

Enantioselective complexation of chiral lariat crown ethers and chiral primary alkylammonium perchlorates

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Received 17.08.2010

In order to investigate the enantiomeric recognition abilities toward 2 chiral alkylammonium perchlorates (AmI, AmII) by ¹H-NMR titration method in CDCl₃, 4 chiral lariat ethers **8-11** with a (*p*-methoxyphenoxy) methyl flexible side arm were used. The most effective enantiomeric recognition was obtained by LCEs **9** and **11** toward AmII, by K_R/K_S 6.58 and K_S/K_R 6.63, respectively. The effect of macroring size, subunit of macroring, and side arm appeared to have strong influence on the binding ability of these alkylammonium ions.

Key Words: Chiral lariat crown ethers, enantioselectivity, complexation properties, molecular recognition, NMR titration

Introduction

Lariat crown ethers (LCEs) are usually depicted as crown ethers with side arms containing donor atoms located at their end.¹ Such lariat ethers are designed to enhance the cation binding ability or selectivity of crown ethers by providing the potential of 3-dimensional complexation. This can lead to the mimicking of the dynamic complexation processes exhibited by natural macrocyclic ionophores.² The structural and chemical similarities between lariat crown ethers and a number of enzymes, where nearly 10% of amino acid side chains are terminated by the aromatic residues benzene (in phenylalanine), phenol (in tyrosine), and indole (in tryptophan), make this type of compound a favored model for biochemists as well as chemists. Side arm participation in metal cation complexation by lariat ether was demonstrated in solid state structures³⁻⁵ and inferred by increased

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stability constant in solution compared with corresponding crown ethers ligand.⁶ In other words, the side arm of the LCEs can lead to significant changes in the complexation behavior of the host molecules.⁷

The enantiomeric recognition of primary alkylammonium salts by chiral macrocyclic receptors is helpful in developing new methods of asymmetric synthesis and chromatographic resolution of enantiomers.⁸ In particular, chiral crown ethers are known to be chiral solvating agents (CSA) toward protonated primary amines and amino acid methyl ester salts.^{9–13} Among these macrocycles, optically active 18-crown-6 ethers have been well investigated.^{14–20} So far, there have been a few reports on the use of the *C*-pivot type of chiral crown ethers as CSAs for metal cations,^{21–24} primary alkylammoniums,^{25,26} and amino acid methyl esters.²⁷ The use of CSAs is one of the most effective and convenient methods for the assessment of the binding constants with guest molecules in NMR spectroscopy. Awareness of the conformational preference of LCE is important for predicting its 3-dimensional properties of molecular structures and binding affinities with guest molecules. This is important in the field of supramolecular chemistry and molecular recognition.²⁸

Our previous study showed that LCEs **8-11** exhibited good chiral recognition toward amino acid methyl esters²⁷ and an excellent enantioselective transport of amino acids and their sodium and potassium salts through the chloroform membrane phase.²⁹ An investigation of the effect of the side arm on the complexation of a solid-state structure of LCE **8** sodium perchlorate complex has also been reported.³⁰

In this study, 4 chiral lariat crown ethers bearing (*p*-methoxyphenoxy) methyl moiety (**8-11**) were designed in order to investigate their complexation ability and molecular recognition with chiral α -phenylethylammonium perchlorate (AmI) and α -(1-naphthyl)ethylammonium perchlorate (AmII) by ¹H-NMR titration method (Scheme). The introduction of aromatic π and n donor side arms into chiral crown ether is regarded as a useful strategy for new types of crown ethers because such aromatic side arms should affect enantiomeric discrimination by the combination of steric and electronic factors. Macrocycles **8-11** were synthesized by ring closure of chiral subunit diol **1** prepared from (*S*)-glycidol and *p*-methoxyphenol as described in our previous report.²⁷ Macrocycles **10** and **11** bear benzo and naphtho units as rigid and lipophilic groups, respectively.

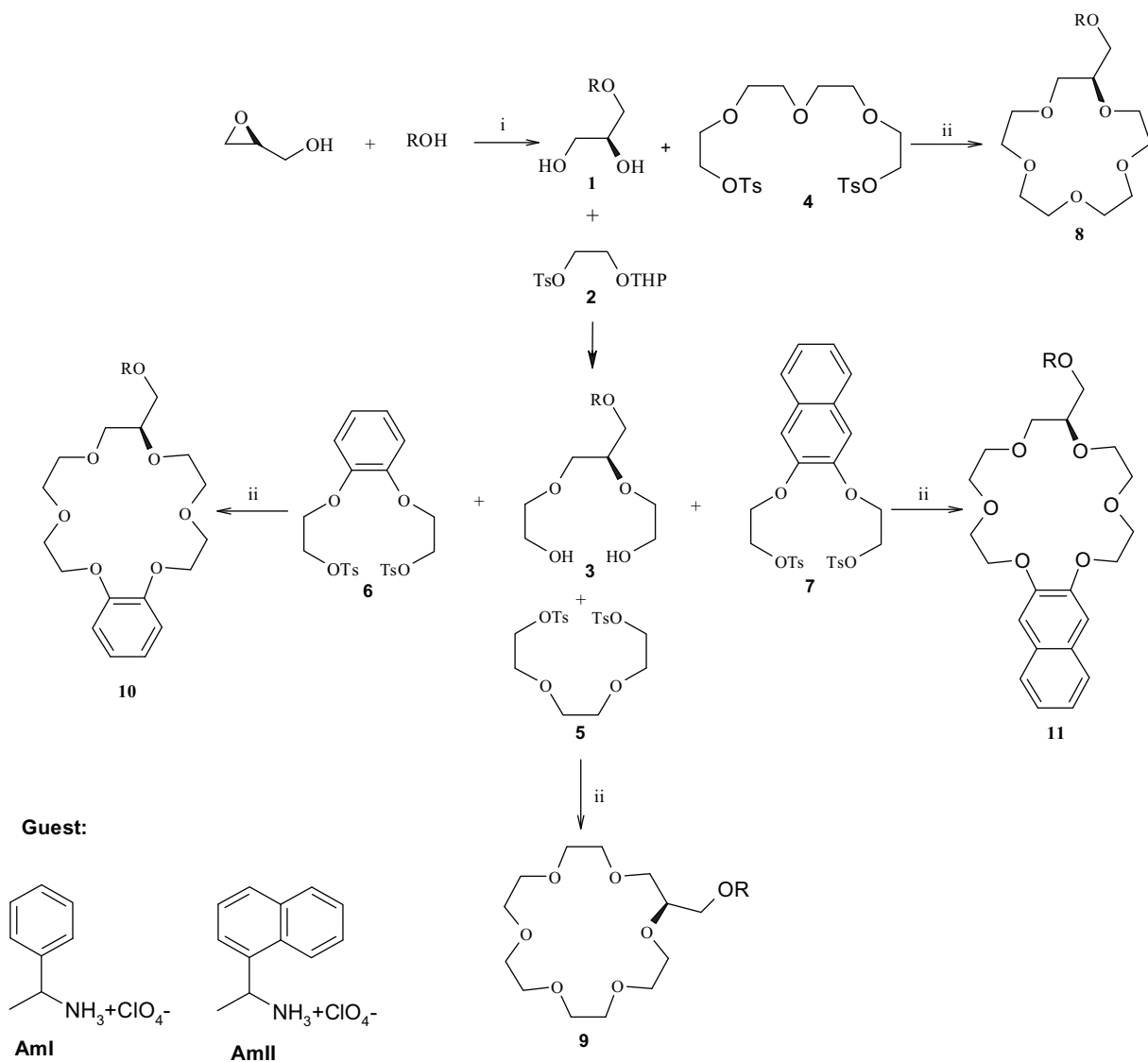
Experimental section

General information

¹H-NMR (400 MHz) and ¹³C-NMR (100 MHz) spectra were recorded on a Bruker Avance-400 MHz high performance digital FT-NMR spectrometer, with tetramethylsilane as the internal standard solution in deuteriochloroform. Hosts **8-11** were synthesized as described in a previous report.²⁷

Evaluation of the stoichiometry of the host-guest complex (Job plots)

The stoichiometric host-guest complexes were determined according to Job's method of continuous variations. Equimolar amounts of host and guest compound were dissolved in CDCl₃ (Figure 1). These solutions were distributed among 9 NMR tubes in such a way that the molar fractions X of host and guest in the resulting solutions increased (or decreased) from 0.1 to 0.9 (and vice versa). The complexation-increased shifts were multiplied by X and plotted against X itself (Job plot).



Scheme. R: *p*-MeOPh-, reagents and condition, i) piperidine hydrochloride, 70-80 °C, 4 h, ii) NaH, THF, reflux, 56 h.

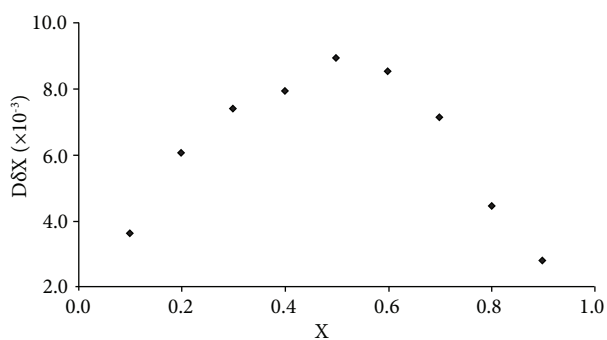


Figure 1. Job plots of compound (*S*)-**11** with (*S*)-**Aml** (*X* = molar fraction of the guest, $\Delta\delta$ = chemical shift change of diastereotopic side arm and macrocyclic protons of (*S*)-**11**).

NMR host-guest titration

The host compound was dissolved in an appropriate amount of solvent (CDCl_3) and the resulting solution was evenly distributed among 9 NMR tubes. The first NMR tube was sealed without any guest. The guest compound was also dissolved in the appropriate amount of solvent and added in increasing amounts to the NMR tubes, so that solutions with the following relative amounts (equiv.) of guest versus host compound (concentration was 4.16×10^{-3} M) were obtained: 0.00, 0.125, 0.25, 0.375, 0.50, 1.00, 2.00, 4.00, and 6.00. K was calculated for compounds **8-11** from the observed $\Delta\delta$ values and the respective host and guest concentrations by the NMR version of the Benesi-Hildebrand equation.^{31,32} The chemical shift change of diastereotopic protons of host **11** toward (*S*)- and (*R*)-AmI can be seen in Figure 2.

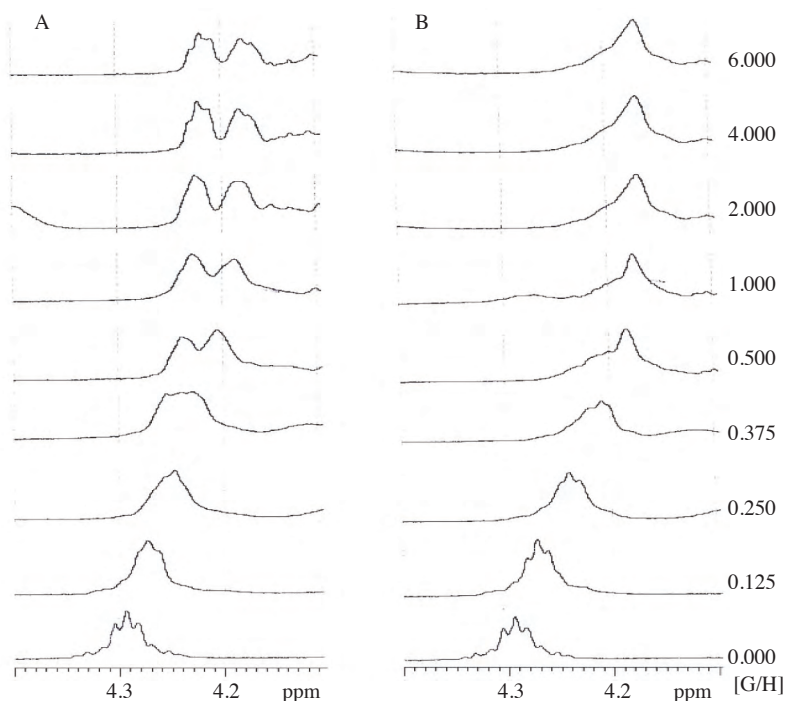


Figure 2. Diastereotopic proton signals of host **11** (4.16×10^{-3} M) by addition of guest compounds (A: (*S*)-AmI, B: (*R*)-AmI) in CDCl_3 at 25 °C.

Results and discussions

It is known that the nature, rigidity, and quality of side arms of hosts are all expected to play an important role in enantiomeric recognition. $^1\text{H-NMR}$ titration is the most reliable method in order to determine the association complex. For inclusion phenomena, chemical shift changes or the appearance of a separate NMR peak are indicative of the formation of the host-guest complex. In the present study, the complexation phenomena between the *C*-pivot type of chiral LCEs **8-11** and alkylammonium perchlorates (AmI and AmII) in CDCl_3 were investigated by $^1\text{H-NMR}$ titration method. Therefore, the $^1\text{H-NMR}$ spectra of pure LCEs **8-11** and their perchlorate complexes were collected. It was observed that the peak at about 4.3-4.2 ppm was considerably

shifted to the higher magnetic field by the addition of alkylammonium salts for all of the LCEs. The peak belonging to the diastereotopic protons of the side arm and macroring, shown by the DEPT and HETCOR spectra of host **11**, is an example (Figures 3 and 4). This means that the electronic structure of both the macroring and side arm was perturbed by the complexation, indicating that the aromatic group of guests AmI and AmII overlapped the macroring's side arm site. This overlapping caused a magnetic shielding effect,³³ resulting in upfield shifts of ^1H -NMR signals. These findings are in agreement with LCE carboxylate-alkali metal complexes in solution.²¹ Upfield shifts of the macroring proton signals were also observed upon complexation with AmII enantiomers in the solution.^{34,35}

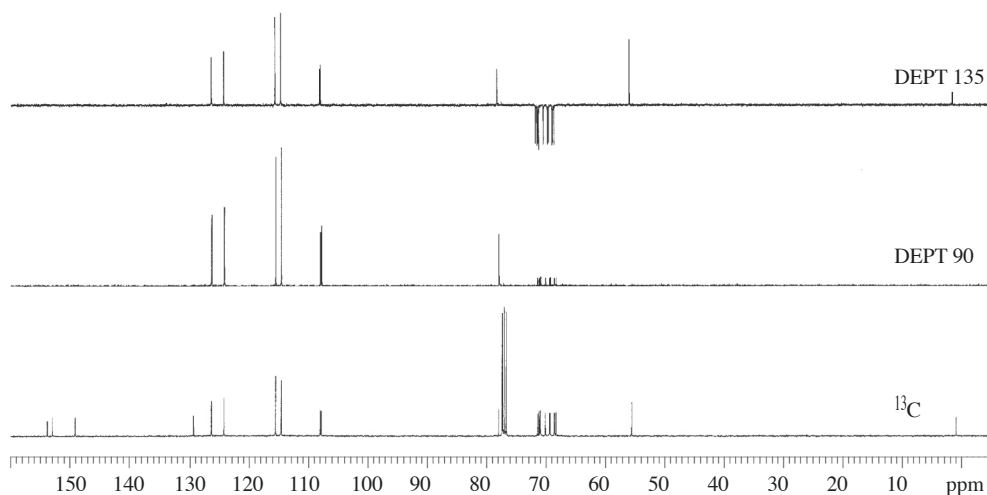


Figure 3. ^{13}C , DEPT 90, and 135 spectra of host **11**.

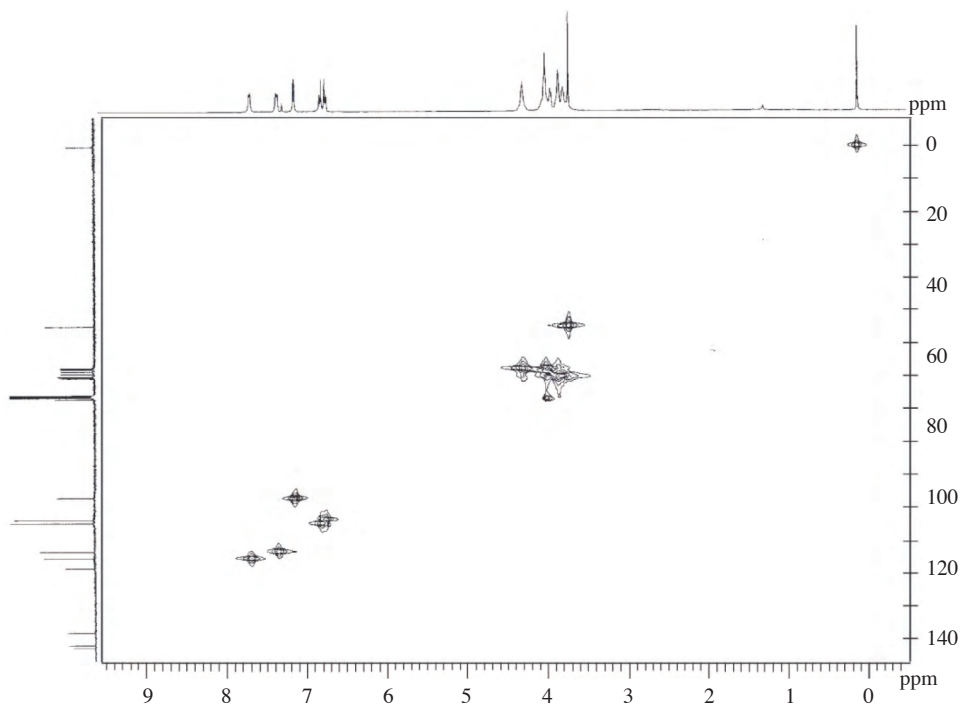


Figure 4. HETCOR spectrum of host **11**.

The binding constants of LCEs **8-11** were determined by the chemical shift differences of this signal at 4.3-4.2 ppm (Table). In each association experiment, 1:1 binding stoichiometry was assumed as the observation for the 1:1 instantaneous complex between host **11** and (*S*)-AmI by Job plots (Figure 1). In addition to this, the titration curves of LCEs **8-11** showed that the changes of this signal difference significantly decreased after formation of the 1:1 complex. These changes were clearly seen from the diastereotopic proton signals of host **11** by addition of guest compounds (*S*)-AmI and (*R*)-AmI (Figure 2).

Table. Binding constants (K), enantioselectivities (K_S/K_R), and Gibbs free energy changes (ΔG°) for the complexation of chiral guests AmI and AmII with chiral hosts (*S*)-**8-11** in CDCl_3 (4.16×10^{-3} M) at 25 °C.

LCEs	Guest	K (dm^3/mol)	K_S/K_R	$-\Delta G^\circ$ (kJ/mol)
(S)-8	(<i>S</i>)-AmI	265 ± 40	3.39	13.827
	(<i>R</i>)-AmI	78 ± 5		10.796
	(<i>S</i>)-AmII	714 ± 114	2.06	16.283
	(<i>R</i>)-AmII	346 ± 45		14.487
(S)-9	(<i>S</i>)-AmI	220 ± 20	2.31	13.365
	(<i>R</i>)-AmI	95 ± 3		11.285
	(<i>S</i>)-AmII	102 ± 6	0.15	11.461
	(<i>R</i>)-AmII	671 ± 174		16.129
(S)-10	(<i>S</i>)-AmI	220 ± 18	2.10	13.365
	(<i>R</i>)-AmI	105 ± 4		11.532
	(<i>S</i>)-AmII	504 ± 150	0.67	15.420
	(<i>R</i>)-AmII	752 ± 188		16.411
(S)-11	(<i>S</i>)-AmI	110 ± 5	1.50	11.648
	(<i>R</i>)-AmI	73 ± 3		10.796
	(<i>S</i>)-AmII	445 ± 40	6.63	15.111
	(<i>R</i>)-AmII	67 ± 2		10.419

Taking into account the binding constants, host **8** exhibited stronger complex ability toward AmI than AmII, by K_S/K_R 3.39 and 2.06, respectively. Crown ethers with 15-crown-5 and 18-crown-6 rings had average cavity sizes of 1.84 and 2.90 Å, respectively.²¹ Therefore, host **8** probably formed perching complexes²¹ rather than 3 hydrogen bonds with polyether ring oxygens, in which the predominant geometry of diastereomeric complexes causes the change of the electronic environment of the side arm. This picture is helpful in understanding the formation of complexes between ammonium ions and the side arm of the macroring.

In the case of host **9**, a higher binding constant and enantioselectivity were obtained for AmII than AmI, by K_R/K_S 6.58 and 2.31, respectively. The enantioselectivity of AmII may be assessed with effective noncovalent interactions and appropriate steric hindrance, which is caused a specific conformational binding including favorable π stacking interaction between the flexible side arm of the host and the aromatic moiety of AmII.

Generally, host **10** has relatively strong binding ability but lower enantioselectivity toward Am II, by K_R/K_S 1.5, than AmI, by K_S/K_R 2.1, due to greater rigidity and the $\pi - \pi$ stacking interaction of the benzo

unit and the aromatic moiety of AmII (Table). Ammonium ions probably bind with the same side of the macroring; therefore, the steric hindrance of the side arm does not significantly influence the enantiomers of guests leading to enantioselectivity.

It is known that the rotation about the single bonds in the side arm is facile and that the diastereotopic side arm protons are magnetically equivalent, leading to a singlet absorption in the $^1\text{H-NMR}$ spectrum. In Figure 2, the diastereotopic side arm proton signals of (*S*)-AmI are seen to be shifted to the higher field together with splitting to 2 signals, but (*R*)-AmI is seen to have shifted without any splitting peaks. This indicates that the diastereotopic side arm protons are nonequivalent, producing an AB pattern by restricts of the side arm. Docking studies (molecular docking) were obtained via MD studies for 1 ns for the hosts and 100 ps for the guests by using AMBER (v. 9).³⁶ Docking of the guests was carried out using the program DOCK (v. 6.0). Structures estimated by the docking study for complexes formed between host **11** and the enantiomers of AmI showed different interactions (Figure 5). While (*S*)-AmI preferred cation- π interaction in complexation, (*R*)-AmI preferred $\pi - \pi$ interaction. On the other hand, host **11** exhibited better enantiomeric recognition toward AmII, by K_S/K_R 6.63, than AmI, by K_S/K_R 1.5, due to the favorable cation- π and $\pi - \pi$ stacking interaction between an enantiomer of AmII and the macroring. Thus, the greater enantioselectivity of AmII may also be explained by the specific binding of (*S*)-AmII by appropriate $\pi - \pi$ stacking interaction between the side arm and guest. Host **11** also exhibited good enantioselectivity toward amino acid methyl ester by the UV-titration method, according to our previous report.²⁷ This result shows that the presence of the naphtho unit on the macroring not only gives rise to the best environment for complexation but also increases enantiomeric recognition due to the specific conformational binding. Consequently, LCEs **8-11** form reasonably stable complexes with guest enantiomers, indicating that the low conformational flexibility of diastereomeric complexes results in a high degree of enantiomeric recognition.

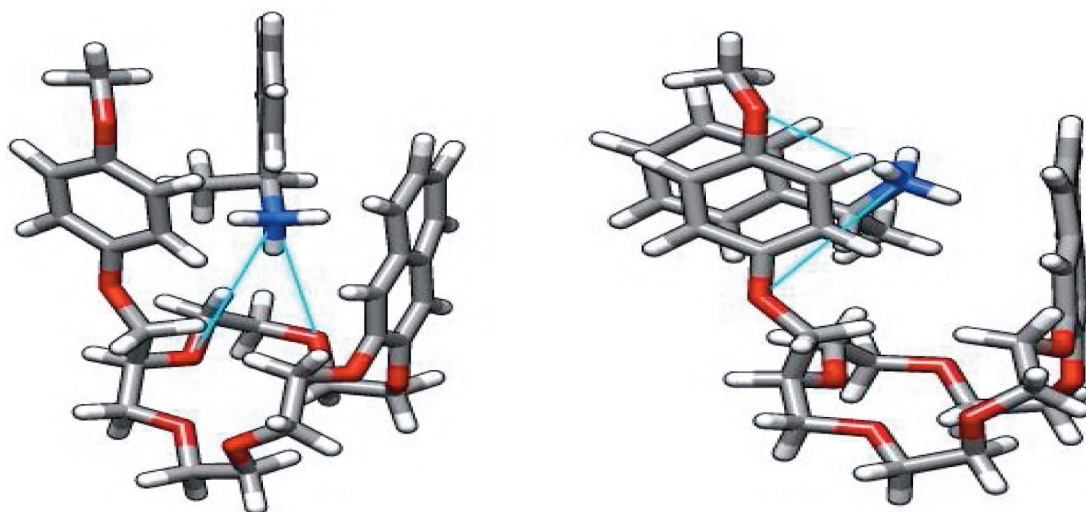


Figure 5. Structures estimated by docking study for the complexes formed between host **11** and (*S*)-AmI (left) and (*R*)-AmI (right), respectively.

Conclusion

C_1 symmetric C-pivot chiral LCEs **8-11** not only exhibit appreciable complexation constants but also show good enantiomeric recognition toward primary alkylammonium perchlorates AmI and AmII. In particular, despite their small cavities, LCE **8** forms stable enantioselective complexes and LCE **9** forms favorable enantioselective complexes with macroring oxygens. On the other hand, LCE **10** has relatively high binding constants and low enantioselectivity due to its planar structure, and LCE **11** forms a stable enantioselective complexation by a specific conformational binding with effective $\pi - \pi$ and cation- π interaction. It was found that the electron donor characters of the side arm appeared to have a strong influence on the binding ability of these alkylammonium ions.

Acknowledgement

This research was supported by the Research Project Council of Dicle University (DÜAPK) (Project No. DÜAPK-09- FF-13).

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