Synthesis of novel chiral monoaza-15-crown-5 ethers and their molecular recognition of amino acid esters

Yilmaz Turgut, Elif Sahin Işgın and Halil Hoşgören*

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

The chiral monoaza-15-crown-5 ethers **4** and **5** were prepared from L-phenylalaninol and L-leucinol, respectively. The molecular recognition of these chiral crown ethers for L-amino acid ethyl esters was characterised by UV-visible spectroscopy. Binding constants (K_a), free-energy changes ($-\Delta G^o$), enthalpy changes (ΔH) and entropy change (ΔS) values were determined for hosts **4** and **5** with L-amino acid ethyl ester hydrochlorides in $CHCl_3$.

Keywords: chiral monoaza-15-crown-5 ethers, amino acid esters

Introduction

Molecular recognition is ubiquitous in nature. Recent success in imitating such phenomena using small synthetic compounds has shown that this biological behaviour can be engineered into simple molecules.[1] Crown ethers, exhibit excellent ability to selectively bind cationic guests[2,3] and are popular as enzyme models.[4-6] The unique complexing characteristic of crown ethers was first reported by Pedersen,[7] This discovery led to the synthesis and complexation studies of a number of macrocyclic compounds. There has been continuing interest in the molecular recognition of amino acid esters by NMR and UV-vis.[8,9] We report herein the synthesis of chiral amino alcohol precursors from L-phenylalanine and L-leucine and two chiral monoaza-15-crown-5 ether derivatives. This paper focus on the characterisation of the host–guest interactions involves these chiral monoaza-15-crown-5 ethers and L-amino acid ethyl ester hydrochloride salts. K_a, $-\Delta G^o$, ΔH, and ΔS values for these host–guest interactions are reported.

Results and discussion

Synthesis

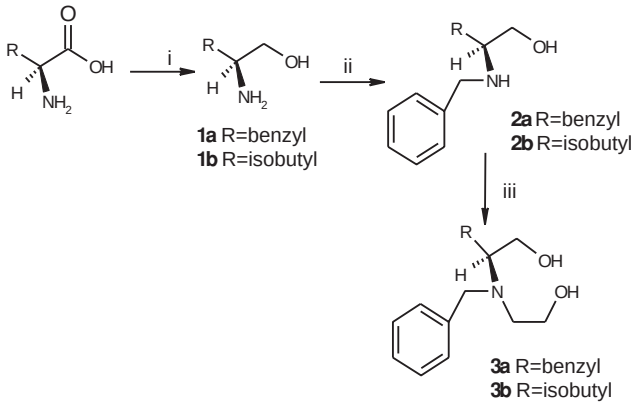
The synthesis of L-phenylalaninol and L-leucinol was accomplished in one step from L-phenylalanine and L-leucine according to procedures described in the literature.[10] The conversion of **1a**–**b** to *N*-benzyl amino alcohol derivatives was carried out using our previous method.[11] The conversion of **2a**–**b** to **3a**–**b** was carried out at –20°C, as shown in Scheme 1. To obtain the product in a solid state (for easier isolation) $NaClO_4.H_2O$ (toxic) was added to macrocyclic crown **4** and **5**. Then, these macrocycles were recovered from their complex form by coloumn chromatography as yellow oil in 48% and 49% yield, respectively as shown in Scheme 2. The structures proposed for these chiral macrocycles and amino alcohols are consistent with data obtained from ^{1}H NMR, ^{13}C NMR, IR spectra and elemental analyses.

Molecular recognition and UV-vis

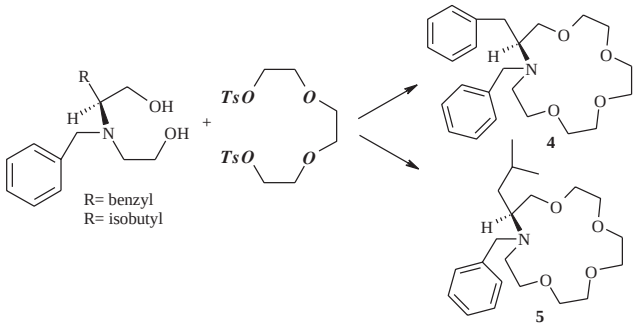
UV-vis spectroscopy is a convenient and widely used method for the study of binding phenomena. When the receptor (or substrate) absorbs light at different wavelengths in the free and complexed states, the differences in the UV-vis spectra may suffice for the estimation of molecular recognition thermodynamics. In UV spectroscopic titration experiments, the addition of varying concentration of guest molecules results in a gradual increase or decrease of characteristic absorptions of the host molecules. The association constants of the supramolecular systems that were formed was calculated according to the modified Benesi–Hildebrand equation, Eqn (1),[12] where $[H]_o$ and $[G]_o$ refer to the total concentration of crown ether and amino acid ethyl ester hydrochloride 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 the addition of amino acid ethyl ester hydrochloride salts.

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

For all guest molecules examined, plots of calculated $[H]_o[G]_o / \Delta A$ values as a function of $[G]_o$ values gave linear relationship. The binding constant, K_a, of the complexes of the crown ether **4** and **5** with L-amino acid ethyl ester hydrochloride salts were determined by the Benesi–Hildebrand equation on the basis of the UV-visible spectrum of the complexes in $CHCl_3$ collected at four different temperatures. The thermodynamic parameters, ($-\Delta G^o$), (ΔH) and (ΔS) for complex formation were determined from the van't Hoff plots of the K_a values and changes are summarised in Table 1. Four amino acid ethyl esters were studied. Two of these, PheAlaOEt, PheGlyOEt, have a benzyl and phenyl group; the other two, LeuOEt, AlaOEt, have isobutyl and methyl groups, respectively. The stability constants



Scheme 1 Condition: (i) $NaBH_4$-I_2, THF; (ii) $PhCH_2Cl$, Na_2CO_3, 110°C; (iii) ethylene oxide, MeOH, –20°C.



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

* Correspondence. E-mail: hosgoren@dicle.edu.tr

Table 1 K_a (dm^3 mol^{-1})-ΔG^0 (k J mol^{-1}), ΔH (k J mol^{-1}) and ΔS (J mol^{-1} K^{-1}) values for the 1:1 complexes between **4**, **5** and amino acid ethyl ester hydrochloride salts

		4				**5**			
Guests	T/K	K_a	-ΔG^0	ΔH	ΔS	K_a	-ΔG^0	ΔH	ΔS
L-PheAlaOEt	288	(2.00)x10^3	18.20			(1.19)x10^4	22.47		
	298	(1.11)x10^3	17.36	–4.18	168.62	(6.67)x10^3	21.80	–10.88	–26.36
	308	(1.00)x10^3	17.66			(4.00)x10^3	21.54		
	318	(1.00)x10^3	18.24			(2.22)x10^3	20.88		
L-PheGlyOEt	288	(4.50)x10^4	25.65			(1.42)x10^4	22.89		
	298	(3.50)x10^4	25.94	–9.62	-41.42	(6.60)x10^3	21.80	–14.23	–30.96
	308	(1.63)x10^4	24.85			(3.00)x10^3	20.50		
	318	(1.13)x10^4	24.64			(1.60)x10^3	19.50		
L-LeuOEt	288	(1.11)x10^3	16.78			(3.00)x10^3	20.67		
	298	(1.10)x10^3	17.36	–0.42	+72.38	(3.00)x10^3	19.83	–1.26	+0.84
	308	(1.09)x10^3	17.91			(3.00)x10^3	20.29		
	318	(1.08)x10^3	18.45			(2.50)x10^3	20.67		
L-AlaOEt	288	(2.23)x10^3	18.48			(5.71)x10^3	20.71		
	298	(2.22)x10^3	19.08	–0.84	+52.07	(5.00)x10^3	21.09	–14.23	+35.98
	308	(2.21)x10^3	19.71			(4.29)x10^3	21.42		
	318	(2.00)x10^3	20.08			(3.82)x10^3	21.80		

for the complexation of amino acids ethyl ester by **4**, exhibit a selectivity order of L-PheGlyOEt>L-AlaOEt>L-PheAlaOEt> L-LeuOEt and by **5** the selectivity order is L-PheAlaOEt> L-PheGlyOEt >L-AlaOEt>L-LeuOEt at 298 K. It can be seen from Table 1, that L-PheGlyOEt, L-PheAlaOEt form stable complex with **4** and **5**, respectively at 298 K. But L-PheGlyOEt forms stable complexes both with **4** and **5** at 288 K. The complexation of the amino acid ethyl esters with **4** and **5** was found to be exothermic, and the ΔS value is negative except in the case of LeuOEt and AlaOEt. This finding indicates that the interactions of all amino acid ethyl esters with the hosts are enthalpy driven. The values of the binding enthalpies for amino acid ethyl esters with **4** and **5** are nearly identical and negative. However, the values of the reaction entropies are quite different both for **4** and **5** with amino acid ethyl ester. It has been demonstrated that the substituent on the chiral centre has very important effect on the chiral recognition. It is also known that for molecular recognition, the steric repulsion between the substituent at chiral centre and the substituent of ammonium cation has been found to be important factor.[13] In conclusion, the chemical structure of the amino acid derivatives also influences the complex formation. This can be seen by comparing the the results of aromatic and alphatic amino acid ester.

Experimental

General information

All chemicals were reagent grade unless otherwise specified. L-Phenyalanine, L-leucine and L-amino acid ethyl ester hydrochloride salts were purchased from Fluka. 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.

UV spectral measurements

The UV-vis spectra were measured at 288, 298, 308, and 318 K with thermostated cell compartment by Shimadzu 160 UV spectrometer. The same concentrations of guest solution were added to the sample cell and reference cell. The maximum wavelength is 242.7 nm for **4** and **5** in $CHCl_3$. The concentrations of the host are 2.0×10^{-4} mol dm^{-3} with the increasing concentration of the added guest.

(S)-N-Benzyl-2-amino-3-phenyl-1-propanol **2a**: *(S)*-phenylalaninol (33 g, 0.218 mol), benzyl chloride (6.96 g, 0.055 mol) and anhydrous Na_2CO_3 (5.8 g, 0.055 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 and the residue was recrystallised from toluene to give compound **2a** (10 g) (77%), b.p. 165–167°C/0.8 mmHg, m.p. 54–56°C; $[\alpha]_D^{20}$= –11.1 (*c* 1.2, MeOH); IR (KBr) 3355, 3289, 3084, 3057, 3026, 2919, 1495, 1451, 1379, 1344, 1114, 1060, 1028, 959, 919, 885, 854, 742, 696 cm^{-1} ; ^{1}H NMR ($CDCI_3$) δ 2.04 (d, 2H, *J*=8 Hz), 2.76–3.00 (m, 3H), 3.35–3.80 (m, 4H), 7.17–7.34 (m, 10H); ^{13}C NMR ($CDCL_3$) δ 38.51, 51.55, 59.84, 62.95, 126.85, 127.50, 128.44, 128.88, 128.99, 129.62, 138.92, 140.42; Anal. Calcd. For $C_{16}H_{19}NO$: C, 79.67; H, 7.88; N, 5.81. Found: C, 79.60; H, 7.80; N, 5.78%.

(S)-N-Benzyl-2-amino-4-methyl-1-pentanol **2b**: This compound was prepared as described above for **2a**, using **1b** (21g, 0.18 mol), benzyl chloride (5.56 g, 0.04 mol) and anhydrous Na_2CO_3 (4.65 g, 0.04 mol). The product was distilled and crystallised from petroleum ether-benzene to give compound **2b** 8 g (88%), b.p. 123–125°C/0.8 mmHg, m.p. 72–73 °C; $[\alpha]_D^{20}$ +33.5 (*c* 1, MeOH); IR (KBr) 3294, 3070, 3024, 2960, 2928, 2909, 1503, 1464, 1387, 1348, 1271, 1208, 1092, 1060, 1022, 970, 880, 841, 783, 746, 707, 617 cm^{-1} ; ^{1}H NMR ($CDCL_3$) δ 0.90–0.96 (dd, 6H, *J*=6.8 Hz), 1.25–1.31 (m, 1H), [1.40–1.47 (dd, 1H, *J*=7.1 Hz; 1.62–1.67(dd, 1H, *J*=6.7)], 2.76–2.78 (m, 1H), [3.28–3.33 (dd, 1H, *J*=6.1), 3.66–3.70 (dd, 1H, *J*=3.99], 3.77–3.85 (dd, 2H, *J*=12.9), 7.26–7.38 (m, 5H); ^{13}C NMR ($CDCL_3$) δ 23.13, 25.37, 41.65, 56.62, 63.58, 77.81, 77.46, 127.53, 128.56, 128.90, 140.46; Anal. Calcd. For $C_{13}H_{21}NO$: C, 75.44; H, 10.20; N, 6.60. Found: C, 75.36; H, 10.36; N, 6.76%.

(S)-N-Benzyl-4-benzyl-3-aza-1, 5-propanediol **3a**: A solution of **2a** (10 g, 0.04 mol) in 250 ml methanol was cooled to –20°C in a 100 ml flask. Ethylene oxide (2 ml, 0.04 mol) in 10 ml of methanol at 20°C was added to the solution dropwise at –20°C. The mixture was kept at –20°C during the addition in a 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 room temperature in a closed flask. Methanol was evaporated in rotary evaporator. The product was purified by distillation under reduced pressure to give compound **3a** 11 g (94%), b.p. 188–192°C/ 0.8 mmHg; $[\alpha]_D^{20}$ –13.2 (*c* 1, MeOH); IR (KBr) 3363, 3087, 3064, 3026, 2941, 1602, 1491, 1453, 1369, 1135, 1033, 916, 869, 745, 698 cm^{-1} ; ^{1}H NMR ($CDCL_3$) δ 2.45–2.51(m, 1H), 2.67–2.73 (m, 2H), 2.77–3.00 (m, 4H), 3.44–3.68 (m, 4H), 7.14–7.36 (m, 10H); ^{13}C NMR ($CDCL_3$) δ 33.31, 51.40, 55.67, 60.46, 61.77, 63.35, 126.63, 127.64, 128.93, 128.99, 129.26, 129.51, 139.92, 140.18; Anal. Calcd. For $C_{18}H_{23}NO_2$: C, 75.70; H, 8.00; N, 4.89. Found: C, 75.79; H, 8.07; N, 4.91%.

(S)-N-Benzyl-4-hydroxymethyl-3-aza-6-methyl-heptane-1-ol **3b**: Prepared as described for **3a**, using **2b** (10 g, 0.05 mol), ethylene oxide (2.5 ml, 0.05 mol). Yield compound **3b** 10 g (83%), b.p. 168–170°C/ 0.8 mmHg; $[\alpha]_D^{20}$ +35.6 (*c* 1, MeOH), IR (KBr) 3358, 3060, 3024, 2960, 1599, 1496, 1478, 1458, 1362, 1162, 1112, 1066, 918, 867, 732, 701 cm^{-1} ; ^{1}H NMR ($CDCl_3$) δ 0.88–0.92 (dd, 6H, *J*=6.5), 1.08–1.13 (m, 1H), 1.38–1.44 (dd, 1H, *J*=4.2) 1.53–1.56 (m, 1H, *J*=7.0), 2.54–2.58 (m, 1H), 2.77–2.87 (m, 2H), 3.37–3.59

(m, 6H) 7.28–7.40 (m, 5H); ^{13}C NMR ($CDCL_3$) δ 22.77, 24.06, 25.82, 35.60, 51.42, 55.19, 59.14, 60.50, 62.37, 127.57, 128.86, 129.24, 140.37; Anal. Calcd. For $C_{15}H_{25}NO_2$: C, 71.71; H, 9.96; N, 5.58. Found: C, 71.70; H, 9.89; N, 5.60.%

(S)-2-Benzyl-N-benzyl-4,7,10,13-tetraoxa-1-azacyclopentadecane **4**: To a suspension of NaH (1.26 g, 0.042 mol, % 80 in mineral oil) in 100 ml dry THF at 0°C was added a solution of diol **3a** (3 g, 0.0105 mol) in 250 ml of THF. The reaction mixture was refluxed for 2 h. After cooling the reaction to 0°C, a solution of triethyleneglycol ditosylate (4.82 g, 0.0105mol) in 250 ml of THF was slowly added. The suspension was refluxed for 50 h. The solvent was evaporated and 150 ml of water was added to the residue. The mixture was extract with CH_2Cl_2 (3×150 ml). The combined organic layers were washed with 100 ml water again, dried over 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 compound **4** 2 g (48%); $[\alpha]_D^{20}$ -6.3 (*c* 2, $CHCl_3$), IR (KBr) 3058, 3025, 1601, 1491, 1454, 1353, 1292, 1253, 1129, 1020, 989, 943, 878, 831, cm^{-1} ; ^{1}H NMR ($CDCl_3$) δ 2.92–3.01 (m, 2H), 2.50–2.65 (m, 3H), 3.21–3.61 (m, 18H), 6.95–7.10 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 34.37, 50.82, 56.69, 62.34, 70.67, 70.80, 70.92, 71.08, 71.29, 71.45, 72.45, 126.14, 127.07, 128.52, 128.61, 128.89, 129.80, 141.15, 141.32; Anal. Calcd. For: $C_{24}H_{33}NO_4$: C, 72.18; H, 8.27; N, 3.10. Found: C, 72.00; H, 8.10; N, 3.10.%

(S)-2-Isobutyl-N-benzyl-4,7,10,13-tetraoxa-1-azacyclopentadecane **5**: This compound was prepared in similar manner for **4** using NaH (1.87 g, 0.0625mol),**3b** (3.50 g, 0.0139 mol) and triethyleneglycol ditosylate (6.37 g, 0.0139 mol). The crude product was purified by flash column chromatography on silica gel (eluent: triethylamine/ ethyl acetate/ petroleum ether 60-80=3/17/80). The product was obtained as an oil 2.5 g (49%), $[\alpha]_D^{20}$ –20.5 (*c* 1, $CHCl_3$), IR (KBr) 3089, 3070, 3024, 2954, 1599, 1496, 1355, 1285, 1246, 1124, 996, 938, 867, 764 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87–0.90 (dd, 6H, *J*=3.6 Hz), 1.20–1.26 and 1.43–1.46 (m, 3H), 1.74–1.79 (m, 1H), 2.72–2.75 and 3.02–3.05 (m, 2H) 3.53–3.72 (m,18H) 7.18–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.94, 23.69, 25.34, 30.09, 38.40, 50.83, 55.29, 58.11, 70.72, 70.75, 70.88, 71.09, 71.28, 71.56, 73.05, 127.02, 128.48, 128.97, 141.44; Anal. Calcd. For $C_{21}H_{35}NO_4$: C, 69.04; H, 9.58; N, 3.80. Found:C, 69.05; H, 9.60 ; N, 3.81.%

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