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Chiral benzimidazole-derived mono azacrowns: synthesis and enantiomer recognition studies with chiral amines and their ammonium salts

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ABSTRACT

Benzimidazole fused chiral mono aza-15-crown-5 **2**, was obtained in a single step from (*S*)-(−)-2-(α-hydroxyethyl) benzimidazole **1**. This new class of aza-crown has a unique structure with the chiral unit being held in a stable conformation due to adjacent benzimidazole ring contributing to its stereodiscrimination ability. The interactions between the host aza-crown and enantiomerically pure amine guests in ionic and neutral forms exhibited the enantio-discrimination ability. The preliminary evaluation of the chiral sensing was monitored using ^{1}H NMR and circular dichroism (CD) analysis of the complexes at their molar equivalence. The binding parameters were determined using electronic absorption spectroscopy.

1. Introduction

Understanding and unravelling the concepts of the origin of life and the associated physiological processes are at the heart of chiral recognition.[1–3] Synthetically designed chiral receptors to study the stereochemical integrity of biologically significant molecules such as amino acids, sugars, drugs etc, and are being continuously developed world wide. It is possible to identify certain structural features that are desired for high levels of enantio-discrimination. Among these the cavity size,[4] symmetry,[5] additional binding sites,[6] conformational rigidity,[7] and availability of a π-rich unit near the stereogenic center are considered to be essential features for the prospective receptors.[8] Molecular recognition in the neutral state of the guest is relatively uncommon.[9–11] Amines are a group of small molecules found extensively in biosystems and in drugs of abuse and therapeutic relevance. Thus monitoring the chemical and enantiomeric purity/assay of amines has gained wide recognition in biochemistry.[12] Chiral recognition is a stringent measure of small energetic differences between diastereomeric complexes and is a consequence of dissimilar extents of stereochemical interactions between a receptor and guest enantiomers.

Enantiomerically pure chiral macrocycles have proven to be useful synthetic hosts for chiral discrimination.[13–15] Heterocycles containing chiral macrocycles are interesting as they offer multiple ligating sites in addition to aromatic π–π interactions.

Crown ethers[16–18] and azacrown ethers have gained importance as an efficient class of sensors for metal ions and (alkyl) ammonium ions.[19–21] Azacrowns offer several advantages such as better binding with wider range of cations, including the softer metal cations and a binding to the neutral guests; these features are noticeably different from oxacrown ethers.[22,23] Several chiral azacrowns with heterocylic residues such as pyridine, pyrimidine, and phenazine have been developed and investigated for their recognition abilities toward chiral amines and amino acids in their neutral and ionic forms.[16–18]

2. Benzimidazole as a chiral synthon

For the practical development of a receptor two considerations are vital; the availability of inexpensive synthons and high yielding simple synthetic protocols. Benzimidazole motifs have found wide applications in chemosensing, catalysis, and pharmaceuticals and so on. The fabrication of benzimidazole derivatives and their applications in chiral processes have been an area of interest for us, with one of the most successful applications being the kinetic resolutions of racemic amines and aminoester.[24,25] Earlier experience in the development of crown ether containing furo-fused BINOL and its effective performance as a chiral discriminator of amines and aminoesters[26] motivated us to synthesize chiral azacrown ether containing a benzimidazole ring as a heterocyclic residue. (*S*)-(−)-2-(α-Hydroxyethyl) benzimidazole **1** can be obtained conveniently[27,28] in a single step reaction between *o*-phenylenediamine and (*S*)-lactic acid. This molecule has good configurational stability. The molecule offers a β-hydroxy amino moiety, which has been used extensively for construction of several azacrowns.[29] A noteworthy feature of the proposed azacrown molecule, is the mutually shared C–N bond between the heterocycle and the

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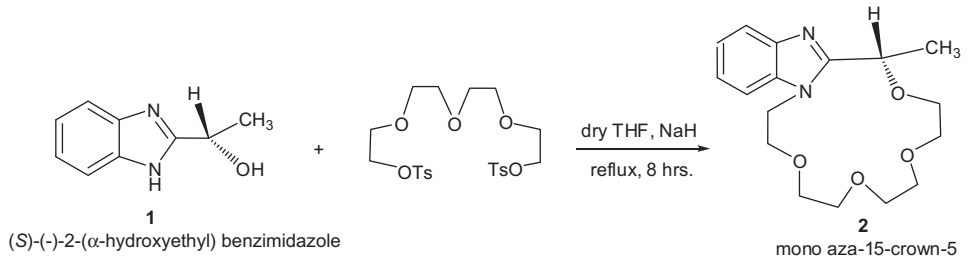

Figure 1. Synthesis of mono aza-15-crown-5 (**2**).

macrocyclic cavity of crown. We anticipated that this arrangement of atoms would result in a highly strained geometry of the crown ring in the vicinity of the benzimidazole ring. This feature was considered to be potentially useful to monitor the associated electronic transitions during recognition events. This unique and novel molecule was worth exploring as a chiral sensor for biomolecules, the efficiency of which would depend on the combined interplay of noncovalent intermolecular interactions such as hydrogen bonding, steric effects, and aromatic π–π interactions with the guest enantiomers.

Herein we report the synthesis of a chiral mono azacrown ether (Fig. 1), and also present our preliminary ^{1}H NMR and circular dichroism (CD) spectroscopic studies on the enantiomeric recognition of the azacrown with the enantiomers of 1-naphthylethylamine and 1-phenylethylamine and their ammonium perchlorate salts along with UV titration studies in order to determine the association constants. These studies revealed that the chiral (*S*)-(−)-2-(α-hydroxyethyl) benzimidazole **1** derived azacrown ether displayed high enantioselectivities for the (*S*)-enantiomers of chiral organic amines and their ammonium salts.

3. Results and discussion

3.1. Synthesis of benzimidazole derived mono aza-15-crown-5 2

The enantiopure benzimidazole-derived mono aza-15-crown-5 **2** was synthesized in a single step (Fig. 1). (*S*)-(−)-2-(α-Hydroxyethyl) benzimidazole **1** was treated with tetraethylene glycol ditosylate in the presence of sodium hydride as the base and anhydrous THF as the solvent at reflux under high dilution conditions under an inert atmosphere. This gave the desired chiral mono aza-15-crown-5 **2** as a white crystalline solid. The racemic azacrown was prepared in a similar manner by starting from racemic 2-(α-hydroxyethyl) benzimidazole **1**.

Chiral HPLC analysis indicated that the mono aza-15-crown-5 **2** was obtained in high enantiomeric excess when prepared from (*S*)-(−)-2-(α-hydroxyethyl) benzimidazole **1**. The newly synthesized crown was characterized by suitable spectroscopic techniques, including single-crystal XRD analysis. The azacrown was obtained in 48% yield. The ^{1}H NMR and ^{13}C NMR showed that the crown had been built by typical signal pattern due to the methylene groups in addition to the aromatic benzimidazole part. The COSY spectrum exhibited correlations for signals due to the CH protons and the methyl protons at the stereogenic center, clearly indicating their proximity. Similarly the signals due to protons present on the aromatic rings correlated among themselves. Apart from the correlations observed in the COSY, the NOE spectrum exhibited energy transfer among the methyl signal at the stereogenic center and the cluster of signals due to the $-CH_2$ protons of the crown ring, which also displayed energy transfer to signals due to the aromatic protons, thus confirming their proximity through space. Single crystal XRD analysis confirmed the structure (Fig. 2).

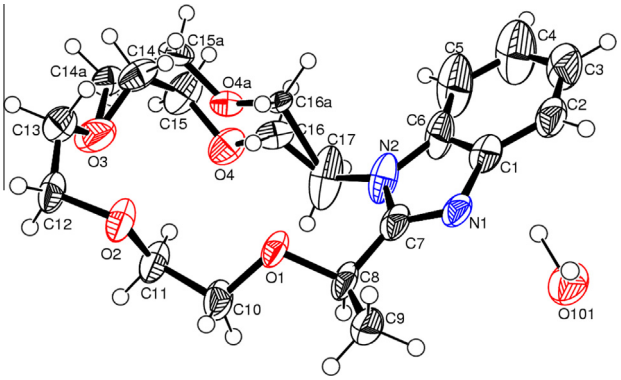

Figure 2. ORTEP representation of the X-ray crystal structure of **2**.

3.2. X-ray crystallographic data of monoaza-15-crown-5 2

Single crystal XRD studies of mono aza-crown **2** revealed that the benzimidazole backbone provided conformational rigidity to the crown cavity, while the portion of macrocycle away from the heteroaryl ring exhibited two major conformations (Fig. 2). As expected, the stereogenic center seemed to be acquiring much needed conformational stability.

One of the nitrogen atoms, N-2 from the benzimidazole ring along with the hydroxyl group present at the stereogenic center are involved in the formation of the chiral azacrown ring. Thus, the N-2 nitrogen atom is shared by the azole as well as the azacrown cavity providing a highly rigid geometry at the interface of the two rings, while another nitrogen atom N-1 is seen in the hydrated form in the single crystal X-ray. This association of the water molecule (neutral) with the azacrown unit was considered interesting since it exhibited its ability to bind to appropriate guests in a neutral state.

3.3. Enantiomer recognition studies

Enantiomer recognition potential for the azacrown was evaluated by various spectroscopic techniques. The preliminary enantiomer sensing ability of the azacrown was evaluated by ^{1}H NMR and circular dichroism methods.[30,31] The UV–vis titration was performed with the azacrown and chiral amines/ammonium perchlorates in order to determine the binding parameters.

Azacrown ethers have been successfully applied for the chiral sensing of amines and amino acids using NMR spectroscopy.[29a,32] The interaction of benzimidazole derived azacrown **2** with enantiopure perchlorate salts of 1-α-phenylethyl amine and 1-α-naphthylethyl amine confirmed the enantiomeric purity of the azacrown molecule as well as displaying the preferential complexation with (*S*)-(−)-enantiomers of organic ammonium perchlorates. A higher upfield chemical shift $\Delta\delta = (0.079$ ppm) of the

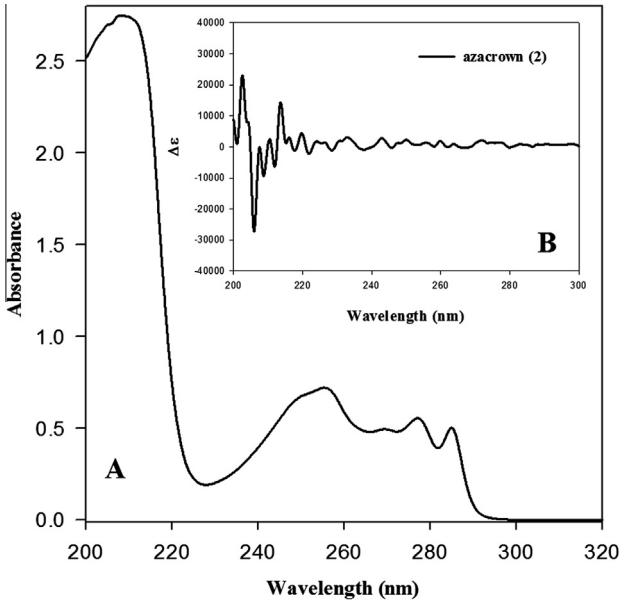

Figure 3. UV–vis and CD (inset) spectral studies of azacrown **2** in acetonitrile (2×10^{-5} M).

methyl doublet at the stereogenic center of **2** in the complex of **2** with (*S*)-(−)-α-1-phenylethylamine perchlorate salt when compared to **2** with (*R*)-(+)-α-1-phenylethylamine perchlorate salt complex ($\Delta\delta$ = (0.074 ppm) confirmed the chiral discrimination ability of **2**. The diastereomeric complex formed between **2** and 1-α-naphthylethylamine perchlorates resulted in a downfield chemical shift of the methyl doublet. A small difference for $\Delta\delta$ of 0.004 ppm was observed for the two diastereomeric complexes of the two enantiomers of 1-α-naphthylethylamine perchlorate salts and the crown **2** complex.

Circular dichroism (CD) is a powerful tool for understanding the structural changes that occur at a molecular level ranging from small organic molecules to bulky bioploymers upon their interaction with other molecules. The mutual interaction of the chromophores present in the two interacting species (host and guest) results in electronic perturbations and if a stereogenic center is in the vicinity of the chromophore, these interactions result in an appreciable difference in the diastereomeric interactions of chiral guest enantiomers, which can be discriminated by CD.[30,31,33] The enantio-discrimination behavior of a chiral host toward the enantiomers of biologically significant molecules such as amines, amino

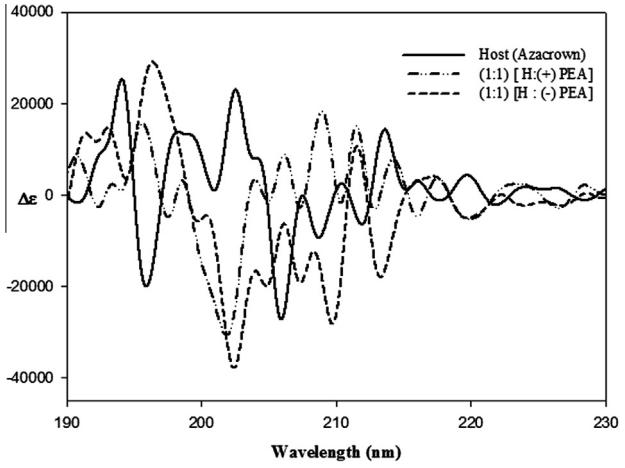

Figure 4. CD spectra of azacrown **2** and 1:1 complexes of **2** (*R*)-(+)-PEA and (*S*)-(−)-PEA.

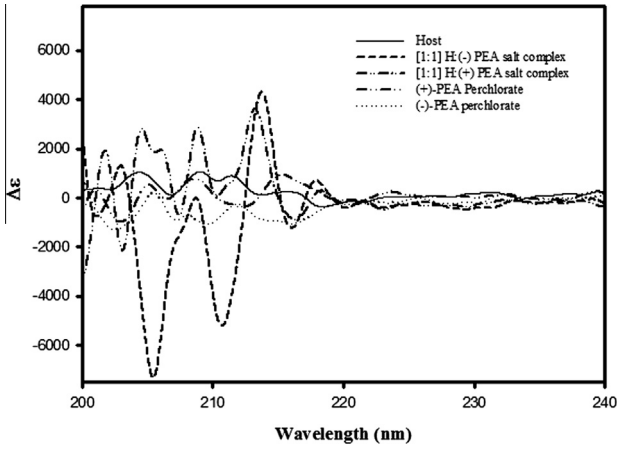

Figure 5. CD spectra of azacrown **2** and 1:1 complexes of **2** (*R*)-(+)-PEA perchlorate and (*S*)-(−)-PEA perchlorate.

acids and so on, has been widely studied using CD.[34] The UV–vis and CD spectra of benzimidazole containing azacrown offers the scope to study H-bonding and π–π interactions from the strong exciton couplets in the CD spectrum.

3.4. CD studies of azacrown 2

The ECD spectrum of azacrown **2** was studied in acetonitrile (2×10^{-5} M) (Fig. 3, inset-B). The Near UV-CD region consists of weak exciton couplets. The Far UV-CD region displays intense cotton effects in the region around 220 nm associated with $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ electronic transitions due to –C=N bonds of benzimidazole. An intense bisignate couplet was observed with a negative band at 217 nm and a positive band at 221 nm, corresponding to the $n \rightarrow \pi^*$ transitions.

3.4.1. Analysis of the ECCD spectra of host–guest complexes

The discriminating efficiency of host **2** was probed by exciton coupled circular dichroism (ECD) spectroscopy using enantiomers of amines and their ammonium salts. The ECD spectra of azacrown **2** were recorded with 1-α-phenylethylamine, 1-α-naphthylethyl amine, and their perchlorate salts in acetonitrile. Chiral azacrown **2** was treated with one molar equivalent of (*S*)-(−)-1-α-phenylethylamine and (*R*)-(+)-1-α-phenylethylamine and the CD spectra were recorded. The CD spectrum of host **2** in the absence and presence of the guest enantiomers was recorded separately. The first

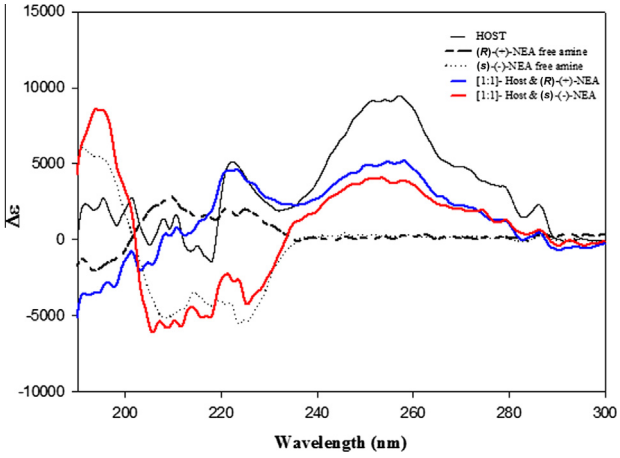

Figure 6. CD spectra of azacrown **2** and 1:1 complexes of **2** with (*R*)-(+)-1-α-NEA and (*S*)-(−)-1-α-NEA.

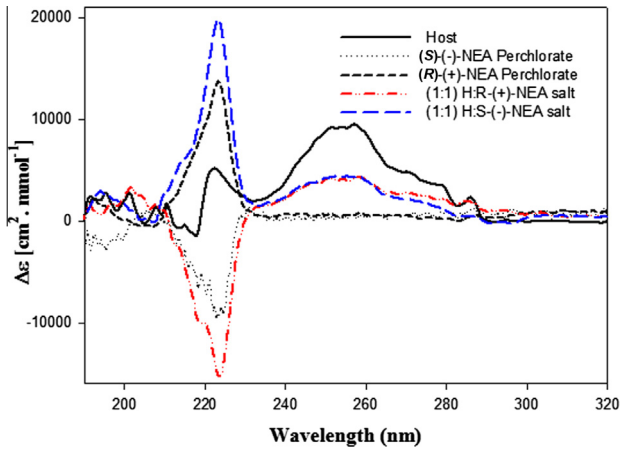

Figure 7. CD spectra of azacrown **2** and 1:1 complexes of **2** (*R*)-(+)-1-α-NEA perchlorate and (*S*)-(−)-1-α-NEA perchlorate.

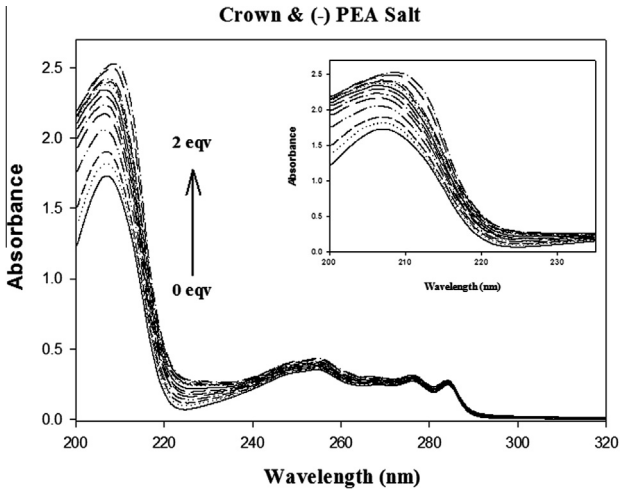

Figure 8. UV–vis spectral changes upon spectrophotometric titration of **2** (1×10^{-5} M) with (*S*)-(−)-1-phenylethyl ammonium perchlorate (1×10^{-6}–2×10^{-5} M).

set of weak oppositely signed bands was seen between 196.3 nm (11.872) and 200 nm (−7.7261). The second pair of the prominent bisignate band was observed at 211.5 nm (−6.459) and 213.5 nm (8.197) while the third pair of bisignate band was observed between between 224.7 nm (−1.524) and 226.7 nm (0.144) bonds (Fig. 4).

The bands observed at 211.5 nm (−6.459) and 213.5 nm (8.197) showed noticeable differences upon complexation with chiral guest molecules. These bands are most likely due to $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions associated to C=N, the part closer to the chiral unit.

The amplitudes (*A*) of the couplet at 213 and 211 nm, in the ECCD spectra of diastereomeric complexes were compared, where Amplitude, $A = (\Sigma|\Delta\varepsilon_{max}|$ of the couplet) $A_{(-)\text{PEA complex}} = \{|(11{,}762) - (14{,}802.6)|\ \text{cm}^2\ \text{mmol}^{-1}\} = (32{,}564.6\ \text{cm}^2\ \text{mmol}^{-1})$.

Conversely **2** with (*R*)-1-α-phenylethyl amine; Amplitude, $A_{(+)\text{PEA complex}} = \{|(7608.34) - (-2750)|\ \text{cm}^2\ \text{mmol}^{-1}\} = (10{,}358.1\ \text{cm}^2\ \text{mmol}^{-1})$ and $\Delta A = \{A_{(-)\text{PEA complex}} - A_{(+)\text{PEA complex}}\}$; $\Delta A = 22{,}205.5\ \text{cm}^2\ \text{mmol}^{-1}$ was found to be reasonably high and indicated the difference in the extent of the complexation of the azacrown between the two enantiomers of 1-α-phenylethyl amine.

When **2** was subjected to complexation with one molar equivalent of ammonium perchlorate salts of 1-α-(*R*)-(+)- and (*S*)-(−)-phenylethylamine, the ECD spectra displayed a weak, oppositely charged couplet at 216.1 and 218.3 nm due to transitions associated with –C=N (Fig. 5).

The bisignate wave couplet between 202.9 and 205 nm was analyzed to better understand the chiral discrimination. The amplitudes (*A*) of this couplet in the ECD spectra of diastereomeric complexes were compared, $\Delta A = 4596.65\ \text{cm}^2\ \text{mmol}^{-1}$ was found to be reasonably good and indicative of the preferential complexation of **2** with (*S*)-(−)-1-α-phenylethyl ammonium perchlorate.

Similarly crown **2** when treated with (*R*)- and (*S*)-isomers of 1-α-naphthylethyl amine, the ECD spectra revealed the diastereomeric nature of interactions (Fig. 6).

Comparing the amplitudes (*A*) of the couplet at 224.5 and 235.4 nm, in the ECD spectra of diastereomeric complexes $\Delta A = 2475.7\ \text{cm}^2\ \text{mmol}^{-1}$ was found to be reasonably good for (*S*)-(−)-(−)-1-α-naphthylethylamine upon interaction with **2** in the neutral form.

The ECD spectra of diastereomeric complexes of **2** with 1-α-naphthylethyl ammonium perchlorate enantiomers displayed prominent cotton effects between 223.6 and 234.0 nm (Fig. 7). The large magnitude of the amplitude *A*, but smaller difference in amplitudes $\Delta A = 1516.6\ \text{cm}^2\ \text{mmol}^{-1}$, indicates strong complexation of **2** with NEA perchlorate salts but lower discrimination among both the enantiomers. The details of CD analyses are provided for all of the complexation experiments carried out in Table 1.

Thus, as expected based on the structural features, the chiral azole chromophore containing part of the crown backbone exhibited the chiral discrimination by forming diastereomeric complexes with primary organic amines and their ammonium perchlorates. Such molecules have found wide application in chromatographic separation science.[35]

3.5. Determination of the binding parameters by UV/vis spectroscopy

UV/vis spectroscopy is a powerful tool for examining chiral sensing protocols[36]. An effective sensor should absorb light of different wavelengths in non-bound and complexed forms. The difference in the characteristic absorbance of the host and chiral

Table 1
CD data of benzimidazole derived aza-crown **2** and its 1:1 complexes with chiral amines and their ammonium perchlorates

Host	Guest	λ[nm] (Δε)	λ[nm] (Δε) ($\text{cm}^2\ \text{mmol}^{-1}$)	$A = (\Sigma\|\Delta\varepsilon_{max}\|$of the couplet)	$\Delta A = [A_{(S)\text{complex}}] - [A_{(R)\text{complex}}]$
2	(*S*)-PEA	213(−17762)	211(14802.6)	32,564.6	22,205.5
	(*R*)-PEA	213(7608.34)	211(−2750.76)	10,359.1	
	(*S*)-PEA salt	205.5(−7246.59)	202.97(1355.4)	8601.99	4596.6
	(*R*)-PEA salt	205.44(1924.88)	202.97(−2080.46)	4005.34	
2	(*S*)-NEA	224.5 (−3386.4)	235.4 (1128.73)	4515.1	2475.7
	(*R*)-NEA	224.5(4286.2)	235.4(2246.8)	2039.4	
	(*S*)-NEA salt	223.6(1485.47)	2234.0(19674.51)	16,672.38	1516.6
	(*R*)-NEA salt	223.6(1418.9)	234.0(−15253.47)	18,189.05	

Table 2
Binding constants $K_{(S)}$ or $K_{(R)}$, enantioselectivities $K_{(S)}/K_{(R)}$ and Gibbs free energy changes ($-\Delta G_0$) for the diastereomeric complex of **2** with enantiomers of amines and their ammonium perchlorates in acetonitrile at 25 °C

Host	Guest[a]	K_a (M^{-1})	$K_{(S)}/K_{(R)}$	$-\Delta G_0$ (kJ mol^{-1})	$-\Delta\Delta G_0$ (kJ mol^{-1})[b]
Azacrown (**2**)	(*S*)-PEA	4.054×10^5	11.9	32	6.14
	(*R*)-PEA	3.4×10^4	(±0.229)	26	
	(*S*)-PEA ion	1.711×10^5	3.03 (±0.068)	30	2.75
	(*R*)-PEA ion	5.64×10^4		27	
	(*S*)-NEA	1.602×10^5	1.122	29	0.43
	(*R*)-NEA	1.428×10^5	(±0.033)	30	
	(*S*)-NEA ion	7.848×10^4	1.193 (±0.015)	27	0.30
	(*R*)-NEA ion	6.576×10^4		28	

[a] PEA = α-phenylethylamine, PEA ion = α-phenylethylammonium perchlorate. NEA = (1-α-naphthylethylamine), NEAion = 1-α-naphthylethylammonium perchlorate. $\Delta G_0 = -RT\ ln\ K$.
[b] $-\Delta\Delta G_0 = -\Delta G_{0(S)} - \Delta G_{0(R)}$.

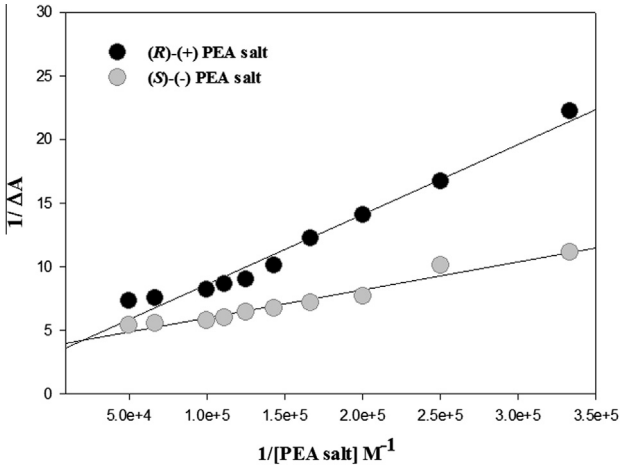

Figure 9. Benesie–Hildebrand plot of sensor **2** (1×10^{-5} M in acetonitrile) in presence of (*R*)-(+) and (*S*)-(−)-1-PEA salt (1×10^{-6} – 1×10^{-5} M).

complex provides useful information with regard to the extent and strength of binding in a quantitative manner.

The UV/vis spectrum of the benzimidazole derived azacrown **2** (2.835×10^{-5} M in acetonitrile) indicated λ_{max} = 254 nm (ε = 7337) (Fig. 3A). The prominent band in the UV/Vis spectrum around 220 nm was an interesting region for study, as the characteristic $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions due to C=N bonds of the benzimidazole ring and the ether linkages of the crown ring occurred in this region. We expected important changes around 220 nm in the spectrum upon complexation of **2** with chiral guests. Different enantiomers were expected to have different levels of electronic perturbation due to the proximity of the stereogenic center to the C=N bond. The absorption at higher wavelengths, that is, 285, 277, and 254 nm is characteristic of aromatic $\pi \rightarrow \pi^*$ transitions.

The qualitative evaluation of aza-crown **2** as a prospective chiral discriminator of biologically significant amines and their organic ammonium salts using ^{1}H NMR and CD spectroscopy studies encouraged us toward quantitative determination of the binding parameters. The following equation represents equilibrium between chiral aza-crown host (*H*) and the guest amine enantiomers (*G*) (Eq. 1):

$$H + G \overset{K_a}{\rightleftharpoons} H \cdot G \tag{1}$$

Spectrophotometric titration experiments of the aza-crown sensor with organic amines and ammonium perchlorate enantiomers were carried out and changes in absorption profile were monitored. The typical UV spectroscopic changes upon the addition of (*S*)-(−)-α-1-phenylethyl amine to **2**, are represented in Figure 8.

The association constants of the enantiomers with the crown molecule were calculated according to the modified Benesie–Hildebrand equation, (Eq. 2)

$$\frac{[H]_0[G]_0}{\Delta A} = \frac{1}{K_a \Delta\varepsilon} + \frac{[G]_0}{\Delta\varepsilon} \tag{2}$$

Further modification results in an equation where a double reciprocal plot can be made with $1/\Delta A$ as a function of $1/[G]_0$. {where $[G]_0 >>> [H]_0$}. (Eq. 3)

$$\frac{1}{\Delta A} = \frac{1}{K_a \Delta\varepsilon [H]_0 [G]_0} + \frac{1}{\Delta\varepsilon [G]_0} \tag{3}$$

Where $[H]_0$ and $[G]_0$ denote the total concentration of crown and guest molecule, respectively, $\Delta\varepsilon$ is the change in the molar extinction coefficient between the free and complexed crown ether and ΔA represents the absorption changes of crown ether upon the addition of organic ammonium salts.

For all of the guest molecules examined, plots of $1/\Delta A$ against $1/[G]_0$ values, gave excellent linear relationships, supporting 1:1 binding between the crown and guest enantiomers. $\Delta\varepsilon$ can be derived from the intercept while K_a (association constant) can be calculated from the slope. The binding constants, $K_{(R)}$ or $K_{(S)}$ and associated free energy changes ($-\Delta G_0$) for the host molecules on complexation were obtained by usual curve fitting analyses (R >0.9850) of the observed absorbance changes as summarized in Table 2.

The typical Benesie–Hildebrand plot to determine the binding parameters upon the addition of (*S*)-phenylethyl ammonium perchlorate to **2** are shown in Figure 9.

The binding constants were determined for the interaction of host **2** with chiral organic amine enantiomers in their neutral and ammonium perchlorate forms. It was observed that **2** bonded to 1-α-phenylethyl amine more effectively when compared to 1-α-naphthylethyl amine as indicated by the higher $-\Delta G_0$ value for **2** and 1-phenylethyl amine based complexes. It was also interesting to observe that (*S*)-(−)-1-α-phenylethyl amine displayed a higher association constant compared to (*R*)-(+)-α-1-phenylethyl amine enantiomer by approximately −6.14 kJmol^{-1} ($\Delta\Delta G_0$). Similarly, (*S*)-(−)-1-α-phenylethyl ammonium perchlorate displayed a higher association constant as compared to (*R*)-(+)-α-1-phenylethyl ammonium perchlorate by approximately −2.75 kJmol^{-1} ($\Delta\Delta G_0$).

In the case of 1-α-naphthylethyl amine, it was observed that **2** bonded to the amine in neutral form more effectively in comparison to the corresponding ammonium perchlorate salts. (*S*)-(−)-1-α-Naphthylethyl amine displayed a higher association constant as compared to (*R*)-(+)-1-α-naphthylethyl amine by approximately −0.43 kJ mol^{-1} ($-\Delta\Delta G_0$). Similarly, (*S*)-(−)-1-α-naphthylethyl ammonium perchlorate displayed a higher association constant with **2** as compared to (*R*)-(+)-1-α-naphthylethyl ammonium perchlorate by approximately −0.30 kJmol^{-1} ($\Delta\Delta G_0$).

4. Conclusion

^{1}H NMR, CD, and UV analyses clearly indicated that the aza-crown **2** exhibited diastereomeric interactions with the two enantiomers of α-phenylethyl amine and 1-α-naphthylethyl amine. The ^{1}H NMR, CD, and UV analyses indicated that the two enantiomers of α-phenylethyl amine as free bases and as their perchlorate salts exhibited better enantiomeric discrimination compared to the two enantiomers of 1-α-naphythylethyl amine.

5. Experimental

5.1. General

Reagents were of AR grade and used without further purification. (*R*)-(+)-/(*S*)-(−)-PEA and NEA were purchased from Sigma–Aldrich. The HPLC chromatogram was recorded on Agilent 1200, Column: ULTRON-ESOVM 4.6 × 150 mm, (*A*:*B*) = 25:75[*A* = ACN, *B* = Ethanol:20 mM KH_2PO_4 Buffer (pH adjusted to 5.5), 0.7 ml/min, UV λ = 229 nm). Optical rotations were measured on a Rudolph polarimeter. Melting points are uncorrected. IR spectra were recorded on a Shimadzu FTIR Spectrometer and ^{1}H NMR spectra were recorded on a 300 MHz Bruker, AV II 300 spectrometer, using TMS as an internal standard. Chemical shifts are given in ppm relative to the internal reference for $CDCl_3$; ^{13}C NMR spectra were recorded on 75 MHz Bruker, AV II 300 spectrometer. GC–MS spectrum was recorded on a Thermoelectron spectrometer. UV spectra were recorded on a Shimadzu UV–visible Spectrophotometer UV-2100. CD spectra were recorded on a J-815 CD spectrometer after calibrating it with D-10-camphorsulfonic acid under a constant nitrogen flow. Solvents used for UV and CD studies were of spectroscopic grade.

5.2. Synthesis of mono aza-15-crown-5 2

In a nitrogen flushed, dry 250 ml 3-necked round bottomed flask fitted with a dropping funnel, a reflux condenser and nitrogen inlet was charged with sodium hydride (240 mg, 6 mmol) and washed twice with hexane (20 ml). Hexane was decanted and dry THF (50 ml) was added and the mixture was refluxed under nitrogen for 30 min. To the refluxing solution was added dropwise a solution of (*S*)-(−)-2-α-hydroxy ethyl benzimidazole **1** (324 mg, 1 mmol) in 75 ml of dry THF in 1 h and the mixture was stirred and refluxed at 70 °C for 2 h. Subsequently a solution of tetraethylene glycol ditosylate in 75 ml dry THF was added dropwise to the reaction mixture in 1hr after which the reaction mixture was refluxed for a further 8 h until the starting material was consumed (monitored by TLC); the reflux was stopped and THF was then concentrated under reduced pressure to afford a light yellow oily residue, which was added to 100 g of ice. The yellow semi solid residue was extracted with $CHCl_3$ (3 × 50 ml) and the organic layer washed with water (2 × 75 ml), and concentrated in vacuo to provide a light yellow viscous oil which was purified by column chromatography on silica gel using petroleum ether/Chloroform (40:60) as eluent to afford a white crystalline solid of monoaza-15-crown-5 **2** in 48% yield. Mp 65 °C, $[\alpha]_D^{20} = -36.5$ (*c* 1, MeOH), FTIR(KBr): 3392, 2947, 2867, 2349, 1672, 1616, 1517, 1466, 1452, 1323, 1123, 1096, 749, 735 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.66 (*d*, 3H, *J* = 6.6 Hz), 3.5–3.6 (m, 10H), 4.0 (*t*, 2H, *J* = 6.6 Hz), 4.3 (*m*, 1H), 4.5 (*m*, 1H), 5.0 (*q*, 1H, *J* = 6.6 Hz), 7.2–7.7 (Ar, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.2, 141.6, 135.6, 122.8, 122.1, 119.6, 109.9, 71.6, 71, 70.9, 70.1, 70, 69.1, 67.9, 63.6, 44.2, 18.9). GC–MS: 319.6 ([M+1]$^+$). Chiral HPLC analyses *ee* = 92.02% (HPLC, ULTRON-ESOVM).

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