Tetrahedron: *Asymmetry* 25 (2014) 411–417

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

Synthesis of rigid and C_2-symmetric pyridino-15-crown-5 type macrocycles bearing diamide–diester functions: enantiomeric recognition for chiral primary organoammonium perchlorate salts

Sevil Şeker [a], Deniz Barış [b], Nevin Arslan [a], Yılmaz Turgut [a], Necmettin Pirinççioğlu [a,*], Mahmut Toğrul [a,*]

[a] University of Dicle, Faculty of Science, Department of Chemistry, 21280 Diyarbakir, Turkey
[b] University of Batman, Faculty of Art and Science, Department of Chemistry, Batman, Turkey

ARTICLE INFO

Article history:
Received 14 October 2013
Revised 16 December 2013
Accepted 16 January 2014

ABSTRACT

Four novel C_2-symmetric macrocyclic compounds with a pyridine function and possessing amide and ester lingeages were prepared. The enantiomeric discrimination abilities of these macrocycles against α-phenylethylammonium and α-(1-naphthyl)ethylammonium perchlorate salts were measured by standard ^{1}H NMR titration techniques in DMSO-d_6. A binding constant ratio of 31 (Kbind(S)/Kbind(R)) for two enantiomers of α-(1-naphthyl)ethylammonium salt with the macrocyclic host (*S*,*S*)-**4** bearing phenyl arms was observed, which corresponds to an enantiomeric discrimination of approximately 94%. Molecular dynamic calculations were performed for some of the supramolecular complexes to in order to gain insight into the mode of molecular recognition between the macrocyclic compounds and ammonium salts; these results were consistent with experimental observations, which may be relevant to those in biochemical processes occurring in organisms.

1. Introduction

Enantiomeric recognition by model systems is essential in our understanding the selectivity of very complex biochemical processes occurring in living organisms, which involves the discrimination of one enantiomer of the guest from the other by a chiral host. Therefore, the design and synthesis of new chiral systems for the selective recognition of small molecules is one of the most challenging topics, which finds broad application, such as enzyme-substrate interactions,[1] asymmetric catalysis,[2] sensing,[3] enantioselective catalysis,[4] separation science,[5] development of pharmaceuticals,[6] biology[7] and the purification and analysis of enantiomers.[8] A number of synthetic models have been designed as chiral host molecules to help chemists better understand the basis of the mechanism of host–guest complexation and chiral recognition. The complexation and chiral recognition mechanism are mainly due to non-covalent interactions such as hydrogen bonds, ion-dipole, dipole–dipole interactions, π-stacking, ion–π interactions and hydrophobic interactions, which are also the main driving forces in the maintenance of 3D structures of biological relevance and their intermolecular interactions. Detailed investigations of chiral recognition phenomena through the elucidation of non-covalent interactions are constantly required for the basis of new approaches in the field of enzyme–substrate interactions, the resolution of enantiomers in chemical processes and asymmetric catalysis. Therefore, the design, synthesis and use of molecules capable of chiral recognition of other molecules are of great interest in these fields.[9]

The study of the recognition of chiral amines and chiral protonated amine compounds is of significance because these compounds are the basic building blocks of biological molecules and therefore, these molecules are frequently used as guests in chiral recognition.[10] Macrocyclic structures have received much attention in the search for artificial receptors, mainly because of their higher degree of preorganization when compared to their acyclic counterparts. A great number of artificial chiral receptors have been synthesized and studied widely.[10] Among these, chiral macrocycles containing pyridine units are dominant structures, due to their ability in chiral discrimination towards organoammonium salts and amino acid derivatives. The pyridine subunits of these macrocycles were reported to be important for tripodal hydrogen bond formation with primary organoammonium salts and π–π interaction with the aromatic moiety of the organoammonium guests.[10,11] It is also well known that the amide group has a high affinity for cations with

* Corresponding authors. Tel.: +90 412 2488550; fax: +90 412 2488300.
E-mail addresses: pirincn@dicle.edu.tr (N. Pirinççioğlu), mtogrul@dicle.edu.tr (M. Toğrul).

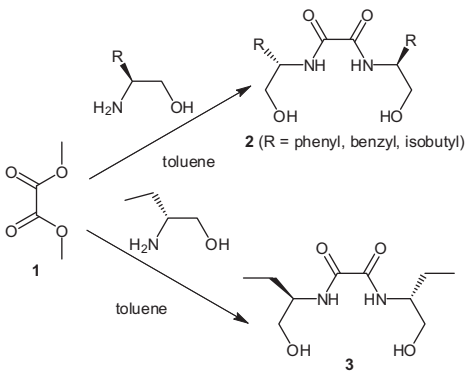
http://dx.doi.org/10.1016/j.tetasy.2014.01.009
0957-4166/

a high charge density. Many ionophores with amide ligands are currently employed as chemical sensors, quantitatively and reversibly measuring cationic analytes.[12] Cyclic esters (lactones) can be considered as crown ether-like rings and hence are predicted to behave in a similar manner to accommodate organoammonium salts. Pyridine macrocyclic diamides and diesters are widely found in nature and constitute an extensive range of natural products with diverse biological activity.[13] These natural compounds are complex structures due to the presence of multi-functional groups and their chirality. A number of pyridine-macrocyclic compounds containing diamide–diester groups have been synthesized.[14,15] However, only a few examples have been reported, that deal with the synthesis and chiral recognition studies of chiral pyridine-macrocyclic containing diamide–diester groups.[15] Herein we report the synthesis of a series of C_2-symmetric, pyridine and diamide–diester groups containing lactone type macrocycles with different side arms via a high dilution technique, for the recognition of α-chiral primary organoammonium perchlorate salts (*Caution*! The perchlorate salts must be handled with care as they are potential explosives). The enantiomeric recognition properties of these new macrocycles towards primary organoammonium salts were estimated by standard ^{1}H NMR titration techniques in DMSO-d_6.

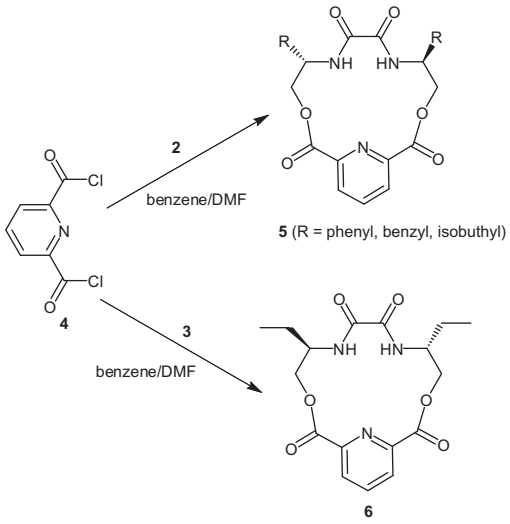
2. Result and discussion

2.1. Synthesis

The procedure for the synthesis of rigid C_2-symmetric pyridino-15-crown-5 type macrocycles (*S*,*S*)-**4**, (*S*,*S*)-**5**, and (*R*,*R*)-**6** containing diamide–diester functions, derived from bis(aminoalcohol) oxalamides (*S*,*S*)-**2**, and (*R*,*R*)-**3** is outlined in Schemes 1 and 2. Chiral bis(amino alcohol)oxalamides were synthesized according to the procedures previously reported, by reacting L-phenylglycinol, L-phenylalanilol, L-leucinol and (*R*)-2-amino-1-buthanol with dimethyloxalate in methanol at room temperature, with almost quantitative yield.[16] Pyridino-15-crown-5 type macrocycles were synthesized from the corresponding chiral bis(amino alcohol)oxalamides. A high dilution technique was employed for the cyclization step to afford the microcycles with high yields. The procedure involves short synthetic sequences and allows high modularity by simply changing the amino alcohol moiety. The functionality of the pyridine, amides and esters ensures a high rigidity, which may play a crucial role in the binding and recognition of small chiral molecules. The structures proposed for these new chiral bis(amino alcohol)oxalamides and macrocycles are consistent with the data obtained from ^{1}H, ^{13}C NMR, IR spectroscopy and elemental analysis. All of ^{1}H and ^{13}C NMR signals were assigned based on DEPT and ^{1}H–^{13}C correlation experiments.



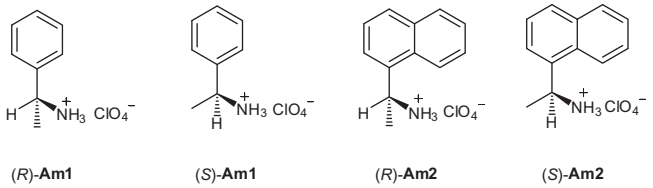
Scheme 1. Synthesis of bis(aminoalcohol)oxalamides.



Scheme 2. Synthesis of pyridino-15-crown-5 type macrocycles.

2.2. Enantiomeric recognition studies: selective cation binding

The enantiomeric recognition can be characterized by various spectroscopic methods, such as NMR, ultraviolet–visible (UV–vis), fluorescence and infrared (IR), which are powerful tools for the examination of the recognition ability of new chiral macrocycles.[17] Standard ^{1}H NMR titration experiments were applied in order to investigate the stability of the complexes of the pyridine-15-crown-5 types macrocycles **5** and **6** with perchlorate salts of enantiomers of **Am1** and **Am2**, since it is one of the most effective tools in studying host–guest supramolecular chemistry.[18] These cations are commonly used as standard guests for the chiral recognition of primary organic ammonium ions and in most cases give the best results. Upon the addition of guest molecules to the macrocycles, the signals in the ^{1}H NMR spectra shifted upfield or downfield depending on the non-covalent interactions between host and guest molecules. Increasing the concentration of organic ammonium cations (guest), which were used as perchlorate salts (Scheme 3) from 0.1 to 6 equiv in the presence of a constant host concentration (1×10^{-3} M), was carried out for ^{1}H NMR titration measurements. The addition of increasing amounts of ammonium salts to the diamide–diester pyridine-macrocycles caused considerable and reproducible upfield or downfield shifts ($\Delta\delta$) in the protons of the NH (amide), the N–CH groups of the diamide–diester pyridine-macrocycles, as well as in the CH and CH_3 protons of the ammonium salts. The NH (amide) protons of diamide–diester pyridine-macrocycles and CH protons of the ammonium salts were greatly affected and displayed significant upfield shifts. The association constants of the complex formation between the host and the guest were calculated according to a modified Benesi–Hildebrand equation where $[H]_0$ and $[G]_0$ refer to the total concentration of the macrocycles and organic ammonium salts, respectively.[19] A key feature of this method is that by working with a large excess of component H the concentration of uncomplexed H, can be set equal to the initial concentration, $[H] = [H]_0$. Relationships between



Scheme 3. Primary ammonium perchlorate salts used as guests.

known quantities (initial concentration) and experimental observations can now be derived. Mathur et al. and Hannah and Ashbaugh independently developed an NMR version of the Benesi–Hildebrand equation.[20,21] For all of the guests examined, the plots of observed $1/\Delta\delta$ values as a function of $1/[G]_0$ give a linear relationship with a slope $1/K_a\Delta\delta_{max}$ and $1/\Delta\delta_{max}$ supporting the 1:1 complex formation. To confirm the 1:1 stoichiometry, Job Plots for the complexed were studied. An example of Job plot for the complex of diamide–diester pyridine-macrocycle **5a** with (*S*)-Am2 is illustrated in Figure 1. For a comparison of the binding constants, the shifts in the NH (amide) protons of the diamide–diester pyridine-macrocycles upon complexation were chosen for the calculation of the binding constants K_a. In general, complex formation led to an upfield shift in the observed NH (amide) protons and a downfield shift in the guest CH protons. In most cases, an approximate 0.15 ppm shift in these protons was observed. The binding constants were calculated with 95% confidence (Table 1). With modern NMR instruments it is possible to obtain good quality spectra with submillimolar concentrations (routinely as low as 10^{-4} M). This suggests that NMR is suitable for obtaining binding constants in supramolecular systems up to and even above 10^6 M^{-1}.

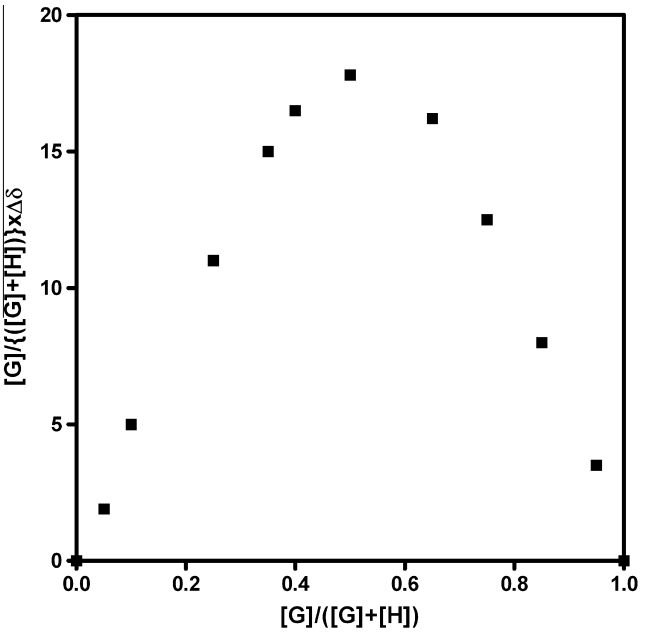


Figure 1. Job plot for the complex of **5a** with (*S*)-**Am2**.

A general trend in the enantiomeric discrimination of the guests by the hosts **5** was observed. It was found that **5** preferred to form more stable complexes with the (*S*)-enantiomers of guests **Am1** and **Am2** although **5b** preferred to form a more stable complex with the (*R*)-enantiomer of **Am2** (Table 1). A general model can be proposed to explain the basis of the discrimination of these ammonium salts by the hosts **5a**, **5b** and **5c**. The representative model for the complex of **5a** with **Am2** is illustrated in Figure 2. It is likely that the bulkiest group, the naphthyl in **Am2** (or phenyl in the case of **Am1**) would lie over the pyridine ring, and thus leave the methyl group to be discriminated between the phenyl rings on **5a** or isobutyl on **5c**. A similar explanation could be proposed for the discrimination of **Am1** by **5b**.

Replacing the phenyl group on the macrocyclic ring of **5a** with a benzyl group produced host **5b**, and reverses the discrimination between the enantiomers of **Am2**, from (*S*) to (*R*). In the case of the complex with the (*R*)-enantiomer, it is likely that the naphthyl group, instead of fully positioning over the pyridine ring, shifts towards the benzyl ring in a sandwiched manner (Fig. 3) through π–π interactions. In this model, the methyl group may also interact

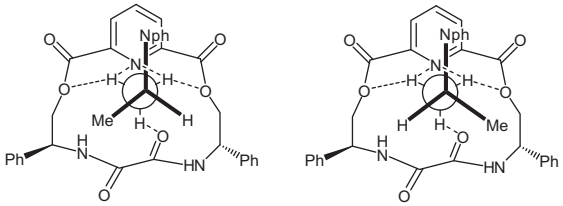


Figure 2. An illustrative representation of the complexes of **5a** with (*R*)-**Am2** (right) and (*S*)-**Am2** (left).

Table 1
Binding constant (K_a), the Gibbs free energy changes (ΔG_o) and enantioselectivities K_R/K_S or $\Delta\Delta G_o$ for the inclusion of the (*R*)- or (*S*)-guest with the chiral host macrocycles in DMSO-d_6 at 25 °C

Entry	Host	Guest[a]	K_a, M^{-1}[b]	K_a^S/K_a^R[c]	$-\Delta G_o$, $kJmol^{-1}$[d]	$\Delta\Delta G_o$[e]	ED[f]
1	(*S*,*S*)-**5a**	(*R*)-**Am1**	33.6 ± 0.3	3.86	8.71	3.34	59 (*S*)
2	(*S*,*S*)-**5a**	(*S*)-**Am1**	129.6 ± 0.5		12.05		
3	(*S*,*S*)-**5a**	(*R*)-**Am2**	327.1 ± 0.2	31.0	14.35	8.50	94 (*S*)
4	(*S*,*S*)-**5a**	(*S*)-**Am2**	10,138 ± 71		22.85		
5	(*S*,*S*)-**5b**	(*R*)-**Am1**	1852 ± 17	1.44	18.64	0.91	18 (*S*)
6	(*S*,*S*)-**5b**	(*S*)-**Am1**	2668 ± 10		19.55		
7	(*S*,*S*)-**5b**	(*R*)-**Am2**	721.4 ± 3.1	0.36	16.31	−2.51	47 (*R*)
8	(*S*,*S*)-**5b**	(*S*)-**Am2**	262.6 ± 2.6		13.80		
9	(*S*,*S*)-**5c**	(*R*)-**Am1**	2559 ± 7	1.05	19.44	0.20	2 (*S*)
10	(*S*,*S*)-**5c**	(*S*)-**Am1**	2681 ± 5		19.56		
11	(*S*,*S*)-**5c**	(*R*)-**Am2**	1126 ± 4	1.34	17.41	0.73	30 (*S*)
12	(*S*,*S*)-**5c**	(*S*)-**Am2**	1511 ± 4		18.14		
13	(*R*,*R*)-**6**	(*R*)-**Am1**	5412 ± 17		21.30		
14	(*R*,*R*)-**6**	(*S*)-**Am1**	nd[g]				
15	(*R*,*R*)-**6**	(*R*)-Am2	4719 ± 9	0.60	20.96	−1.27	25 (*R*)
16	(*R*,*R*)-**6**	(*S*)-Am2	2833 ± 7		19.69		

[a] **Am1**: α-phenylethylammonium perchlorate salts; **Am2**: α-(1-naphthyl)ethylammonium perchlorate salts.
[b] The binding constants between the hosts and the guests observed by ^{1}H NMR titration.
[c] The ratios of the binding constants for each enantiomer.
[d] The binding free energy change for the complexes, calculated by $\Delta G_o = -RT\ln K_a$.
[e] $\Delta\Delta G_o = -(\Delta G_{o(R)} - \Delta G_{o(S)})$.
[f] Enantiomeric discrimination factor.
[g] Not determined.

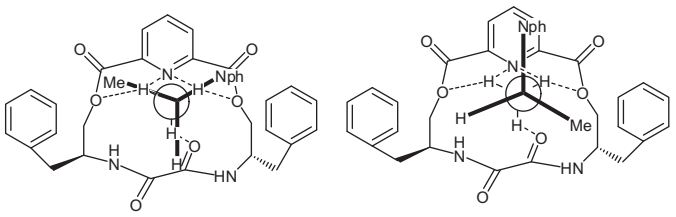


Figure 3. An illustrative representation of the complexes of **5b** with (*R*)-**Am2** (left) and (*S*)-**Am2** (right).

with another benzyl group via CH/π interactions, which are known to be very significant in the molecular recognition that occurs in biochemical processes and in maintaining 3D structures of biological macromolecules.[22] The complex of **5b** with an (*S*)-configuration lacks these two favourable interactions and therefore is less stable compared to the (*R*)-enantiomer. Host **6** displayed a similar trend to form complexes with the guests, but with inverted enantiomeric discrimination, that is it forms a more stable complex with the (*R*)-enantiomers (Table 1) since it has inverted stereogenic centres compared to **5**.

2.3. Computational modelling

It was previously reported that computational modelling produces valuable information regarding the mode of complexes of crown-ethers possessing C_2 symmetry with chiral ammonium salts,[30] and therefore a similar approach could be used to predict the complexation mode of the current macrocyclics with the same guests. Conformers of the hosts **5a** and **5b** with the largest population obtained from molecular dynamic (MD) calculations are shown in Figure 4. It can be seen that the ring has a rather flat structure with the two phenyl and benzyl groups aligned on opposite sides of the ring. The superimposed conformers of the complex of these hosts with the enantiomers of **Am2** having the largest populations obtained from MD calculations are shown in Figure 5. In the case of complex of **5a**, the naphthyl group is aligned over the pyridine ring and thus in the complex of the host with the (*R*)-enantiomer, the methyl group in the guest has unfavourable steric interactions with the phenyl group, leading to a less stable complex formation compared to that with the (*S*)-enantiomer. With regard to the complex of the host **5b** with the **Am2** enantiomers, it seems that the (*R*)-enantiomer has more favourable interactions with the host **5b** compared to the (*S*)-enantiomer (Fig. 5). This may be attributed to the fact that in the case of the complex with an (*R*)-configuration, the naphthyl group slides towards the benzyl group to gain more complimentary interactions with this group as well as with the pyridine ring via π–π interactions because the unsubstituted ring of the naphthalene in the (*R*)-enantiomer has a better spatial orientation for such interactions compared with the (*S*)-enantiomer (Fig. 5). These observations are consistent with the models proposed earlier (Figs. 3 and 4).

3. Conclusion

The preparation of four novel C_2-symmetric macrocyclic compounds was successfully achieved and their enantiomeric discrimination abilities against various chiral primary ammonium salts were estimated by standard ^{1}H NMR titration techniques as models to better understand the non-covalent interactions and the basis of molecular recognition in biological systems; these are perhaps more relevant as chiral scaffolds in the separation of enantiomers, which is of great importance in the synthesis of new pharmaceuticals.

Molecular dynamic calculations provide very significant results to determine the nature of the complexes between the macrocylic compounds and ammonium salts, and were consistent with experimental results.

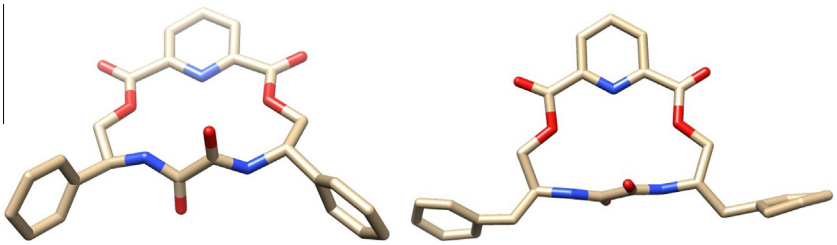


Figure 4. Conformers of the hosts **5a** (left) and **5b** (right) with the largest population obtained from molecular dynamic calculations. For the sake of simplicity, hydrogens are omitted.

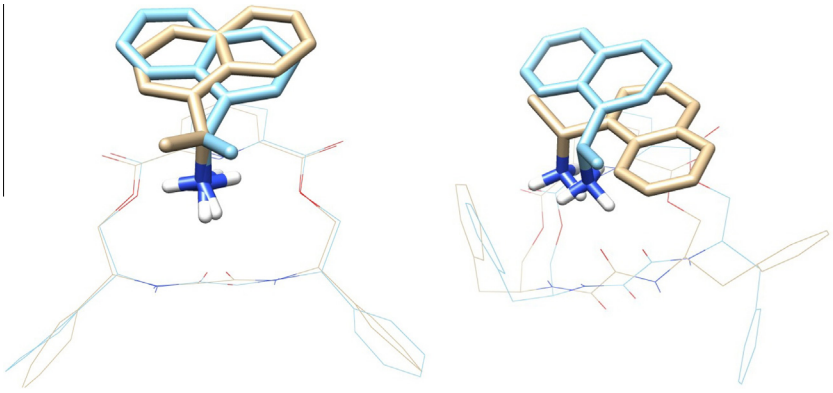


Figure 5. The superimposed conformers of the complex of the hosts **5a** (left) and **5b** (right) with the enantiomers of **Am2** having the largest populations obtained from MD calculations. Open brown represents the complex of the (*R*)-enantiomer while the open blue represents the complex of *S* enantiomer. For the sake of simplicity, hydrogens, except those involved in hydrogen bond interactions, are omitted.

4. Experimental

4.1. General

Melting points were determined with a GALLENKAMP Model apparatus with open capillaries and are uncorrected. Infrared spectra were recorded on a MIDAC-FTIR Model 1700 spectrometer. The Elemental analyses were obtained with CARLO-ERBA Model 1108 apparatus. Optical rotations were taken on a Perkin Elmer 341 Model polarimeter. ^{1}H (400 MHz), ^{13}C (100 MHz) ^{1}H NMR titration and two dimensional NMR (DEPT, COSY, HETCOR, HMQC, HMBC) spectra were recorded on a BRUKER DPX-400 High Performance Digital FT-NMR spectrometer in the solvents indicated. Chemical shifts are expressed in part per million (δ) using residual solvent protons as the internal standards.

4.2. Synthesis

4.2.1. Aminoalcohols

(*R*)-(−)-2-Amino-1-butanol and L-phenylglycinol were purchased from Fluka, and used without further purification. The synthesis of L-leucinol and L-phenylalanilol was accomplished in one step from L-leucine and L-phenylalanine according to procedures described in the literature.[23]

4.2.2. Dimethyloxalate 1

A solution of oxalylchloride (38.0 g, 0.3 mol) in benzene (250 mL) was added dropwise to a solution of methanol (38.4 g, 1.2 mol) and pyridine (47.4 g, 0.6 mol) over 3 h under a dry N_2 atmosphere. The reaction mixture was then refluxed for 3 h. Next, the mixture was kept at room temperature for one day. The solution was then filtered, and the solvent evaporated in vacuo. The solid residue was extracted with ice-cold ether (3 × 50 mL) and a white solid was obtained after evaporation. The product was recrystallized from ether–petroleum ether (2:1) (32.6 g, 92%); mp 54.0–54.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.58 (s, 6H, OCH_3). Anal. Calcd for $C_4H_6O_4$: C 40.69, H 5.12. Found: C 40.68; H 5.13.

4.2.3. General procedure for the synthesis of diamidediols 2 and 3

To a solution of the desired aminoalcohol (32 mmol) in MeOH (25 mL), a solution of dimethyloxalate **1** (16 mmol) was added dropwise at room temperature. The reaction mixture was stirred for a further 5 min after which the resulting white solid precipitate was collected and washed with a small portion of diethyl ether to give a white solid compound consisting of (*S*,*S*)-**2** or (*R*,*R*)-**3**.

4.2.4. *N*,*N*′-[Bis(1*S*)-1-phenyl-2-hydroxyethyl]ethanediamide (*S*,*S*)-2a

Yield: 96%; mp 226–228 °C; $[\alpha]_D^{25} = -35.2$ (*c* 1.0, DMSO); IR (KBr) *v* 3420 (O–H), 3296 (N–H), 3070 (Ar-H), 3043 (Ar-H), 1654 (C=O, first amide band), 1515 (C=O, second amide band), 1042 (C–O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 3.49–3.75 (6H, m), 4.85–4.90 (2H, m), 7.21–7.42 (10H, m), 9.00 (2H, d, *J* = 8.8 Hz); ^{13}C NMR (DMSO-d_6): δ 56.21, 64.42, 127.48, 127.53, 128.64, 128.73, 160.22.

4.2.5. *N*,*N*′-[Bis(1*S*)-1-benzyl-2-hydroxyethyl]ethanediamide (*S*,*S*)-2b

Yield: 99%; mp 252–253 °C; $[\alpha]_D^{25} = -43.8$ (*c* 0.03, MeOH); IR (KBr) *v*, 3416 (O–H), 3274 (N–H), 3063 (Ar-H), 3037 (Ar-H), 1658, (C=O, first amide band), 1523 (C=O, second amide band), 1047 (C–O)cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.77 (dd, *J* = 13.5, *J* = 5.4 Hz, 2H, CH_2Ar (a)), 2.91 (dd, 13.5, 5.4 Hz, 2H, CH_2Ar (b)), 3.43 (m, 4H, CH_2O), 3.95 (m, 2H, CH–N), 4.93 (br s, 2H, OH), 7.3–7.1 (m, 10 H, ArH), 8.4 (d, *J* = 9.2 Hz, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 36.6 (t, CH_2Ar), 53.4 (d, CH–N), 62.7 (t, CH_2OH), 126.4, 128.6, 129.4 (d, aromatic CH), 139.3 (quaternary aromatic), 159.9 (s, C=O). Anal. Calcd for $C_{20}H_{24}N_2O_4$: C 67.40, H 6.79, N 7.86. Found: C 67.39, H 6.81, N 7.85.

4.2.6. *N*,*N*′-[Bis(1*S*)-2-hydroxyethyl-1-isobutyl]ethanediamide (*S*,*S*)-2c

Yield: 99%; mp 175–176 °C; $[\alpha]_D^{25} = -30.5$ (*c* 1.0, DMSO); IR (KBr) *v* 3453 (O–H), 3288 (N–H), 1657 (C=O, first amide band), 1535 (C=O, second amide band), 1099 (C–O) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.95 (d, *J* = 6.5 Hz, 6H, CH_3, (a)), 0.96 (d, *J* = 6.4 Hz, 6H, CH_3, (b)), 1.38 (m, 2H, $CH(CH_3)_2$), 1.40 (dd, *J* = 8.6, *J* = 4.4 Hz, 2H, CH_2–$CH(CH_3)_2$, (a)), 1.65 (dd, *J* = 8.6, *J* = 4.4 Hz 2H, CH_2–$CH(CH_3)_2$, (b)), 3.51 (m, 4H, CH_2O), 3.80 (m, 2H, CH–N), 4.78 (br s, 2H, OH), 8.2 (d, *J* = 9.2 Hz, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 22.3 (q, $CH(CH_3)_2$, (A)), 23.6 (q, $CH(CH_3)_2$, (B)), 24.8 (d, $CH(CH_3)_2$), 40.0 (t, CH_2–$CH(CH_3)_2$), 50.1 (d, CH–N), 63.8 (t, CH_2OH), 160.2 (s, C=O). Anal. Calcd for $C_{14}H_{28}N_2O_4$: C 58.30, H, 9.79, N, 9.71. Found: C 58.31, H 9.77; N 9.69.

4.2.7. *N*,*N*′-[Bis(1*R*)-1-ethyl-2-hydroxyethyl]ethanediamide (*R*,*R*)-3

Yield: 99%; mp 212–213 °C; $[\alpha]_D^{25} = +30.3$ (*c* 1.0, DMSO); IR (KBr) *v* 3365 (O–H), 3280 (N–H), 1665(C=O, first amide band), 1530 (C=O, second amide band), 1048 C–O) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.85 (t, *J* = 7.4 Hz, 6H, CH_3), 1.42 (m, 2H, CH_2CH_3 (a)), 1.55 (m, 2H, CH_2CH_3 (b)), 3.30 (m, 4H, CH_2OH), 3.71 (m, 2H, CH–N), 4.70 (br s, 2H, OH), 8.2 (d, *J* = 9.2 Hz, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 11.4 (q, CH_3), 24.4 (t, CH_2CH_3), 54.2 (d, CH–N), 63.7 (t, CH_2OH), 161.7 (s, C=O). Anal. Calcd for $C_{10}H_{20}N_2O_4$: C 51.71, H 8.68, N 12.06. Found C 51.69, H 8.71, N 12.02.

4.2.8. (5*S*,10*S*)-5,10-Diphenyl-3,12-dioxa-6,9,18-triazabicyclo-[12.3.1]octadeca-1(18),14,16-triene-2,7,8,13-tetraone [Macrocycle (*S*,*S*)-5a]

This experiment was conducted under high dilution. A two litre, 4-necked, round-bottomed flask, fitted with a mechanical stirrer and two jacketed condenser was charged with 1 L of benzene and triethylamine equivalent to the HCl produced. The solution was refluxed vigorously while (*S*,*S*)-**2a** (1.5 g, 4.2 mmol) in dry THF/DMF (w:w,70/30 = 100 mL) and 2,6-pyridinedicarbonyl dichloride **4** (0.86 g, 5 mmol) in dry benzene (100 mL) were added dropwise at the same rate. After the addition was complete, the reaction mixture was refluxed for 5 days. The solution was cooled to room temperature, filtered and the solvent evaporated under vacuum. The white solid obtained was crystallized from an ethanol–acetonitrile mixture (2:1). Macrocycle (*S*,*S*)-**5a**; yield (1.26 g, 63%); mp 289–290 °C; IR (KBr): *v* 3298 (N–H), 3086 (Ar-H), 3059 (Ar-H), 3028 (Ar-H), 1759 (C=O, ester), 1731 (C=O, ester), 1659 (C=O, first amide band), 1516 (C=O, second amide band), 1130 (C–O–C), 1053 (C–O–C), cm^{-1}; $[\alpha]_D^{34} = -58$ (*c* 0.04, CH_3CN); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.75–2.87 (m, 4H, CH_2Ar), 3.75–3.88 (m, 6H, CH_2O and CH–N), 4.25–4.57 (m, 4H, O–CH_2–C=O), 7.17–7.26 (m, 10H, ArH), 8.60 (d, *J* = 10 Hz, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 35.04 (t, CH_2Ar), 50.70 (d, CH–N), 65.77 (t, CH–CH_2O), 65.82 (t, OCH_2C=O), 126.71, 128.69, 129.33 (d, aromatic CH), 138.42 (s, quaternary aromatic), 160.12 (s, C=O amide), 169.56 (s, C=O ester). Anal. Calcd for $C_{24}H_{26}N_2O_7$: C 63.42, H 5.77, N, 6.16. Found: C 63.41, H 5.78; N 6.15.

4.2.9. (5*S*,10*S*)-5,10-Dibenzyl-3,12-dioxa-6,9,18-triazabicyclo-[12.3.1]octadeca-1(18),14,16-triene-2,7,8,13-tetraone [Macrocycle (*S*,*S*)-5b]

The reaction was carried out by the high-dilution technique as described before. Macrocycle (*S*,*S*)-**5b**; yield (0.98 g, 49%). mp

278–279 °C; IR (KBr): ν 3297 (N–H), 1751 (C=O, ester), 1728 (C=O, ester), 1659 (C=O, first amide band), 1520 (C=O, second amide band), 1277 (O=C–O–C), 1130 (C–O–C) cm^{-1}. $[\alpha]_D^{33} = -62.0$ (c 0.1, CH_3CN); ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.84 (d, J = 7.2 Hz, 6H, CH_3 (a)), 0.86 (d, J = 7.2 Hz, 6H, CH_3 (b)), 1.12–1.20 (m, 2H, $CH(CH_3)_2$), 1.49–1.60 (m, 4H,NCHCH_2CH), 3.79–4.66 (m, 10H, CHN, CHN–CH_2–C=O and O–CH_2–C=O), 8.50 (d, J = 10 Hz, 2H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 21.91 (q, CH_3 (a)), 23.54 (q, CH_3 (b)), 24.76 (d, $CH(CH_3)_2$), 37.77 (t, $CH_2CH(CH_3)_2$), 47.75 (d, CH–N), 65.81 (t, CH–CH_2–O), 66.31 (t, O–CH_2–C=O), 160.43 (s amide C=O), 169.52 (s, ester C=O). Anal. Calcd for $C_{18}H_{30}N_2O_7$: C 55.95, H 7.83, N 7.25. Found: C 55.93, H 7.81, N 7.24.

4.2.10. (5*S*,10*S*)-5,10-Bis(2-methylpropyl)-3,12-dioxa-6,9,18-triazabicyclo[12.3.1]octadeca-1(18),14,16-triene-2,7,8,13-tetraone [Macrocycle (*S*,*S*)-5c]

The reaction was carried out by the high-dilution technique as described before. Macrocycle (*S*,*S*)-**5c**; yield (0.88 g, 44%). mp 280–282 °C. IR (KBr): ν 3282 (N–H), 1763 (C=O, ester), 1736 (C=O, ester), 1659 (C=O, first amide band), 1524 (C=O, second amide band), 1284 (O=C–O–C), 1149 (C–O–C) cm^{-1}; $[\alpha]_D^{34} = +153.0$ (c 0.03, CH_3CN); ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.85 (t, J = 3.8 Hz, 6H, CH_2CH_3), 0.89 (d, J = 4.0 Hz, 6H, $CHCH_3$), 1.04–1.11 (m, 2H, CH_2CH_3 (a)), 1.38–1.40 (m, 2H, CH_2CH_3 (b)), 1.68–1.70 (m, 2H, $CHCH_3$), 3.81–3.93 (m, 2H, CH–N), 3.97–4.65 (m, 8H, NCHCH_2O and OCH_2C=O), 8.44 (d, J = 12 Hz, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 10.76 (q, CH_2CH_3), 15.84 (q, $CHCH_3$), 25.78 (t, $CHCH_2CH_3$), 34.66 (d, $CHCH_3$), 53.42 (d, N–CH–), 64.95 (t, CH_2O), 66.22 (t, OCH_2C=O), 160.72 (s, amide C=O), 169.61 (s, ester C=O). Anal. Calcd for $C_{18}H_{30}N_2O_7$: C 55.95, H 7.83, N 7.25. Found: C 55.94, H 7.84, N 7.23.

4.2.11. (5*R*,10*R*)-5,10-Diethyl-3,12-dioxa-6,9,18-triazabicyclo-[12.3.1]octadeca-1(18),14,16-triene-2,7,8,13-tetraone [Macrocycle (*R*,*R*)-6]

The reaction was carried out by the high-dilution technique as described above. Macrocycle (*R*,*R*)-**6**; yield (1.14 g, 57%). mp 266.5–268 °C. IR (KBr): ν 3282 (N–H), 1767 (C=O, ester), 1735 (C=O, ester), 1659 (C=O, first amide band), 1520 (C=O, second amide band), 1296 (O=C–O–C), 1149 (C–O–C) cm^{-1}; $[\alpha]_D^{34} = +96.0$ (c 0.2, CH_3CN); ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.84 (t, J = 7.4 Hz, 6H, CH_3), 1.46–1.52 (m, 4H, CH**CH_2**CH_3), 3.82–4.66 (m, 10H, CH–N, CH_2O and O–CH_2–C=O), 8.45 (d, J = 10 Hz, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 10.99 (q, CH_3), 22.39 (t, CH_2CH_3), 51.15 (d, CH–N), 65.87 (t, CH–CH_2–O), 65.97 (t, O–CH_2–C=O), 160.73 (s, amide C=O), 169.56 (s, ester C=O). Anal. Calcd for $C_{14}H_{22}N_2O_7$: C 50.91, H 6.71, N, 8.48. Found: C 50.88, H 6.72, N 8.46.

4.3. Computational section

4.3.1. Molecular dynamics simulations

Molecular dynamics (MD) simulations were carried out in a Linux-Cluster system to determine the conformations for each complex studied. All simulations were conducted by using AMBER (version 9.0) suite of programs.[24] The host and ligands were designed by GaussView 3.09, followed by optimization with Gaussain 03[25] using the semi-empirical AM1 method.[26] AM1-Bcc (Austian model with Bond and charge correction)[27] atomic partial charges for the host and the guests were determined by an antechamber module of AMBER (v9) package and the General AMBER Force Field (GAFF)[28] was adopted in the simulation because it handles small organic molecules.

The host molecule was minimized with a total of 5000 steps, 2500 of steepest descent followed by 2500 of conjugate gradient (maxcyc-ncyc), using a nonbonded cutoff of 999 Å and a generalized Born solvent model (igb = 0). The system was then heated from 0 to 700 K over 14 steps for a period of 350 ps and then was simulated at 700 K for a period of 20,000 ps (igb = 0). A cluster analysis was performed with 167 intervals out of 500,000 frames to obtain a conformer with a larger population to represent the lower energy conformer. Each ligand was manually placed on the surface of the host ring so that the maximum contact points between ammonium and the ring donors were achieved. The complexes were minimized with a total of 5000 steps, 2500 of steepest descent, followed by 2500 of conjugate gradient, using a nonbonded cutoff of 999 Å and a generalized Born solvent model (igb = 0). The system was then heated from 0 to 700 K over 14 steps for a period of 350 ps and then was simulated at 700 K for a period of 20,000 ps (igb = 0). A cluster analysis was performed with 50 intervals out of 20,000 frames and the coordinates of the structure with the largest population were recorded and this was minimized followed by cooling from 700 to 300 K over 8 steps for a period 200 ps and then was computed at 300 K for a period of 20,000 ps. Molecular dynamic coordinates were recovered with 1.0 ps intervals. A cluster analysis was used to obtain the conformer with the largest population for each complex.

Energy changes and root-mean-square displacement (RMSD) analysis for the hosts and complexes were carried out on the trajectories by the ptraj module of AMBER (v9). 3D structures were displayed using by Chimera (UCSF)[29] and potential energy and RMSD graphics are shown by GraphPad Pris 4 pocket programme.

Acknowledgements

We are grateful to the Scientific and Technical Research Council of Turkey (TUBITAK) for supporting the project (106T395) and Dicle University Research Council (DUBAP) for supporting the projects (10-FF-10 and 10-FF-11). We are also grateful to DA Case (University of California, San Francisco) for providing a waiver of AMBER.

References

1. (a) Horvath, G.; Hutszthy, P.; Szarvas, S.; Szokan, G.; Redd, J. T.; Bradshaw, J. S.; Izatt, R. M. *Ind. Eng. Chem. Res.* **2000**, *39*, 3576; (b) Qing, G.; Sun, T.; Chen, Z.; Yang, X.; Wu, X.; He, Y. *Chirality* **2009**, *21*, 363; (c) Demirtas, H. N.; Bozkurt, S.; Durmaz, M.; Yilmaz, M.; Sirit, A. *Tetrahedron* **2009**, *65*, 3014.
2. (a) Izatt, R. M.; Wang, T.; Hathaway, J. K.; Zhang, X. X.; Curtis, J. C.; Bradshaw, J. S.; Zhu, C. Y.; Huszthy, P. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, *17*, 157; (b) Tang, Z.; Cun, L. F.; Cui, X.; Mi, A. Q.; Jiang, J. Z.; Gong, L. Z. *Org. Lett.* **2006**, *8*, 1263.
3. (a) Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486; (b) Thomas, C. M.; Ward, T. R. *Chem. Soc. Rev.* **2005**, *34*, 337; (c) Ballester, P.; Vidal-Ferran, A. In *Supramolecular Catalysis*; van Leeuwen, P. W. N. M., Ed.; Wiley-VCH Gmbh & Co. KGaA: Weinheim, 2008; pp 1–24; (d) Pirkle, W. H; Pochapsky, T. C. *Chem. Rev.* **1989**, *89*, 347; (e) Kubo, Y.; Maeda, S.; Tokita, S.; Kuba, M. *Nature* **1996**, *382*, 522; (f) Wan, H.; Blomberg, L. G. *J. Chromatogr. A* **2000**, *875*, 43; (g) Tanaka, H.; Matile, S. *Chirality* **2008**, *20*, 307; (h) Su, X.; Luo, K.; Xiang, Q.; Lan, J.; Xie, R. *Chirality* **2009**, *21*, 539.
4. (a) Koskinen, A. *Pure Appl. Chem.* **1993**, *65*, 1465; (b) Sanders, J. K. M. *Chem. Eur. J.* **1998**, *4*, 1378; (c) Tsukube, H.; Shinoda, S.; Tamiaki, H. *Coord. Chem. Rev.* **2002**, *226*, 227; (d) Simonneaux, G.; Maux, P. L. *Coord. Chem. Rev.* **2002**, *228*, 43.
5. (a) Kyba, E. B.; Koga, K.; Sousa, L. R.; Siegel, M. G.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 2692; (b) Turgut, Y.; Sahin, E.; Togrul, M.; Hosgoren, H. *Tetrahedron: Asymmetry* **2004**, *15*, 1583; (c) Toth, T.; Huszthy, P.; Kupai, J.; Nyitrai, J. *Arkivoc* **2008**, *3*, 66; (d) Ozer, H.; Kocakaya, S. O.; Akgun, A.; Hosgoren, H.; Togrul, M. *Tetrahedron: Asymmetry* **2009**, *20*, 1541–1546; (e) Kupai, J.; Levai, S.; Antal, K.; Balogh, G. T.; Toth, T.; Huszthy, P. *Tetrahedron: Asymmetry* **2012**, *23*, 415.
6. (a) Choi, S. H.; Huh, K. M.; Ooaya, T.; Yui, N. *J. Am. Chem. Soc.* **2003**, *125*, 6350; (b) Bae, Y.; Fukushima, S.; Harada, A.; Kataoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 4640.
7. Peczuh, M. W.; Hamilton, A. D. *Chem. Rev.* **2000**, *100*, 2479.
8. (a) Moberg, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 248; (b) Pu, L. *Chem. Rev.* **2004**, *104*, 1154.
9. (a) Chin, J.; Lee, S. S.; Lee, K.; Park, S.; Kim, D. H. *Nature* **1999**, *401*, 254; (b) Schmuck, C. *Chem. Eur. J.* **2000**, *6*, 709; (c) Togrul, M.; Askin, M.; Hosgoren, H. *Tetrahedron: Asymmetry* **2005**, *16*, 2771; (d) Zhu, L. H.; Song, L. X.; Yang, J.; Pan, S. Z.; Yang, J. *Supramol. Chem.* **2011**, *23*, 598.

10. (a) Zhang, X. X.; Bradshaw, J. S.; Izatt, R. M. *Chem. Rev.* **1997**, *95*, 3313; (b) Schnopp, M.; Haberhauer, G. *Eur. J. Org. Chem.* **2009**, *26*, 4458; (c) Spaeth, A.; König, B. *Beilstein J. Org. Chem.* **2010**, *6*, 32.
11. (a) Huszthy, P.; Oue, M.; Bradshaw, J. S.; Zhu, C. Y.; Wang, T.; Dalley, N. K.; Curtis, J. C.; Izatt, R. M. *J. Org. Chem.* **1992**, *57*, 5383; (b) Lee, C. S.; Teng, P. F.; Wong, W. L.; Kwong, H. L.; Chan, A. S. C. *Tetrahedron* **2005**, *61*, 7924.
12. (a) Arnoud, N.; Picard, C.; Cazaux, L.; Tisnes, P. *Tetrahedron* **1997**, *53*, 13757; (b) Du, C. P.; You, J. S.; Yu, X. Q.; Liu, C. L.; Lan, J. B.; Xie, R. G. *Tetrahedron: Asymmetry* **2003**, *14*, 3651.
13. (a) Roxburgh, C. J. *Tetrahedron* **1995**, *51*, 9767; (b) Frensch, V. K.; Vogtle, F. *Tetrahedron Lett.* **1997**, *38*, 2573; (c) Kuroda, T.; Imashiro, R.; Seki, M. *J. Org. Chem.* **2000**, *65*, 4213.
14. (a) Gao, M. Z.; Gao, J.; Xu, Z. L.; Zingaro, R. A. *Tetrahedron Lett.* **2002**, *43*, 5001; (b) Gao, M. Z.; Reibenspies, J. H.; Wang, B.; Xu, Z. L.; Zingaro, R. A. *J. Heterocycl. Chem.* **2004**, *41*, 899.
15. Sunkur, M.; Baris, D.; Hosgoren, H.; Togrul, M. *J. Org. Chem.* **2008**, *73*, 2570.
16. Baris, D.; Seker, S.; Hosgoren, H.; Togrul, M. *Tetrahedron: Asymmetry* **2010**, *21*, 1893.
17. (a) de Boer, J. A. A.; Reinhoud, D. N. *J. Am. Chem. Soc.* **1985**, *107*, 5347; (b) Samu, E.; Huszthy, P.; Horvath, G.; Szollosy, A.; Neszmelyi, A. *Tetrahedron: Asymmetry* **1999**, *10*, 3615; (c) Tsubaki, K.; Tanaka, H.; Kinoshita, T.; Fuji, K. *Tetrahedron* **2002**, *58*, 1679; (d) Ozbey, S.; Kaynak, F. B.; Togrul, M.; Demirel, N.; Hosgoren, H. *J. Incl. Phenom. Macrcycl. Chem.* **2003**, *45*, 123; (e) Ozbey, S.; Kaynak, F. B.; Togrul, M.; Demirel, N.; Hosgoren, H. *Z. Kristallogr.* **2003**, *218*, 381; (f) Togrul, M.; Turgut, Y.; Hosgoren, H. *Chirality* **2004**, *16*, 351; (g) Wang, W.; Ma, F.; Shen, X.; Zhang, C. *Tetrahedron: Asymmetry* **2007**, *18*, 832.
18. (a) Fielding, L. *Tetrahedron* **2000**, *56*, 6151; (b) Hirose, K. *J. Inclusion Phenom.Macrocyclic Chem.* **2001**, *39*, 193.
19. Benesi, H. A.; Hildebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703.
20. Mathur, R.; Becker, E. D.; Bradley, R. B.; Li, N. C. *J. Phys. Chem.* **1963**, *67*, 2190.
21. Hanna, M. W.; Ashbaugh, A. L. *J. Phys. Chem.* **1964**, *68*, 811.
22. For a review of CH/π interaction: Nishio, M.; Umezawa, Y.; Hirota, M.; Takeuchi, Y. *Tetrahedron* **1995**, *51*, 8665.
23. McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568.
24. Case, D. A.; Darden, T. A.; Cheatham, T. E., III; Simmerling, C. L.; Wang, J.; Duke, R. E.; Luo, R.; Merz, K. M.; Pearlman, D. A.; Crowley, M.; Walker, R. C.; Zhang, W.; Wang, B.; Hayik, S.; Roitberg, A.; Seabra, G.; Wong, K. F.; Paesani, F.; Wu, X.; Brozell, S.; Tsui, V.; Gohlke, H.; Yang, L.; Tan, C.; Mongan, J.; Hornak, V.; Cui, G.; Beroza, P.; Mathews, D. H.; Schafmeister, C.; Ross, W. S.; Kollman, P. A. *AMBER 9*; University of California: San Francisco, 2006.
25. Gaussian 03, Revision C.02, Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., Cheeseman, J. R., Montgomery, Jr., J. A., Vreven, T., Kudin, K. N., Burant, J. C., Millam, J. M., Iyengar, S. S., Tomasi, J., Barone, V., Mennucci, B., Cossi, M., Scalmani, G., Rega, N., Petersson, G. A., Nakatsuji, H., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Klene, M., Li, X., Knox, J. E., Hratchian, H. P., Cross, J. B., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R. E., Yazyev, O., Austin, A. J., Cammi, R., Pomelli, C., Ochterski, J. W., Ayala, P. Y., Morokuma, K., Voth, G. A., Salvador, P., Dannenberg, J. J., Zakrzewski, V. G., Dapprich, S., Daniels, A. D., Strain, M. C., Farkas, O., Malick, D. K., Rabuck, A. D., Raghavachari, K., Foresman, J. B., Ortiz, J. V., Cui, Q., Baboul, A. G., Clifford, S., Cioslowski, J., Stefanov, B. B., Liu, G., Liashenko, A., Piskorz, P., Komaromi, I., Martin, R. L., Fox, D. J., Keith, T., Al-Laham, M. A., Peng, C. Y., Nanayakkara, A., Challacombe, M., Gill, P. M. W., Johnson, B., Chen, W., Wong, M. W., Gonzalez, C., Pople, J. A., Gaussian, Inc., Wallingford CT, 2004.
26. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. A.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
27. Jakalian, A.; Bush, B. L.; Jack, D. B.; Bayly, C. I. *J. Comput. Chem.* **2000**, *21*, 132; Jakalian, A.; Jack, D. B.; Bayly, C. I. *J. Comput. Chem.* **2002**, *23*, 1623.
28. Wang, J.; Wolf, R. M.; Caldwell, J. W.; Kollman, P. A.; Case, D. A. *J. Comput. Chem.* **2004**, *25*, 1157.
29. Pettersen, E. F.; Goddard, T. D.; Huang, C. C.; Couch, G. S.; Greenblatt, D. M.; Meng, E. C.; Ferin, T. E. *J. Comput. Chem.* **2004**, *25*, 1605.
30. Karakaplan, M.; Ak, D.; Çolak, M.; Kocakaya, S. O.; Pirinccioglu, N. *Tetrahedron* **2013**, *69*, 349.