Journal of Inclusion Phenomena and Macrocyclic Chemistry (2006) 54: 29–33
DOI 10.1007/s10847-005-3125-1

Synthesis of Novel Chiral C_2-symmetric Diaza-18-crown-6 Ether Derivatives and Their Enantioselective Recognition of Amino Acid Derivatives

YıLMAZ TURGUT* NADIR DEMIREL and HALIL HOŞGÖREN
*Faculty of Science, Department of ChemistryUniversity of Dicle, 21280, Diyarbak*ır*, Turkey*

(Received: 23 January 2005; in final form: 02 March 2005)

Key words: amino acid, chiral aza crown ether, complexation, molecular recognition

Abstract

New chiral diaza-18-crown-6 ether derivatives, **5** and **6** were synthesized from (*R*)-(-)-2-amino-1-bütanol. These chiral artificial receptors exhibit pronounced chiral recognition toward the enantiomers of L- and D- amino acid derivatives. The highest enantioselectivity was observed in the case of Trp-OMe·HCl ($K_D/K_L = 12.5$).

Introduction

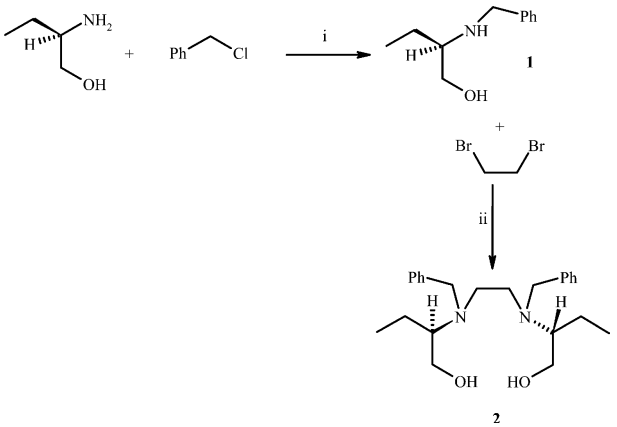
Amino acids are the most important targets for molecular recognition by artificial host compounds. This is due to their relevance in biological world and their rich chemistry. For this reason chemists have been studying host–guest binding of amino acids as an instrument for manipulation of their reactivity. Therefore, the design and synthesis of different kinds of synthetic macrocycles have been one of the objectives of host–guest chemistry. Since Cram *et al*. reported their fascinating research on the use of chiral macrocyclic ligands in enantiomer recognition [1], a great number of chiral artificial receptors have been synthesized and studied. The most dominant chiral macrocyclic compounds are cyclophanes [2], crown ethers [3] and cyclodextrins [4]. So far, a lot of work has been done to design and synthesize new receptor molecules incorporating binaphthyl, sugars, tartaric acid [5, 6], steroids [7], amino acids [8] etc. The chiral nature of crown ether, the rigidity of micro-environment of its cavity and the quality of the side arm are all expected to play an important role in enantioselective induction. Recently, Homochiral molecular tweezers [9] and chiral polyamide macrocycles [10] containing pyridily sidearms have been synthesized and used for molecular recognition of amino acids derivatives. We recently have studied molecular recognition of amino acids as their sodium and potassium salts by UV–vis titration method and transport experiments [11, 12] and also molecular recognition of chiral ammonium salts by optically active crown ethers [13, 14].

We know that the symmetry of macrocycle is crucial for molecular recognition, so we focused on synthesis of C_2- symmetric chiral crown ethers derived from chiral amino alcohol. In addition, benzene units are incorporated into the ring structure and side arm in order to investigate the effect of steric and π–π interactions on enantiomeric recognition. Our previous results [15] show that the benzo substitution has profound effect on complexation of crown ethers. We report here the synthesis of chiral amino alcohol precursors and C_2- symmetric chiral diaza-18-crown-6 ethers derivatives and molecular recognition behavior towards the amino acids derivatives by spectroscopic method.

Result and discussion

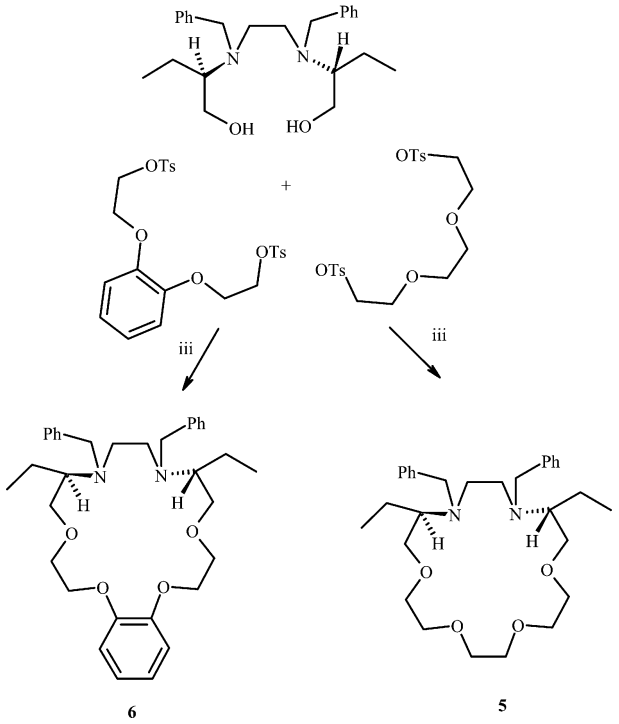
Synthesis

The synthesis of chiral amine alcohol **1**, **2** and artificial host **5**, **6** were carried out as described in Scheme 1 and Scheme 2, respectively. Compound **2** was prepared in



Scheme 1. Reagent and conditions: (i) $Na_2CO_3$12 h, 110 °C (ii) Na_2CO_3 14 h, 110 °C.

* Author for correspondence. E-mail: yturgut@dicle.edu.tr



Scheme 2. Reagent and conditions: (iii) NaH THF, 50 h.

good yield from **1** and 1,2-dibromoethane. For further purification the HCl salt of amine alcohol, **2**, was prepared and then free amine alcohol was recovered by treating basic Na_2CO_3 and then following by column chromatography on silica jel. The macrocycle **5** and **6** were synthesized by cyclization of two different ditosylate with using NaH as base in THF. The macrocycle **5** and **6** were recovered by column chromatography as yellow oil in good yield. The structures proposed for these chiral macrocycles, and **1**, **2** are consistent with data obtained from ^{1}H NMR, ^{13}C NMR, IR spectra and elemental analyses.

Molecular recognition

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 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.

Under the conditions employed, herein, L-, D-amino acid methyl ester hydrochlorides were selected as the guest molecules. The association constants of the supramolecular systems formed were calculated according to the modified Benesi-Hildebrand equation, Equation (1) [16], where $[H]_o$ and $[G]_o$ refer to the total concentration of crown ether and amino acid derivatives 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 derivatives. The stoichiometry of the complex between **5**, **6** and amino acid enantiomer was determined by continuous variation plot (Job plot) according to method described in literature [17].

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

For all guest molecules examined, plots of calculated $[H]_o[G]_o/\Delta A$ values as a function of $[G]_o$ values give an excellent linear relationship, supporting the 1:1 complex formation. The binding constants (K_a) and free-energy changes ($-\Delta G^o$) of these hosts with guest molecules obtained from usual curve fitting analyses ($R^2 > 0.9847$) of observed absorbance changes are summarized in Table 1. The binding constant, K_a, of the complexes of

Table 1. Binding constants (K), the Gibbs free energy changes ($-\Delta G_o$), enantioselectivities K_L/K_D and $-\Delta\Delta G_o$ calculated from $-\Delta G_o$ for the complexation of L/D guest with the chiral host **5** and host **6** in $CHCl_3$:MeOH (25:2) at 25 °C[a]

Host	Guest[b]	K (dm^3 mol^{-1})[c]	K_{L/K_D}	$-\Delta G_o$ (kJ mol^{-1})	[d]$\Delta\Delta G_o$ (kJ mol^{-1})
5	(L)-AlaOMe·HCl	1.50×10^4	1.20	23.80	0.40
	(D)-AlaOMe·HCl	1.25×10^4		23.40	
	(L)-Phe-OMe·HCl	5.00×10^3	0.75	21.10	0.70
	(D)-Phe-OMe·HCl	6.67×10^3		21.80	
	(L)-Trp-OMe·HCl	1.23×10^3	2.46	17.70	−2.30
	(D)-Trp-OMe·HCl	5.00×10^2		15.40	
	(L)-AlaOMe·HCl	1.50×10^4	0.14	23.80	5.00
	(D)-AlaOMe·HCl	1.11×10^5		28.80	
	(L)-Phe-OMe·HCl	1.00×10^4	3.33	22.80	−3.00
	(D)-Phe-OMe·HCl	3.00×10^3		19.80	
	(L)-Trp-OMe·HCl	2.86×10^2	0.08	14.00	6.01
	(D)-Trp-OMe·HCl	3.33×10^3		20.01	

[a] The concentration of the hosts: 2.0×10^{-4} mol dm^{-3}. [b] Ala-OMe·HCl: alanine methyl ester hydrochloride; Phe-OMe·HCl: phenylalanine methyl ester hydrochloride; Trp-OMe·HCl: tryptophane methyl ester hydrochloride. [c] Binding constants were represented according to data treatment ba-sed on student's t-distribution method described in literature [17]. The spreadsheet for the statistical teatment was used. The estimated error was less than ±5%. [d] $\Delta\Delta G_o = G_o(L)\text{-}\Delta G_o(D)$.

the crown ether **5** and **6** with amino acid derivatives were determined by the Benesi-Hildebrand equation on the basis of the UV–vis spectrum of the complexes in MeOH:$CHCl_3$(2:25) collected at 25 °C.

It is well known that in acidic medium the amino acid is bound to through the ammonium ion. And also known that binding of amino acids by their natural receptors is thought to occur via a combination of non-covalent interactions (electrostatic interactions, H-bonding, π–π interactions, π–cation interaction).

Taking into account the binding studies in Table 1 chiral macrocycle **5** and **6** exhibit a pronounced chiral recognition towards the Trp-OMe·HCl, K_L/K_D 2.46 and K_D/K_L 12.5 respectively. Although the calculated binding constant for L-, D-Ala-OMe·HCl was the highest for macrocycle **5** and **6** respectively, the observed enantioselectivity was the lowest for **5** and **6**. This attitude may be explained the bulkiness of L-, D-Phe-OMe·HCl and L-, D-Trp-OMe·HCl compared to L-, D-Ala-OMe·HCl. As a result L-, D-Ala-OMe·HCl has formed stronger complex (without pronounced chiral discrimination). Since the crown ethers possess two diasteretopic, non equivalent faces, it is essential that the complexation should occur from the more hindered side of the crown ethers. The highest enantioselectivity in Trp-OMe·HCl compared to Phe-OMe·HCl may be result of strong steric interaction of the indolic group relatively to phenyl one. The attitude of macrocycle **6** deserves a special treatment. The benzo substitution on 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 diminishes the cavity. As a result the highest chiral discrimination was achieved by **6** for three amino acid ester hydrocholoride compared to **5**. In general, we may conclude that the overall binding strength could not effect from π–π interaction, cation–π interactions but the chiral discrimination may be achieved by π–π interaction, cation–π interactions between hosts and guest.

Experimental

General information

All chemicals were reagent grade unless otherwise specified. L/D amino acid methyl ester hydrochlorides were purchased from sigma. 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. ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker DPX-400 High Performance Digital FT-NMR Spectrometer.

UV spectral measurement

The abilities of crown ethers to coordinate to amino acid derivatives were investigated using UV spectroscopic titration. The UV–vis spectra were measured at 298 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 242.4 and 276.8 nm for **5** and **6** in (MeOH:$CHCl_3$, 2:25). The concentrations of the host are 2.0×10^{-4} mol dm^{-3} with the increasing concentration of the added guest (see figure 1) .

Job plot

The stoichiometry of the complex between **5**, **6** and amino acid enantiomer was determined by continuous variation plot (Job plot) according to method described in literature [17]. The total concentration of crown ethers and amino acid derivatives in the solution was kept constant at 2 mM and the molar fraction of the amino acids derivatives varied in the range 0.1– 0.9. UV spectra for each sample were taken at 25 °C (see figures 2 and 3) .

R-(-)-N-Benzyl-2-amino-1-butanol 1

R-(-)-2-amino-1-butanol (71.2 g, 0.8 mol), benzyl chloride (25.3 g, 0.2 mol) and Na_2CO_3 (20 g, 0.18 mol)

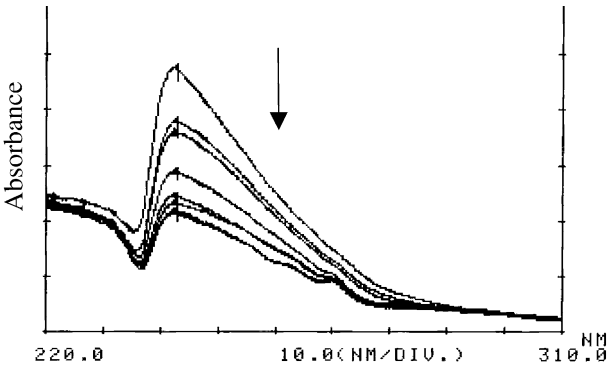


Figure 1. UV–Vis spectra of **5** (2×10^{-4} mol dm^{-3}) in the presence of L-Ala-OMe·HCl (5×10^{-5}–3×10^{-3} mol dm^{-3}).

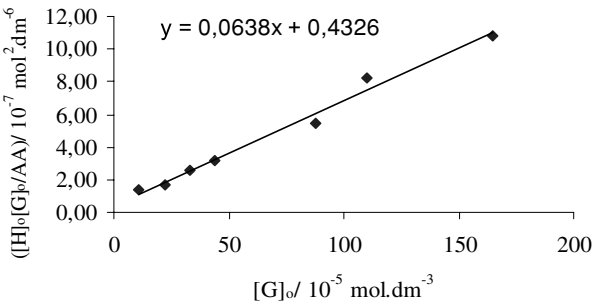


Figure 2. Typical plot of $[H]_o[G]_o/\Delta A$ versus $[G]_o$ for the host–guest complexation of **5** and L-Ala-OMe·HCl in $CHCl_3$: MeOH (25:2), at 25 °C.

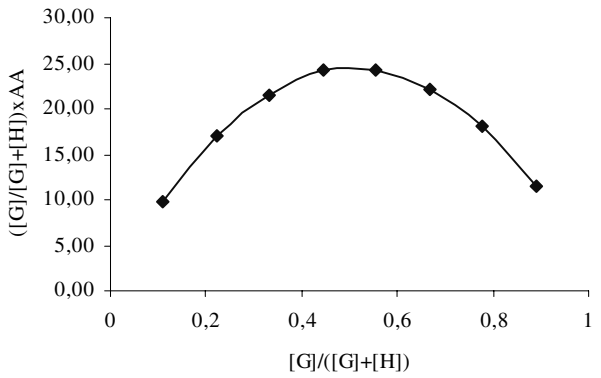


Figure 3. Job plots for L-Ala-OMe·HCl and **5**.

were placed in a 250 mL two-necked round bottomed flask equipped with an addition Dean Stark apparatus. The mixture was stirred at 100 °C for 8 h under dry N_2. Then the mixture was cooled and $CHCl_3$ (100 mL) was added to the mixture and refluxed for 1 h. The $CHCl_3$ layer was separated from the solid phase. The remaining solid was re-extracted with $CHCl_3$ (3 × 25 mL).The combined $CHCl_3$ layers were dried (Na_2SO_4) and evaporated. The product was distilled at reduced pressure to give 33 g (94%), $[\alpha]^{20}{}_D = -25.63$ (c 0.8, EtOH). b.p. 98–100 °C/0.1 mm Hg, m.p. 71–72 °C. M.w. 179 g (Found: C, 73.67; H, 9.63; N, 7.74; $C_{11}H_{17}NO$ requires C, 73.70; H, 9.56; N, 7.80); ir ν: 3287, 3076, 2931, 2836, 1467, 1361, 1068 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.98 (3H, t, $J = 7.48$ Hz), 1.48–1.63 (2H, m), 2.64–2.68 (1H, m), 3.38–3.85 (2H, ddd), 3.75–3.85 (2H, dd), 7.29–7.39 (5H, m); ^{13}C NMR $CDCl_3$) δ 10.73, 24.64, 51.48, 60.21, 63.05, 127.45, 128.86, 140.83.

(3R,8R)-(-)-Dihydroxymethyl-N,N′-dibenzyl-4, 7-diaza-decane 2

R-(-)-*N*-Benzyl-2-amino-1-butanol (22 g, 0.12 mol), 1,2-dibromoethane (3.83 g, 0.02 mol) and Na_2CO_3 (2.17 g, 0.02 mol) were stirred at 110 °C for 12 h under N_2. Then the mixture was cooled and $CHCl_3$ (100 mL) was added to the mixture and refluxed for 1 h. The $CHCl_3$ layer was separated from the solid phase. The remaining solid was re-extracted with $CHCl_3$ (3 × 25 mL).The combined $CHCl_3$ layers were dried (Na_2SO_4) and evaporated. The excess amine (1) was distilled at reduced pressure at 98–100 °C/0.1 mm Hg. After the excess amine was distilled, the product was purified by flash column chromatography on silica gel (eluent: ethyl acetate/n-hexane 1/2) to give 6.2 g (78.76 %). $[\alpha]^{25}_D = -58$ (*c* 1.2, $CHCl_3$); ir: ν 3326, 3108, 2975, 2937, 1497, 1464, 1335, 1214, 1109, 703, 625 cm^{-1} ; ^1H NMR ($CDCI_3$) δ 0.96 (t, $J = 7.5$ Hz, 6H), 1.46 (m, 4H), 2.50 (m, 2H), 2.70–2.85 (dd, 4H), 3.38–3.60 (ddd, 4H), 3.67–3.71 (m, 4H) 7.20–7.40 (m, 10H); ^{13}C NMR ($CDCI_3$) δ 10.51, 25.40, 45.80, 56.63, 62.85, 63.25, 126.50, 127.98, 129.10, 14.46; Anal. Calcd. For $C_{24}H_{36}N_2O_2$: C, 74.96; H, 9.44; N, 7.28; Found: C, 74.21 H, 9.68; N, 6.98.

1,2-Bis-(2-hydroxy ethoxy)benzene

This compound prepared according to the procedure recorded in the literature [18] from catechol (11.0 g, 0.1 mol) diethylamine hydrochloride (as a catalyst) and ethylene oxide (9.8 mL, 0.2 mol) to give 18.8 g, 95%; m.p. 81–83 °C.

1,2-Bis-(2-p-tolylsulphonyl ethoxy)benzene

This compound was prepared according to the procedure recorded in the literature [18] from 1,2-Bis-(2-hydroxy-ethoxy)benzene (26.73 g, 0.135 mol), pyridine (110 mL) at −10 °C and *p*-toluenesulphonylchloride (51.43 g, 0.27 mol) to give 66 g, 96%; m.p. 95–95.5 °C.

(5R,18R)-N,N′-dibenzyl-5,18-diethyl-1,4-diaza-4,7,10,13-tetraoxacyclooctadecane 5

To a suspension of NaH (0.53 g, 0.0176 mol, % 80 in mineral oil) in 120 mL dry THF at 0 °C was added a solution of (3*R*,8*R*)-(-)-dihydroxymethyl-N,N′-dibenzyl-4,7-diazadecane (1.5 g, 0.00391 mol) in 200 mL of THF. The reaction mixture was refluxed for 1.5 h. The reaction after cooling to 0 °C, a solution of triethyl-eneglycol ditosylate (1.79 g, 0.00391 mol) in 200 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 extract with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with 80 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 1 g (52%) of an oil; $[\alpha]^{25}_D = +30.5$ (c 1.4, $CHCl_3$), ir: ν 3089, 3063, 3029, 2960, 2928, 1612, 1503, 1458, 1362, 1304, 1246, 1118, 1034, 732, 701 cm^{-1} ; ^1H nmr ($CDCl_3$) δ 0.73–0.79 (t, $J = 8.00$, 6H), 1.15–1.22 and 1.26–1.33 (m, 4H), 2.38–2.68 (m, 6H),3.31–3.66 (m, 20H), 7.07–7.22 (m, 10H); ^{13}C nmr ($CDCI_3$) δ 11.94, 21.66, 49.68, 55.53, 61.35, 70.81, 70.92, 71.07, 72.34, 126.40, 127.95, 128.58, 141.63; Anal. Calc. For $C_{30}H_{46}N_2O_4$: C, 72.29; H, 9.24; N, 5.62, Found: C, 72.00; H, 9.50; N, 5.60.

(5R,18R)-N,N′-dibenzyl-5,18-diethyl-11,12-benzo-1, 4-diaza-4,7,10,13-tetraoxacyclooctadec-11-ene 6

To a suspension of NaH (0.50 g, 0.0176 mol, % 80 in mineral oil) in 150 mL dry THF at 0 °C was added a solution of (3*R*,8*R*)-(-)-dihydroxymethyl-N,N′-dibenzyl-4,7-diazadecane (1.5 g, 0.00391 mol) in 200 mL of THF. The reaction mixture was refluxed for 1.5 h. The reaction after cooling to 0 °C, a solution of 1,2-bis-(2-*p*-tolylsulphonyl ethoxy)benzene (1.98 g, 0.00391 mol) in 200 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 extract with CH_2CI_2 (3 × 100 mL). The combined

organic layers were washed with 80 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 1.3 g (61%) of an oil; $[\alpha]_D^{25} = +17.2$ (c 2, $CHCl_3$), ir: ν 3063, 3031, 2966, 2935, 1645, 1592, 1510, 1452, 1266, 1214, 1182, 1131, 1053, 932, 822, 732 cm^{-1}; ^1H nmr ($CDCI_3$) δ 0.72–0.81 (t, $J = 7.90$, 6H), 1.14–1.33 and 1.34–1.50 (m, 8H), 2.55–2.70 (m, 2H), 3.42–3.58 (m, 10H), 3.74–3.76 (m, 4), 4.26–4.28 (m, 2H), 6.84–6.91 (m, 4H), 7.06–7.23 (m, 10H); ^{13}C nmr ($CDCI_3$) δ 12.58, 24.95, 50.60, 54.20, 68.70, 70.10, 71.80, 72.20, 115.40, 122.70, 127.60, 128.92, 129.50, 140.45, 149.23; Anal. Calc. For $C_{34}H_{46}N_2O_4$: C, 74.73; H, 8.42; N, 5.13, Found: C, 74.98; H, 8.00; N, 5.60.

References

1. E.B. Kyba, K. Koga, L.R. Sousa, M.G. Siegel, and D.J. Cram: *J. Am. Chem. Soc.* **95**, 2692 (1973).
2. For cyclophanes, see: (a) P.C. Kearney, L.S. Mizoue, R.A. Kumpf, J.E. Forman, A. McCurdy, and D.A. Dougherty: *J. Am. Chem. Soc.* **115**, 9907 (1993); (b) R.J. Pieters, J. Cuntze, M. Bonnet, and F. Diedrich: *J. Chem. Soc., Perkin Trans.* **2**, 1891 (1997); (c) S.M. Ngola, P.C. Kearney, S. Mecozzi, K. Russell, and D.A. Dougherty: *J. Am. Chem. Soc.* **121**, 1192 (1999).
3. For crown ethers, see: (a) J.S. Bradshaw, P. Huszthy, C.W. McDaniel, C.Y. Zhu, N.K. Dalley, R.M. Izatt, and S. Lifson: *J. Org. Chem.* **56**, 4193 (1991); (b) X.X. Zhang, J.S. Bradshaw, and R.M. Izatt: *Chem. Rew.* **95**, 3313 (1997); (c) E. Samu, P. Huszthy, L. Somogyi, and M. Hollosi: *Tetrahed: Asymm.* **10**, 2775 (1999); (d) E. Samu, P. Huszthy, G. Horvath, A. Szöllosy, and A. Neszmelyi: *Tetrahed: Asymm.* **10**, 3615 (1999); (e) H. Zhaou and W. Hua: *J. Org. Chem.* **65**, 2933 (2000); (f) J.S. Bradshaw, K.E. Krakowiak, and R.M. Izatt: *J. Heterocycl. Chem.* **26**, 565 (1989).
4. For cyclodextrins, see: (a) M. Maletic, H. Wennemers, and D.Q. McDonald: *Angew. Chem. Int. Ed. Engl.* **35**, 1490 (1996); (b) R. Breslow, Z. Yang, R. Ching, G. Trojiandt, and F. Odobel: *J. Am. Chem. Soc.* **120**, 3536 (1998).
5. J.F. Stoddart and Chiral: *Top. Stereochem.* **17**, 207 (1987).
6. G.W. Gokel: In J.F. Stoddart (ed.), *Crown Ethers and Cryptands, Monographs in Supramolecular Chemistry*, The Royal Society of Chemistry, Cambridge, England (1991) .
7. J.-P. Joly and G. Schröder: *Tetrahedron Lett.* **38**, 8197 (1997).
8. D.J. Chadwick, I.A. Cliffe, and I.O. Sutherland: *J. Chem. Soc., Chem. Commun.*, 992 (1981)..
9. C.-P. Du, J.-S. You, X.-Q. Yu, C.-L. Liu, J.-B. Lan, and R.-G. Xie: *Tetrahed: Asymm.* **14**, 3651 (2003).
10. X. Chen, D.-M. Du, and W.-T. Hua: *Tetrahed: Asymm.* **14**, 999 (2003).
11. N. Demirel and Y. Bulut: *Tetrahed.: Asymm.* **14**, 2633 (2003).
12. N. Demirel, Y. Bulut, and H. Hoşgören: *Tetrahed: Asymm.* **15**, 2045 (2004).
13. Y. Turgut and H. Hoşgören: *Tetrahed.: Asymm.* **14**, 3815 (2003).
14. Y. Turgut, E. Şahin, M. Toğrul, and H. Hoşgören: *Tetrahed: Asymm.* **15**, 1583 (2004).
15. M.Z. Köylü, N. Demirel, F. Doganal, A. Yilmaz, H. Hoşgören, M. Balci, *J. Incl. Phenom. Macrocycl. Chem.* **52**, 51 (2005).
16. (a) J. Polster and H. Lachman, *Spectrometric Titrations*. VCH: Wienheim, 1989. (b) K.A. Connors, *Binding Constans. The Measurement of Molecular Complex*. Wiley: New York, 1987. (c) H.A. Benesi and J.H. Hildebrand, *J. Am. Chem. Soc.* **71**, 2703 (1949).
17. K. Hirose: *J. Incl. Phenom. Macrocycl. Chem.* **39**, 193 (2001).
18. G. Topal, N. Demirel, M. Toğrul, Y. Turgut, and H. Hoşgören: *J. Heterocycl. Chem.* **38**, 281 (2001).