Tetrahedron: *Asymmetry* 19 (2008) 2020–2025

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Synthesis of new chiral calix[4]azacrowns for enantiomeric recognition of carboxylic acids

Havva Nur Demirtas, Selahattin Bozkurt, Mustafa Durmaz, Mustafa Yilmaz, Abdulkadir Sirit *

Department of Chemistry, Selçuk University, 42099 Konya, Turkey

ARTICLE INFO

Article history:
Received 16 June 2008
Accepted 18 August 2008
Available online 8 September 2008

ABSTRACT

Two novel chiral calix[4]azacrown ethers **4** and **5** bearing a furfuryl group on the nitrogen atom were developed by the reaction of dibromo- or ditosyl derivatives of *p*-*tert*-butylcalix[4]arenes **2** and **3** with a chiral diol, **1**. The enantioselective recognition of these receptors towards the enantiomers of racemic carboxylic acids has been studied by ^{1}H NMR spectroscopy. The molar ratio and the association constants of the chiral compounds **4** and **5** with each of the enantiomers of guest molecules were determined by using Job plots and a nonlinear least-squares fitting method, respectively. The Job plots indicate that both of the hosts form 1:1 instantaneous complexes with (*R*)- or (*S*)-mandelic acid and (L)- or (D)-dibenzoyltartaric acid. The receptors exhibited different chiral recognition abilities towards the enantiomers of racemic guests.

1. Introduction

Chiral recognition is an essential phenomenon in biological systems such as enzymes, antibodies or genes.[1] In this process, the functional groups of molecular receptors form complexes preferentially with one of the enantiomers of a chiral molecule by noncovalent interactions such as hydrogen bonding, electrostatic interaction and hydrophobic interaction.[2]

Several approaches have already been developed for the evaluation of chiral recognition, including spectroscopic, chromatographic and electrochemical techniques. Among them, NMR spectroscopy has been shown to be a powerful method for investigating the chiral recognition interaction between a chiral receptor and an analyte in solution.[3] Detailed information regarding the nature of these interactions and the structure of the complexes can also be provided from NMR experiments. NMR spectra of enantiomers in an achiral medium display the same chemical shifts. Enantiodifferentiation in the spectra requires the use of a chiral medium that converts the mixture of enantiomers into a mixture of diastereomeric complexes. These complexes are held together by weak intermolecular interactions such as van der Waals forces and/or hydrogen bonds.[4]

Chiral carboxylic acids are the basic building blocks of many natural products, biological molecules and drugs. Therefore, the study of the enantiomeric recognition of these compounds is of particular significance for an understanding of the interactions between biological molecules,[5] and offer new perspectives for the development of novel enantioselective sensors, asymmetric catalysts[6] and other molecular devices.[7]

Among the several types of host molecules for recognition, calixarenes[8] offer a number of advantages in terms of their selectivity and efficiency of binding. Despite the increasing use of calixarenes as receptors for anions, cations and neutral molecules,[9] relatively few investigations have been reported for chiral guests such as amines,[10] organic ammonium salts,[11] amino alcohols,[12] carboxylic acids[13] and amino acids.[14] The most frequently used strategies for introducing chiral recognition ability into calixarenes are anchoring chiral subunits at either the lower or the upper rims of the calixarene macrocyclic ring. Chiral receptors that are based on the calixarene platform may have potential applications in the preparation, separation and analysis of enantiomers. In this regard, investigations conducted on the synthesis and chiral recognition properties of chiral calix[4]arene derivatives have attracted considerable attention.

Previously, we had reported the synthesis of novel chiral calix[4]arenes containing various functionalities including crown[15] and azacrown ethers,[16] amides,[17] Schiff bases,[18] as well as their enantiomeric recognition properties towards chiral amines and amino acid derivatives. Herein, we report the synthesis of novel calix[4]arene derivatives bearing a chiral azacrown-5 moiety at the lower rim, and their recognition abilities for racemic mandelic and dibenzoyltartaric acid by ^{1}H NMR spectroscopy.

2. Results and discussion

2.1. Synthesis

Calix[4]azacrowns containing a calix[4]arene platform and an azacrown unit in their framework have received much attention because of their special structures and favourable complexing

* Corresponding author. Tel.: +90 332 3238220/5405; fax: +90 332 3238225.
E-mail address: asirit42@yahoo.com (A. Sirit).

0957-4166/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2008.08.015

properties towards anions and cations.[19] The basicity of the nitrogen atom in the azacrown loop can also play a major role in the enantioselective recognition of carboxylic acids. Thus, a suitably designed chiral calix[4]azacrown derivative might be a good candidate. This can be realized by incorporating a chiral azacrown ether moiety as a binding site into the molecular framework of a calix[4]arene. A multistep route for preparing the furfuryl-armed calix[4]azacrown ethers is shown in Schemes 1 and 2.

Thus, following the literature procedure,[20] one of the starting materials, chiral diol **1**, was prepared by the ring opening of the (*R*)-styrene oxide with furfuryl amine in high yield. The furfuryl-armed calix[4]azacrowns were obtained in 41 and 53% yields by the reaction of the p-*tert*-butylcalix[4]arene derivatives **2**[21] or **3**[22] with chiral amino diol **1** in DMF.

The products were characterized by a combination of ^{1}H NMR, ^{13}C NMR, FAB MS, IR and elemental analysis. The conformational characteristics of calix[4]arenes were conveniently estimated by way of the splitting pattern of the $ArCH_2Ar$ methylene protons in the ^{1}H and ^{13}C NMR spectra. ^{1}H and ^{13}C NMR data showed that chiral *p-tert*-butylcalix[4]arene derivatives **4** and **5** are in a cone conformation.

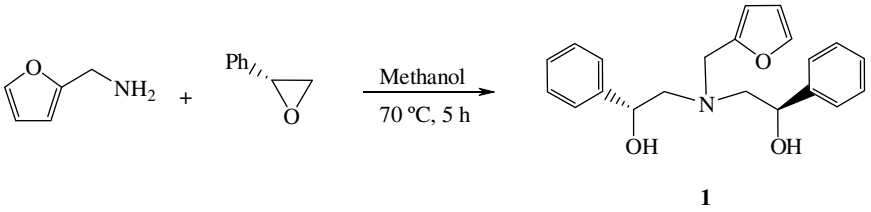
2.2. Chiral recognition by ^{1}H NMR of host–guest complexes

Next, NMR experiments were undertaken to assess the chiral recognition properties of ligands **4** and **5** by ^{1}H NMR, and the racemic guests, mandelic acid and dibenzoyltartaric acid were chosen as probes. The signal of the methine hydrogen of mandelic acid and dibenzoyltartaric acid is a sharp singlet and does not overlap with the peaks of the other proton signals in their ^{1}H NMR spectra. Therefore, it is an ideal probe for discrimination.

Figure 1 shows the ^{1}H NMR spectra for mandelic acid (10 mM) in the absence and presence of the chiral receptors **4** and **5** (10 mM). When a solution of racemic mandelic acid (10 mM in $CDCl_3$) was gradually added to a 10 mM solution of **4** and **5** in $CDCl_3$ until the ratio reached 1:1, the methine proton signals of mandelic acid separated into two singlets with an upfield shift. The chemical shift differences were determined to be 0.24 and 0.29 ppm for compound **4** (Fig. 1d), and 0.21 and 0.28 ppm for compound **5** (Fig. 1e), respectively. A similar phenomenon was observed when a solution of racemic dibenzoyltartaric acid (10 mM in $CDCl_3$) was treated with an equimolar amount of receptors **4** and **5** (Fig. 2), the methine proton signals of dibenzoyltartaric acid separated into two singlets with an upfield shift (from δ 6.01 ppm to 5.93 and 5.92 ppm for **4**, and to 5.97 and 5.96 ppm for **5**). The methine proton of (*S*)-mandelic acid and D-dibenzoyltartaric acid appeared at lower field than that of (*R*)-mandelic acid and L-dibenzoyltartaric acid, which was confirmed by an increase of the methine proton signal of (*S*)- and D-guest when (*S*)-mandelic acid and D-dibenzoyltartaric acid were added into the complex of racemic guests with **4** or **5**.

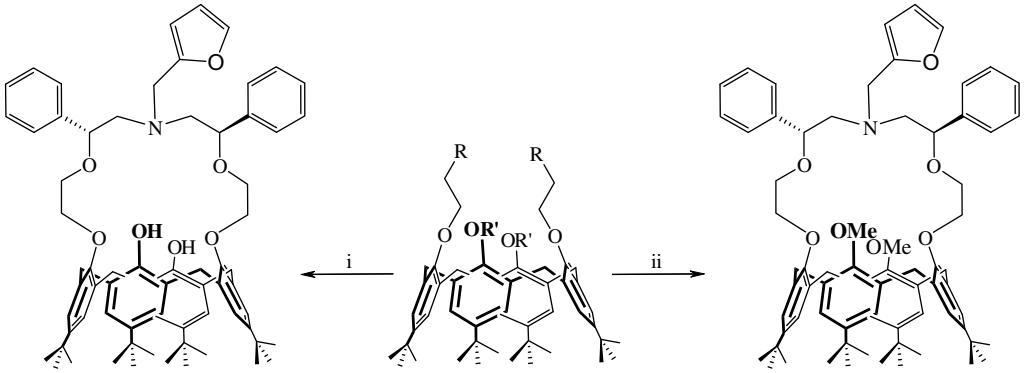
The stoichiometry of the complexes between the receptors **4** and **5** and the guests was determined by a continuous variation plot. The total concentration of the hosts and the guest was kept constant (10 mM) in $CDCl_3$, whilst the molar fraction of the guest {[G]/([H]+[G])} was continuously varied. The Job plots of **4** with (*R*)- and (*S*)-mandelic acid and L- and D-dibenzoyltartaric acid are illustrated in Figures 3 and 4, respectively. Maxima were observed when the molar ratio of the compound **4** and (*R*)- or (*S*)-mandelic acid and L- or D-dibenzoyltartaric acid was 1:1 (X = 0.5), which indicated that host **4** and the guests formed 1:1 instantaneous complexes. It is apparent that the chemical shift changes of (*R*)-mandelic acid and D-dibenzoyltartaric acid were greater than that of corresponding enantiomers (*S*)-mandelic acid and L-dibenzoyltartaric acid in the presence of compound **4**. Meanwhile, all Job plots recorded for **5** indicated that 1:1 instantaneous complexes were also formed with all these enantiomerically pure guests, respectively.

In order to further evaluate the complexation and discrimination abilities of **4** and **5**, the titration curves of compounds **4** and



1

Scheme 1. Preparation of amino diol **1**.



4 **2**: R = Br, R' = H; **3**: R = OTs, R' = Me **5**

Scheme 2. Reagents: (i)–(ii) Chiral amino diol **1**, NaH, DMF, reflux.

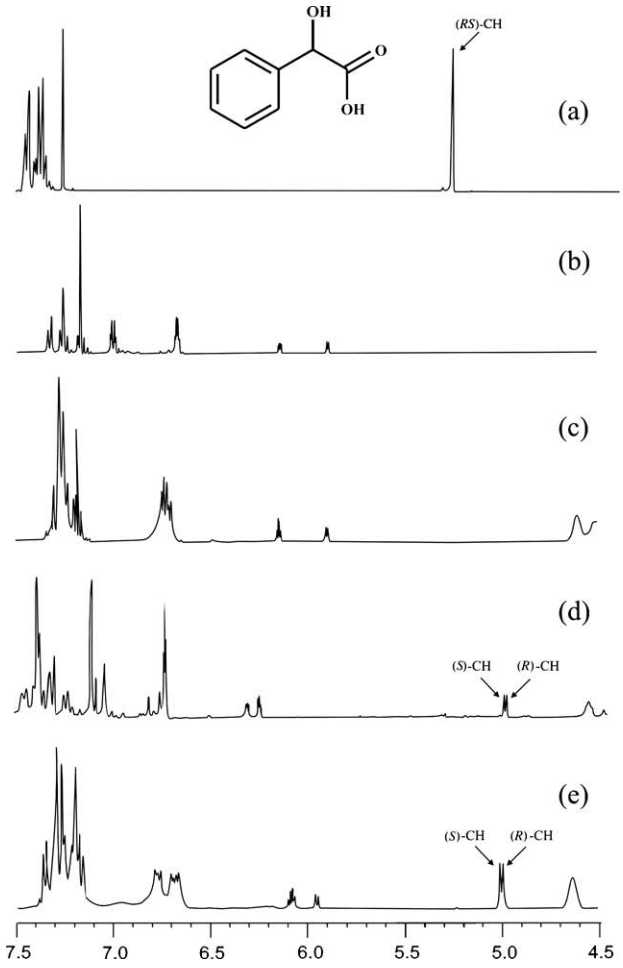


Figure 1. The 400 MHz ^{1}H NMR spectra of the racemic mandelic acid (a); **4** (b); **5** (c); and the complexes between **4** and **5** (10 mM) and racemic mandelic acid (10 mM) in $CDCl_3$ (d); (e).

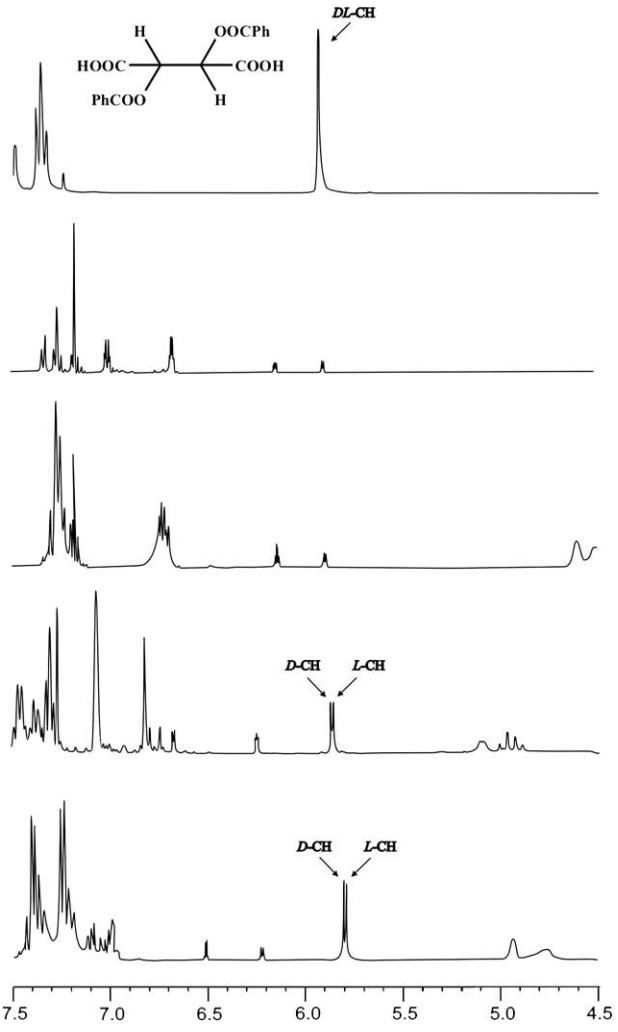


Figure 2. The 400 MHz ^{1}H NMR spectra of the (±)-dibenzoyltartaric acid (a); **4** (b); **5** (c); and the complexes between **4** and **5** (10 mM) and (±)-dibenzoyltartaric acid (10 mM) in $CDCl_3$ (d); (e).

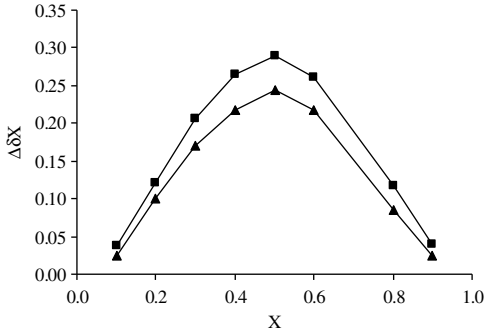


Figure 3. Job plots of **4** with (*R*)- and (*S*)-mandelic acid [X = molar fraction of mandelic acid, $\Delta\delta$ = chemical shift change of the methine proton of (*R*)- and (*S*)-mandelic acid]. (■) With pure (*R*)-mandelic acid, (▲) with pure (*S*)-mandelic acid.

5 with the enantiomers of mandelic acid or dibenzoyltartaric acid were plotted, respectively (Figs. 5 and 6). It was found that the signals of the methine protons of (*R*)- and (*S*)-mandelic acids or D- and L-dibenzoyltartaric acids in the ^{1}H NMR spectra continuously shifted upfield and reached a limiting value along with the concentration of compounds **4** and **5** gradually increasing. Moreover, the signals of various protons of the hosts were shifted downfield. These shifts are due to specific host–guest complexation, and indicated that the interaction between the host and guest also happened by multiple hydrogen bonds.

The formation of diastereomeric host–guest complexes possibly occurs through interaction of the nitrogen atom in the azacrown loop and the carboxyl group in the chiral carboxylic acid. Noncovalent interactions between the guests and hydrogen bonding sites defined by ethylene oxygens, furan oxygen and phenolic oxygen contribute to the stabilization of these complexes as well as π–π interactions. The association constants of **4** and **5** with enantiomerically pure guests were determined from the titration curves by the nonlinear least-squares fitting method[23] (Table 1). The results showed that (*R*)- and L-enantiomers of the guests were more strongly bound to **4** and **5** than (*S*)- and D-enantiomers. Moreover, the binding ability of host compounds with mandelic acid was much stronger than that with dibenzoyltartaric acid. This confirmed further that enantioselective recognition had occurred between receptors **4** and **5** and the racemic guests.

From Table 1, we found that both compounds had shown good chiral recognition ability towards the enantiomers of the racemic carboxylic acids we had chosen. The chiral receptors (**4** and **5**) are structurally similar in that both contain a group capable of hydrogen bonding as part of a stereogenic centre attached directly to a phenyl group. Though the number of recognition sites that are necessary for producing chiral recognition is due to the shape of the receptor, three ordinary recognition sites are required in the receptor molecules.[24] In this study, chiral calix[4]crowns **4** and **5**

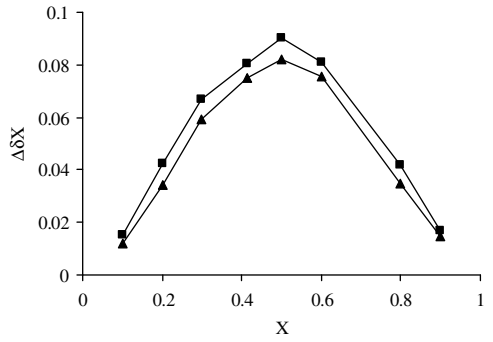


Figure 4. Job plots of **4** with L- and D-dibenzoyltartaric acid [X = molar fraction of dibenzoyltartaric acid, $\Delta\delta$ = chemical shift change of the methine proton of L- and D-dibenzoyltartaric acid]. (■) With pure L-dibenzoyltartaric acid, (▲) with pure D-dibenzoyltartaric acid.

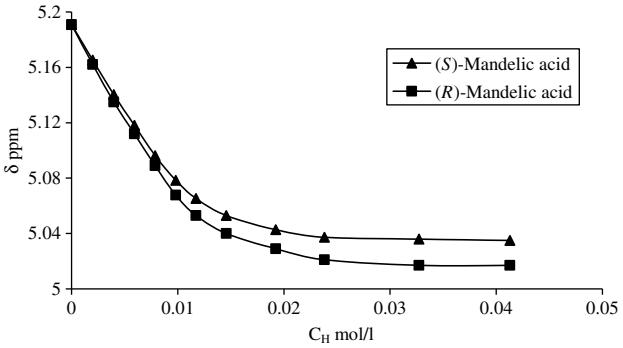


Figure 5. ^{1}H NMR titration curves of compound **4** with (*R*)- and (*S*)-mandelic acids.

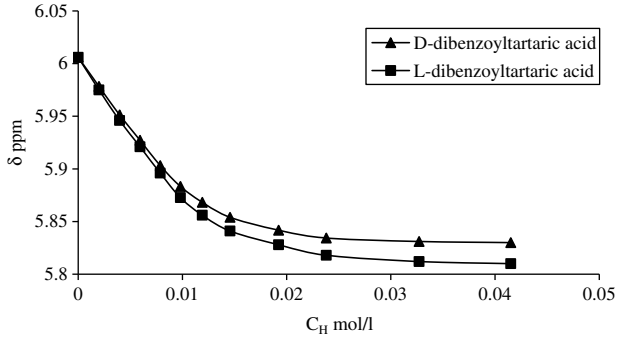


Figure 6. ^{1}H NMR titration curves of compound **4** with (L)- and (D)-dibenzoyltartaric acids.

Table 1
Association constants K_a $(mol/L)^{-1}$ of **4** and **5** with chiral carboxylic acids

Entry	Host	Guests	K_a $(mol/L)^{-1}$	K_a (*R* or L)/K_a (*S* or D)
1	**4**	(*R*)-Mandelic acid	$(1.27 \pm 0.07) \times 10^3$	1.86
2	**4**	(*S*)-Mandelic acid	$(0.68 \pm 0.05) \times 10^3$	
3	**4**	L-DBTA	$(2.92 \pm 0.26) \times 10^2$	1.25
4	**4**	D-DBTA	$(2.34 \pm 0.19) \times 10^2$	
5	**5**	(*R*)-Mandelic acid	$(1.03 \pm 0.08) \times 10^3$	1.43
6	**5**	(*S*)-Mandelic acid	$(0.72 \pm 0.06) \times 10^3$	
7	**5**	L-DBTA	$(1.98 \pm 0.24) \times 10^2$	1.11
8	**5**	D-DBTA	$(1.79 \pm 0.19) \times 10^2$	

interact with a minimum of three of the possible recognition groups (ethylene oxygens, amine nitrogen, furan oxygen, aromatic groups and phenolic oxygens) in order to exhibit enantioselective binding to the mandelic acid and dibenzoyltartaric acid.

According to Table 1, we also found that compounds **4** and **5** had shown much better chiral recognition ability to mandelic acid than to dibenzoyltartaric acid. Among the guest molecules, mandelic acid contains a hydroxy group at the α-position of the carbonyl group. This oxygen function may act as an additional binding site and play a crucial role for chiral recognition.[5a] Since the methine protons are adjacent to the hydroxy group, these protons must be significantly influenced by the possible recognition groups of the chiral calix[4]azacrown derivative.

3. Conclusions

In conclusion, two novel chiral calix[4]azacrown ethers in which a furfuryl group is attached on the nitrogen atom were synthesized by the reaction of dibromo- or ditosyl derivatives of *p*-*tert*-butylcalix[4]arene with a chiral diol. The enantioselective recognition of these receptors has been studied by ^{1}H NMR spectroscopy. The receptors exhibited different chiral recognition abilities towards the enantiomers of racemic mandelic acid and dibenzoyltartaric acid. The stoichiometric ratio of the host–guest complexes was determined as 1:1 instantaneous complexes according to Job's method of continuous variations. The results indicate that the multiple hydrogen bonding, steric hindrance, structural rigidity or flexibility and π−π stacking between the aromatic groups may be responsible for the enantiomeric recognition.

4. Experimental

4.1. Reagents and general methods

Melting points were determined on an Electrothermal 9100 apparatus in a sealed capillary, and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Varian 400 MHz spectrometer in $CDCl_3$. IR spectra were obtained on a Perkin Elmer 1605 FTIR spectrometer using KBr pellets. Optical rotations were measured on an Atago AP-100 digital polarimeter. The HPLC measurements were carried out on Agilent 1100 equipment connected with a Zorbax RX-C18 column. Elemental analyses were performed using a Leco CHNS-932 analyzer. FAB-MS spectra were taken on a Varian MAT 312 spectrometer.

Analytical TLC was performed using Merck prepared plates (Silica Gel 60 F_{254} on aluminium). Flash chromatography separations were performed on a Merck Silica Gel 60 (230–400 mesh). All reactions, unless otherwise noted, were conducted under a nitrogen atmosphere. All starting materials and reagents used were of standard analytical grade from Fluka, Merck and Aldrich, and were used without further purification. Toluene was distilled from CaH_2 and stored over sodium wire. Other commercial grade solvents were distilled, and then stored over molecular sieves. The drying agent employed was anhydrous $MgSO_4$.

4.2. Syntheses

4.2.1. (*R*,*R*)-2-[Furfuryl-(2-hydroxy-2-phenylethyl)-amino]-1-phenylethanol 1

To a cooled solution of furfurylamine (1.07 g, 9.985 mmol) in 2 mL of methanol, (*R*)-styrene oxide (2.40 g, 19.975 mmol) in 4 mL of methanol was added at 0 °C and stirred for 1 h. It was then refluxed for 4 h. After the completion of the reaction, the solvent was removed under reduced pressure to give isomeric diols as syrupy mass which on flash column chromatography using ethylacetate/hexane (20:80) as eluent yielded the major isomer as an oil (yield 86%); $[\alpha]_D^{25} = -72$ (*c* 1, $CHCl_3$). IR (KBr): 3342, 3281, 3102,

2994, 2826, 1490, 1368, 1350, 1275, 1174, 1060, 726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.32 (dd, 1H, J_1 = 1.7 Hz, J_2 = 0.8 Hz, Ar*H*, furfuryl), 7.26–7.19 (m, 10H, Ar*H*), 6.27 (dd, 1H, J_1 = 3.3 Hz, J_2 = 1.8 Hz, Ar*H*, furfuryl), 6.16 (dd, 1H, J_1 = 3.3 Hz, J_2 = 0.6 Hz, Ar*H*, furfuryl), 4.68 (dd, 2H, J_1 and J_2 = 4.7 Hz, –C*H*-phenyl), 4.34 (2H, br s, –O*H*), 3.85 (d, 1H, J = 15.1 Hz, NCH_2-furfuryl), 3.78 (d, 1H, J = 15.1 Hz, NCH_2-furfuryl), 2.74–2.68 (m, 4H, NCH_2CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 146.2, 144.1, 143.4, 128.3, 127.4, 125.2, 113.9, 105.1, 72.5, 63.9, 54.1; FAB-MS *m/z*: (360.28) $[M+Na]^+$. Anal. Calcd for $C_{21}H_{23}NO_3$ (337.41): C, 74.75; H, 6.87; N, 4.15. Found: C, 74.52; H, 6.96; N, 3.98.

4.2.2. General procedure for the synthesis of compounds 4 and 5

To a suspension of NaH (60% in mineral oil) 0.14 g (3.56 mmol) in DMF (3 mL) was added a solution of **1** 0.31 g (0.89 mmol) in DMF (5 mL) dropwise at 0 °C under a nitrogen atmosphere. The mixture was stirred at room temperature for 2 h. Then **2** or **3** (0.89 mmol) in DMF (20 mL) was added slowly to the mixture. The mixture was stirred at room temperature for 2 days. The DMF extract was evaporated and water (10 mL) was added to the remaining residue. The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and combined organic phase was dried over $MgSO_4$. The solvent was evaporated and the crude product was purified by flash chromatography on silica gel (EtOAc/hexane 1:15 as eluent) to afford **4** or **5** as white crystals.

4.2.2.1. Compound 4. Yield 41%; white crystal; Mp 114–118 °C; $[\alpha]_D^{25} = +17$ (*c* 1, $CHCl_3$). IR (KBr): 3422, 2961, 2866, 1486, 1458, 1362, 1198, 1120, 1025, 872, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.36–6.95 (m, 17H, Ar*H* and ArO*H*), 6.72–6.68 (m, 4H, Ar*H*), 6.16 (dd, 1H, J_1 = 3.3 Hz, J_2 = 0.6 Hz, Ar*H*, furfuryl), 5.91 (d, 1H, J = 3.1 Hz, Ar*H*, furfuryl), 4.39 (d, 2H, J = 12.9 Hz, ArCH_2-Ar), 4.35 (d, 2H, J = 12.9 Hz, ArCH_2Ar), 4.22 (t, 2H, J = 5.4 Hz, –OC*H*ph), 4.03–3.93 (m, 4H, –OCH_2CH_2), 3.71–3.63 (m, 2H, phCH_2N), 3.57–3.51 (m, 4H, –OCH$_2$CH_2), 3.25 (d, 2H, J = 13.1 Hz, ArCH_2Ar), 3.23 (d, 2H, J = 13.1 Hz, ArCH_2Ar), 3.03 (d, 4H, J = 5.7 Hz, –CHCH_2N), 1.25 (s, 18H, C(CH_3)$_3$), 0.84 (s, 18H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 154.3, 151.3, 150.4, 146.8, 142.0, 141.6, 141.1, 132.8, 128.5, 127.5, 125.7, 125.2, 110.2, 107.9, 82.6, 75.5, 67.3, 61.8, 53.0, 34.5, 34.1, 32.1, 31.7, 31.6, 31.3; FAB-MS *m/z*: (1061.22) $[M+Na]^+$. Anal. Calcd for $C_{69}H_{83}NO_7$ (1038.40): C, 79.81; H, 8.06; N, 1.35. Found: C, 80.06; H, 8.57; N, 1.19.

4.2.2.2. Compound 5. Yield 53%; white crystal; Mp 113–116 °C; $[\alpha]_D^{25} = -6.0$ (*c* 1, $CHCl_3$). IR (KBr): 2962, 2866, 1482, 1362, 1203, 1121, 1023, 870, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.36–7.22 (m, 15H, Ar*H*), 6.75–6.69 (m, 4H, Ar*H*), 6.16 (br, 1H, Ar*H*, furfuryl), 5.94 (br, 1H, Ar*H*, furfuryl), 4.48 (br, 2H, ArCH_2-Ar), 4.44 (br, 2H, ArCH_2Ar), 4.20 (t, 2H, J = 5.4 Hz, –OC*H*ph), 4.08–3.96 (m, 4H, –OCH_2CH_2), 3.90 (br, 6H, –OCH_3), 3.72–3.65 (m, 2H, phCH_2N), 3.60–3.53 (m, 4H, –OCH$_2$CH_2), 3.10–3.20 (m, 4H, ArCH_2-Ar), 3.00 (br, 4H, –CHCH_2N), 1.22 (br, 18H, C(CH_3)$_3$), 1.08–0.90 (br, 18H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 155.2, 151.3, 150.8, 146.9, 142.4, 141.6, 132.9, 127.3, 125.6, 125.2, 110.2, 108.0, 82.6, 74.7, 67.6, 61.1, 52.4, 34.3, 34.1, 32.3, 31.9, 31.5, 31.2, 22.6; FAB-MS *m/z*: (1089.30) $[M+Na]^+$. Anal. Calcd for $C_{71}H_{87}NO_7$ (1066.45): C, 79.96; H, 8.22; N, 1.31. Found: C, 80.24; H, 8.68; N, 1.03.

4.3. NMR experiments

Samples for analysis were obtained by mixing equimolar amounts of **4** or **5** with the guests in $CDCl_3$, making the concentrations of the hosts (or guests) normally 10 mM.

4.4. Evaluation of the stoichiometric ratio of the host–guest complex (Job plots)

The stoichiometric ratio of the host–guest complex was determined according to Job's method of continuous variations.[25] Equimolar amounts of host and guest compounds were dissolved in $CDCl_3$. These solutions were distributed among nine NMR tubes, with the molar fractions *X* of host and guest in the resulting solutions increasing (or decreased) from 0.1 to 0.9 (and vice versa). The compellation-induced shifts ($\Delta\delta$) were multiplied by *X* and plotted against *X* itself (Job plot).

4.5. NMR host–guest titrations

The guest compound was dissolved in an appropriate amount of solvent and the resulting solution evenly distributed among 10 NMR tubes. The first NMR tube was sealed without any host. The host compound was also dissolved in the appropriate amount of solvent and was added in increasing amounts to the NMR tubes, so that solutions with the following relative amounts (equiv) of host versus guest compound (concentration was 1.0×10^{-2} M) were obtained: 0, 0.20, 0.40, 0.60, 0.80, 1.00, 1.20, 1.50, 2.00, 2.50, 3.50 and 4.50. K_a was calculated by a nonlinear least-squares fitting method for compounds **4** and **5** from the observed $\Delta\delta$ values and the respective host and guest concentrations.

Acknowledgements

This work was supported by the Scientific and Technical Research Council of Turkey (TUBITAK-106T091) and Research Foundation of Selçuk University (BAP-06401067). The provision of studentships (to H.D. and M.D.) by TUBITAK is gratefully acknowledged.

References

1. (a) Lehn, J.-M. *Supramolecular Chemistry. Concepts and Perspectives*; VCH: Weinheim, 1995; (b) Lehn, J.-M. *Angew. Chem., Int. Ed.* **1988**, *27*, 90–112; (c) Crossley, R. Chirality and the Biological Activity of Drugs; CRC: New York, 1995.
2. (a) Marchi-Artzner, V.; Artzner, F.; Karthaus, O.; Shimomura, M.; Ariga, K.; Kunitake, T.; Lehn, J.-M. *Langmuir* **1998**, *14*, 5164–5171; (b) Bohanon, T. M.; Caruso, P.-L.; Denzinger, S.; Fink, R.; Mobius, D.; Paulus, W.; Preece, J. A.; Ringsdorf, H.; Schollmeyer, D. *Langmuir* **1999**, *15*, 174–184; (c) Russell, K. C.; Leize, E.; Van Dorsselaer, A.; Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 209–230; (d) Baudoin, O.; Gonnet, F.; Teulade-Fichou, M.-P.; Vigneron, J.-P.; Tabet, J.-C.; Lehn, J.-M. *Chem. Eur. J.* **1999**, *5*, 2762–2771.
3. (a) Machida, Y.; Nishi, H.; Nakamura, K. *J. Chromatogr., A* **1998**, *810*, 33–41; (b) Schneider, H.-J.; Hacket, F.; Rudiger, V.; Ikeda, H. *Chem. Rev.* **1998**, *98*, 1755–1785; (c) Chankvetadze, B.; Blaschke, G. *J. Chromatogr., A* **2001**, *906*, 309–363; (d) Lee, W.; Bang, E.; Baek, C.-S.; Lee, W. *Magn. Reson. Chem.* **2004**, *42*, 389–395.
4. Dodziuk, H.; Kozminski, W.; Ejchart, A. *Chirality* **2004**, *16*, 90–105.
5. (a) Yang, X.; Wu, X.; Fang, M.; Yuan, Q.; Fu, E. *Tetrahedron: Asymmetry* **2004**, *15*, 2491–2497; (b) Li, B.; Yang, X.; Wu, X.; Luo, Z.; Zhong, C.; Fu, E. *Supramol. Chem.* **2006**, *18*, 507–513.
6. Bozkurt, S.; Durmaz, M.; Yilmaz, M.; Sirit, A. *Tetrahedron: Asymmetry* **2008**, *19*, 618–623.
7. (a) Reinhoudt, D. N. In *Comprehensive Supramolecular Chemistry*; Pergamon Press: New York, 1996; Vol. 10; (b) Kubo, Y.; Maeda, S.; Tokita, S.; Kubo, M. *Nature* **1996**, *382*, 522–524; (c) Murakami, Y.; Kikuchi, J.; Hisaeda, Y.; Hayashida, O. *Chem. Rev.* **1996**, *96*, 721–758; (d) Sanders, J. K. M. *Chem. Eur. J.* **1998**, *4*, 1378–1383; (e) Peczuh, M. W.; Hamilton, A. D. *Chem. Rev.* **2000**, *100*, 2479–2494; (f) Wong, W. L.; Huang, K. H.; Teng, P. F.; Lee, C. S.; Kwong, H. L. *Chem. Commun.* **2004**, 384–385; (g) Hernández, J.; Almaraz, M.; Raposo, C.; Martin, M.; Lithgow, A.; Crego, M.; Caballero, C.; Moran, J. R. *Tetrahedron Lett.* **1998**, *39*, 7401–7404.
8. (a) Gutsche, C. D. *Calixarenes*; The Royal Society of Chemistry: Cambridge, 1989; (b) Vicens, J.; Böhmer, V. *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Kluwer Academic Publishers: Norwell, MA, 1991.
9. (a) Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713–1734; (b) Liu, Y.; Zhao, B.-T.; Zhang, H.-Y.; Ju, H.-F.; Chen, L.-X.; He, X.-W. *Helv. Chim. Acta* **2001**, *84*, 1969–1975; (c) Tuntulani, T.; Thavornyutikarn, P.; Poompradub, S.; Jaiboon, N.; Ruangpornvisuti, V.; Chaichit, N.; Asfari, Z.; Vicens, J. *Tetrahedron* **2002**, *58*, 10277–10285; (d) Asfari, Z.; Böhmer, V.; Harrowfield, M. McB.; Vicens, J. Calixarenes 2001; Kluwer Academic Publishers: Dordrecht, 2001; (e) Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486–516; (f) Kang, S. O.; Begum, R.

A.; Bowman-James, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7882–7894; (g) Hartley, H. J.; James, D. T.; Ward, J. C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3155–3184.
10. (a) Jennings, K.; Diamond, D. *Analyst* **2001**, 1063–1067; (b) Bitter, I.; Köszegi, É.; Grün, A.; Bakó, P.; Pál, K.; Grofcsik, A.; Kubinyi, M.; Balázs, B.; Tóth, G. *Tetrahedron: Asymmetry* **2003**, *14*, 1025–1035; (c) Lynam, C.; Jennings, K.; Nolan, K.; Kane, P.; McKervey, M. A.; Diamond, D. *Anal. Chem.* **2002**, *74*, 59–66.
11. (a) Shizuma, M.; Kadoya, Y.; Takai, Y.; Imamura, H.; Yamada, H.; Takeda, T.; Arakawa, R.; Takahashi, S.; Sawada, M. *J. Org. Chem.* **2002**, *67*, 4795–4807; (b) Bradshaw, J. S.; Huszthy, P.; Wang, T.-M.; Zhu, C.-Y.; Nazarenko, A. Y.; Izatt, R. M. *Supramol. Chem.* **1993**, *1*, 267–275; (c) Izatt, R. M.; Zhang, X. X.; Huszthy, P.; Zhu, C. Y.; Hathaway, J. K.; Wang, T.; Bradshaw, J. S. *J. Inclusion Phenom. Macrocycl. Chem.* **1994**, *18*, 353–367.
12. (a) Sansone, F.; Barboso, S.; Casnati, A.; Sciotto, D.; Ungaro, R. *Tetrahedron Lett.* **1999**, *40*, 4741–4744; (b) Arena, G.; Casnati, A.; Contino, A.; Lombardo, G. G.; Sciotto, D.; Ungaro, R. *Chem. Eur. J.* **1999**, *5*, 738–744.
13. (a) Zheng, Y.-S.; Zhang, C. *Org. Lett.* **2004**, *6*, 1189–1192; (b) Liu, X.-X.; Zheng, Y.-S. *Tetrahedron Lett.* **2006**, *47*, 6357–6360; (c) Zheng, Y.-S.; Xiao, Q. *Chin. J. Chem.* **2005**, *23*, 1289–1291; (d) He, Y.; Xiao, Y.; Meng, L.; Zeng, Z.; Wu, X.; Wu, C.-T. *Tetrahedron Lett.* **2002**, *43*, 6249–6253; (e) Ishi-i, T.; Crego-Calama, M.; Timmerman, P.; Reinhoudt, D. N.; Shinkai, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1924–1929.
14. (a) Qing, G.-Y.; He, Y.-B.; Zhao, Y.; Hu, C.-G.; Liu, S.-Y.; Yang, X. *Eur. J. Org. Chem.* **2006**, 1574–1580; (b) Arena, G.; Contino, A.; Gulino, F. G.; Magri, A.; Sansone, F.; Sciotto, D.; Ungaro, R. *Tetrahedron Lett.* **1999**, *40*, 1597–1600; (c) Araki, K.; Inada, K.; Shinkai, S. *Angew. Chem., Int. Ed.* **1996**, *35*, 72–74.
15. Karakucuk, A.; Durmaz, M.; Sirit, A.; Yilmaz, M.; Demir, A. S. *Tetrahedron: Asymmetry* **2006**, *17*, 1963–1968.
16. (a) Sirit, A.; Karakucuk, A.; Memon, S.; Kocabas, E.; Yilmaz, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3595–3600; (b) Sirit, A.; Kocabas, E.; Memon, S.; Karakucuk, A.; Yilmaz, M. *Supramol. Chem.* **2005**, *17*, 251–256.
17. (a) Kocabas, E.; Karakucuk, A.; Sirit, A.; Yilmaz, M. *Tetrahedron: Asymmetry* **2006**, *17*, 1514–1520; (b) Kocabas, E.; Durmaz, M.; Alpaydin, S.; Sirit, A.; Yilmaz, M. *Chirality* **2008**, *20*, 26–34.
18. (a) Durmaz, M.; Alpaydin, S.; Sirit, A.; Yilmaz, M. *Tetrahedron: Asymmetry* **2006**, *17*, 2322–2327; (b) Durmaz, M.; Alpaydin, S.; Sirit, A.; Yilmaz, M. *Tetrahedron: Asymmetry* **2007**, *18*, 900–905.
19. (a) Oueslati, I.; Thuéry, P.; Shkurenko, O.; Suwinska, K.; Harrowfield, J. M.; Abidi, R.; Vicens, J. *Tetrahedron* **2007**, *63*, 62–70; (b) Queslati, I. *Tetrahedron* **2007**, *63*, 10840–10851; (c) Banthia, S.; Samanta, A. *Org. Biomol. Chem.* **2005**, *3*, 1428–1434; (d) Kim, J. S.; Shon, O. J.; Ko, J. W.; Cho, M. H.; Yu, Y., III; Vicens, J. *J. Org. Chem.* **2000**, *65*, 2386–2392.
20. Prabagaran, N.; Abraham, S.; Sundararajan, G. *Arkivoc* **2002**, *7*, 212–226.
21. Li, Z.-T.; Ji, G.-Z.; Zhao, C.-X.; Yuan, S.-D.; Ding, H.; Huang, C.; Du, A.-L.; Wei, M. *J. Org. Chem.* **1999**, *64*, 3572–3584.
22. Kerdpaiboon, N.; Tomapatanaget, B.; Chailapakul, O.; Tuntulani, T. *J. Org. Chem.* **2005**, *70*, 4797–4804.
23. (a) Macomber, R. S. *J. Chem. Ed.* **1992**, *69*, 375–378; (b) Fielding, L. *Tetrahedron* **2000**, *56*, 6151–6170.
24. (a) Mizutani, T.; Ema, T.; Tomita, T.; Kuroda, Y.; Ogoshi, H. *J. Am. Chem. Soc.* **1994**, *116*, 4240–4250; (b) Kubo, Y.; Hirota, N.; Maeda, S.; Tokita, S. *Anal. Sci.* **1998**, *14*, 183–189.
25. Connors, K. A. *Binding Constants. The Measurement of Molecular Complex*; Wiley: New York, 1987.