 6.28, 4H, NCH_2); 3.31–3.37 (m, 8H, OCH_2, Ar-OCH_2); 3.66–3.68 (q, *J* 6.69, 2H, CHN); 3.76–3.81 (m, 4H, OCH_2CH_2O); 6.54–6.65 (m, 4H, Ar-H); 7.00–7.19 (m, 10H, Ar-H); ^{13}C NMR: δ 17.69, 50.35, 51.37, 61.70, 69.03, 71.06, 71.62, 113.63, 121.23, 127.21, 128.11, 128.61, 145.05, 149.35. Anal. calcd for: $C_{32}H_{42}N_2O_4$: C, 74.09; H, 8.16; N, 5.40. Found: C, 74.12; H, 8.12; N, 5.46.

3.6. *N*,*N*′-Di-(*R*)-(+)-1-phenylethyl-7,16-diaza-1,4,10,13-tetraoxa-2,3,11,12-dibenzo-cyclooctadeca-2,11-diene 6

To a mixture of tripropylamine (14.3 g, 100 mmol) in xylene (500 ml) 1,2-bis-(2-*p*-tolylsulphonylethoxy)-benzene **2** (5.06 g, 10 mmol) and 1,2-bis-[2-(*N*-(*R*(+)-1-phenylethylamino)ethoxy] benzene **3** (4.04 g, 10 mmol) was added simultaneously. The mixture was stirred for 2 days at 120°C. The mixture was then cooled to the rt. The xylene was then evaporated. The concentrated crude product was washed with hot water and extracted with $CHCl_3$ (3×50 ml) and dried (Na_2SO_4). The chloroform was then evaporated. The product crystallized from ethyl acetate to afford **6** (2.54 g) in yield 45% as white solid had a mp 137–138°C. $[\alpha]_D^{20}$ +23.2 (*c* 0.05, CH_2Cl_2); IR;*v* 3066, 3058, 3035, 2963, 2925, 2863, 1585, 1500, 1453, 1351, 1249, 1225, 1210, 1171, 1117, 1017, 921, 810, 779, 748, 701, 663, 547; ^{1}H NMR: δ 1.40–1.42 (d, *J* 6.65, 6H, CH_3); 3.18–3.25 (m, 10H, NCH_2, NCH); 3.91–3.96 (m, 8H, OCH2); 6.67–6.79 (m, 8H, Ar-H); 7.23–7.41 (m, 10H, Ar-H); ^{13}C NMR: δ 17.14, 50.69, 61.82, 68.91, 112.12, 120.75, 127.26, 128.07, 128.64, 145.00, 148.85. Anal. calcd for: $C_{36}H_{42}N_2O_4$: C, 75.76; H, 7.95; N, 3.68. Found: C, 75.43; H, 7.81; N, 3.72.

3.7. *N*,*N*′-Di *R*-(+)-1-phenylethyl-1,7,10,16-tetraoxa-4,13-diaza-cyclooctadecane 7

To a mixture of tripropylamine (14.3 g, 100 mmol) in xylene (500 ml) triethylene glycol ditosylate (4.58 g, 10 mmol) and 1,10-di-*R*-(+)-1-phenylethyl-4,7-dioxa-1,10-diazadecane **4** (3.56 g, 10 mmol) was added simultaneously. The mixture was stirred for two days at 120°C. The mixture was then cooled to the rt. The xylene was then evaporated. The concentrated crude product was washed with hot water to remove tripropylamine salt, was then extracted with $CHCl_3$ (3×50 ml) and dried (Na_2SO_4). The residue was purified by column chromatography (200 mesh Si-gel, ethyl acetate:petroleum ether:triethylamine 17:80:3) to afford **7** (2.25 g) in yield 48% as yellow oil. $[\alpha]_D^{20}$ +19.2 (*c* 0.05, CH_2CI_2), IR; *v* 3091, 3053, 3029, 2972, 2931, 2869, 1605, 1478, 1455, 1376, 1352, 1298, 1201, 1121, 1067, 1034, 980, 911, 833, 770, 731, 708; ^{1}H NMR: δ 1.38–1.40 (d, *J* 6.76, 6H, CH_3); 2.78–2.86 (m, 8H, NCH_2); 3.56–3.61 (m, 16H, OCH_2CH_2O, OCH_2); 3.86–3.88 (q, *J* 6.72, 2H, NCH); 7.23–7.40 (m, 10H, ArH); ^{13}C NMR: δ 17.65, 51.24, 61.48, 71.15, 71.38, 127.09, 128.10, 128.48, 144.81. Anal. calcd for: $C_{28}H_{42}N_2O_4$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.38; H, 8.76; N, 5.87.

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