

Synthesis of chiral tripodal receptors under solvent-free conditions using microwave irradiation for investigation of anion and cation recognition properties

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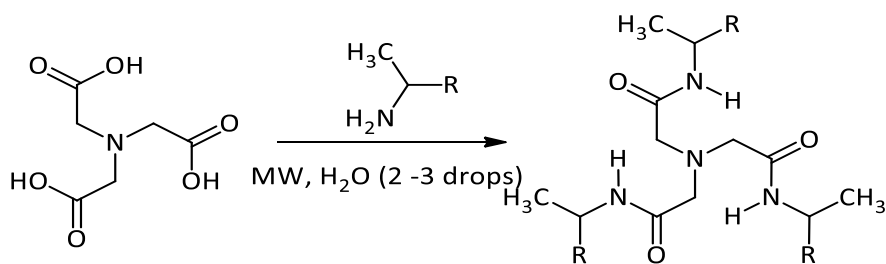
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Abstract

Amide based chiral tripodal receptor derivatives were synthesized under microwave irradiation in quite high yields (76%- 84%) and they were characterized by IR and 1D, 2D, ¹H- and ¹³C-NMR spectroscopies. The recognition properties of these tripodal receptors towards some anions and organic ammonium salts were investigated by ¹H-NMR titration in DMSO-*d*₆. The tripodal (*S*)-phenyl receptor demonstrated a highly significant enantiomeric selectivity towards the (*S*)-(-)-1-phenyletylammonium perchlorate (ERF= 91.74 S).



- 1 R= (*R*)-phenyl-
- 2 R= (*S*)-phenyl-
- 3 R= (*R*)-naphthyl-
- 4 R= (*S*)-naphthyl-

Keywords: Molecular recognition, tripodal receptors, cation and anion recognition, microwave, NMR titration

Introduction

Recognition of anionic substrates has contributed strongly to the development of supramolecular chemistry in the last decades^{1,2,3} and subsequently the subject has a wide range of applications, such as in biological, industrial and environmental areas¹. For this purpose, it is important to properly design and synthesize versatile receptors for recognition of anions and cations. Recently, simple molecular clefts have been shown as viable systems for binding anions due to their structural flexibility in the organization of binding sites⁴⁻⁹. Indeed, a high degree of selectivity could be achieved by a careful design of a host with a pre-organized cavity for a guest.¹⁰

There are some considerations in the design of anion receptors: (i) host–guest geometric structures, (ii) nature of non-covalent interactions, (iii) basicity of the anionic guests, (iv) the solvent used.^{11,12} In terms of their electrostatic charge, two different types of anion receptors have been developed: cationic and neutral receptors. As to neutral receptors, the most common motifs involve ureas¹³, thioureas¹⁴⁻¹⁶, amides, etc.¹⁷ Selectivity of a tripodal receptor largely depends on cavity size and rigidity of the side arms^{18,19} and, therefore, they are known to exhibit several advantages over those of monopodal and bipodal receptors. Tripodal receptors usually bind metal ions very strongly as a result of their enhanced chelating influence. In addition, the bulkiness of tripodal ligands make them more reactive towards metal ions. Because of the distinctive features of synthetic tripodal receptor systems, their design and development remain a very active field of study in supramolecular chemistry.²⁰⁻²³

Amide functional groups are important in the recognition of anions. Therefore, the synthesis of compounds containing amide functionality is of great interest in synthetic chemistry. The use of microwave technology in organic chemistry has widely been investigated in the past decade, and hence a great number of papers reported that many chemical transformations can be carried out successfully by this technique. The microwave technique significantly reduces reaction time thus providing high yield, less by-product formation, consistent with green chemistry, solvent free organic conversion, atom economy and selective reactivity.²⁴ Therefore, the synthesis of tripodal receptors based on amide formation has been carried out by condensation of carboxylic acids and amines, employing the microwave technique that allows direct conversion of carboxylic acids to amides. Otherwise, conversion of carboxylic acids to more reactive intermediates would be necessary to obtain amides.²⁴⁻³⁰

Herein, we report the synthesis of a series of novel chiral tripodal receptors based on the formation of amide bonds under microwave irradiation, and an evaluation of their molecular recognition abilities towards a wide range of anions (H_2PO_4^- , HSO_4^- , $\text{C}_6\text{H}_5\text{CO}_2^-$, CH_3CO_2^- , ClO_4^- , F^- , Cl^- , Br^-). The study also involves the investigation of chiral discrimination abilities of these receptors against chiral organic ammonium salts, AM1 (phenylethylammonium perchlorate) and AM2 (naphthylethylammonium perchlorate). ^1H -NMR titration method was employed to obtain binding constants between receptors and anions as well as cations.

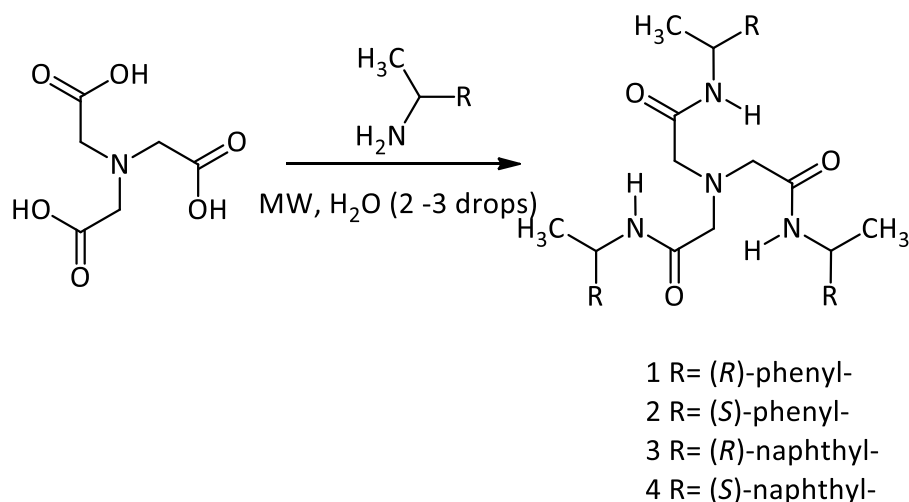
Results and Discussion

Synthesis

Amide-based tripodal receptor ligands (**1-4**) were synthesized under microwave irradiation (Scheme 1), and the binding affinities of anions (H_2PO_4^- , HSO_4^- , $\text{C}_6\text{H}_5\text{CO}_2^-$, CH_3CO_2^- , ClO_4^- , F^- , Cl^- , Br^-) as tetrabutylammonium (TBA) salts as well as against two chiral organic ammonium salts were investigated using the ^1H -NMR titration method. Structures of the synthesised compounds were elucidated using IR, ^1H -NMR, ^{13}C -NMR, DEPT, 2D NMR

(COSY, HETCOR) spectroscopic techniques. All three receptors showed amide first band between at around 1650 cm^{-1} and the amide second band 1550 cm^{-1} in IR spectrum. The chiral hydrogen of tripodal receptors showed pentet at around 5.74 ppm in ^1H NMR spectrum.

The reactions were performed using microwave irradiation, at atmospheric pressure, using a 1000 W microwave lab-station at $150\text{ }^\circ\text{C}$ for maximum 42 minutes (generally 2-3 drops of water were added). All amides were obtained with very high yields (76%-84%) (Scheme 1). Products were purified using crystallisation and chromatographic methods.



Scheme 1. Synthesis of chiral tripodal-based ligands (**1-4**).

^1H -NMR Titration

Many methods have been reported for the determination of complexation constants.^{31,32} ^1H -NMR spectra were recorded monitoring the proton chemical shift in the tripodal receptors as a function of the concentrations of the guest ions. A representative example is illustrated in Figure 1 depicting the ^1H -NMR spectra of the enantiomeric (*R*)-tripodal receptor **3** obtained at different concentrations of the guest acetate anion. It indicates that significant chemical shift displacement ($\Delta\delta$) corresponding to the $-\text{NH}$ proton of receptor **3** that take place upon the addition of the anion solution. For cation recognition, the chemical shift (δ) of the methine ($-\text{CH}$) proton in the tripodal receptor **3** was monitored against cation concentration.

Determination of the stoichiometry of the complex formation between host (H, the receptor) and guest (G, being an anion or a cation) is crucial for estimation of the binding constants of host-guest (H.G) complexes in molecular and enantiomeric recognition studies.^{29,33} Although a variety of methods have been used for this purpose, the Job's Plot method has become the most commonly used. A typical Job's Plot of the proton chemical shift displacement ($\Delta\delta$) of the tripodal receptor multiplied by the host mole fraction (X_{H}) against the respective mole fraction (X_{H}) in $\text{DMSO}-d_6$ shows the maximum at a molar fraction of 0.5 [Figure 2: tripodal receptor **3** complexing with the dihydrogen phosphate anion (H_2PO_4^-) and; Figure 3: tripodal receptor **3** complexing with the chiral phenylethyl ammonium cation of (*S*)-AM1]. Both figures suggest that tripodal receptors complex with anionic and/ or cationic guests with a 1:1 stoichiometry. Similar results were obtained for all tripodal receptors used in this work. The dissociation constants (K_d) of the complexes of anion and cation guests with tripodal receptors **1-4** were calculated by nonlinear curve fitting, using Eq. 4 below (derived from Eqs. 1-3), as described in literature.³³



$$K_d = [R][G_0] / [R.G_0] \quad (2)$$

$$G_0 = G_{\text{free}} + G_{\text{complexes}} \quad (3)$$

$$\Delta\delta = (\delta_0 K_d + \delta_{\text{max}} G_{\text{tot}}) / (K_d + G_{\text{tot}}) \quad (4)$$

A range of stock solutions of the guests ($0\text{--}6 \times 10^{-3} \text{ M}$) containing a constant amount of the tripodal receptors ($1 \times 10^{-3} \text{ M}$) in $\text{DMSO-}d_6$ was prepared and their ^1H NMR were collected at 298 K at ambient probe temperature and calibrated using tetramethylsilane as an internal reference. The proton chemical shift displacements ($\Delta\delta$) of the tripodal receptor, such as that of amide proton ($-\text{NH}$), are normally monitored against the corresponding guest concentration then fitted to Eq. 4, derived from Eqs. [1-3].

Typical plot of $\Delta\delta$ versus G_0 for the complex of tripodal receptor **3** with the H_2PO_4^- anion guest from (TBAH_2PO_4) is shown in Figure 4. The calculated $\Delta\delta$ values are plotted against G_0 to yield what looks like a nonlinear relationship (Figures 7 and 8). The chemical shift of the $-\text{CH}$ (methine, $\delta = 4.9633 \text{ ppm}$) resonance of the phenylethylammonium perchlorate salt was monitored against the corresponding salt concentration. The two ^1H -NMR spectral segments depicting the chemical shift displacements ($\Delta\delta$) of the $-\text{CH}$ (methine) proton, corresponding to the two guest enantiomeric forms (*R*)-AM1 (left) and (*S*)-AM1 (right), on complexation with tripodal receptor **3** are shown in Figure 5. During titration, the resonance of the chiral $-\text{CH}$ (methine) proton of the phenylethylammonium cation of AM1 shifted downfield on complexation with the tripodal receptor **3** molecules (Figure 5).

The ^1H NMR titration technique was employed to estimate the binding constants for complexes of tripodal receptors **1-4** with guest anions using their tetrabutylammonium salts [*n*-Bu₄N]⁺A[−] (A[−] = H_2PO_4^- , HSO_4^- , $\text{C}_6\text{H}_5\text{CO}_2^-$, CH_3CO_2^- , ClO_4^- , F[−], Cl[−], Br[−]) and guest chiral organic ammonium cations (AM1: 1-phenylethylammonium perchlorate and AM2: 1-(1-)-naphthylethylammonium perchlorate). The results are listed in Table 1 and Table 2 respectively.

Anion recognition

The topology of the receptor is of importance in determining the overall receptor-ion interactions. Tripodal receptors, occupy a class somewhere in between cyclic and acyclic ligands with regards to preorganization, are believed to be able to complex with ions more effectively than analogous acyclic ligands. The molecular design allows a rational control of their binding properties such as complex stability and selectivity. The selectivity of a tripodal receptor largely depends on the rigidity of its arm sites and cavity size. As a recognition motif, tripodal-based receptors have been reported to be successfully used as recognition components in ion-selective electrode membranes and optical sensors.

The main features for the design of tripodal anion receptors are: (i) There is a sufficient number of positively charged or neutral electron-deficient groups in the ligand to serve as interaction sites. (ii) Receptors with a flexible tripodal structure have a strong affinity for trigonal oxoanions, such as carbonate, phosphate and chlorate, because the geometry and the orientation of the host molecules favour the formation of a stable host-guest complex.^{21,22} In addition to the proton donor properties of the tripodal amides, they also have proton acceptor properties. Therefore, this offers them double binding effect on the anions and opposite cations recognition. The results indicate that tripodal receptors exhibit a better affinity towards HSO_4^- and H_2PO_4^- anions followed by CH_3CO_2^- . However, they do not bind to ClO_4^- and only weakly bind to $\text{C}_6\text{H}_5\text{CO}_2^-$ anions. As to the halide (F[−], Cl[−] and Br[−]) anions, their affinities towards the four tripodal receptors vary with no apparent trend (Table 1).

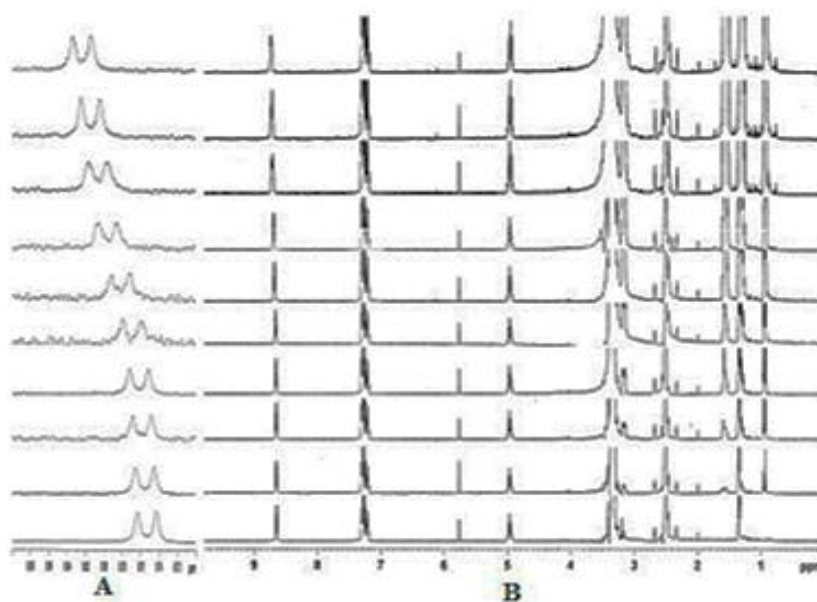


Figure 1. Section **A** of the ^1H -NMR spectra represent an expanded part (δ 8.71 and 8.89 ppm) of the larger spectrum **B** corresponding to the tripodal receptor **3**, showing the chemical shift displacements caused by an increase in the acetate anion concentration, on the addition of the tetrabutyl ammonium acetate $[\text{Bu}_4\text{N}]^+\text{CH}_3\text{CO}_2^-$ salt at an increasing initial concentration (0, 0.2, 0.3, 0.7, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0 mM), while holding the initial concentration of Tripodal Receptor **3** constant at 1 mM.

Table 1. Dissociation constant (K_d , M) of tripodal receptors **1-4** with various anions in $\text{DMSO}-d_6$ collected at $25 \pm 0.1^\circ\text{C}$

Entry	Anion*	K_d (M)			
		1	2	3	4
1	H_2PO_4^-	18.71 ± 9.09	0.86 ± 0.14	7.86 ± 4.39	nd
2	HSO_4^-	1.58 ± 1.23	nd	0.50 ± 1.95	0.99 ± 0.67
3	$\text{C}_6\text{H}_5\text{CO}_2^-$	52.24 ± 42.45	0.50 ± 0.11	nd	314.5 ± 5.71
4	CH_3CO_2^-	21.66 ± 7.30	13.02 ± 2.10	8.76 ± 2.10	19.81 ± 8.19
5	ClO_4^-	nd	17.65 ± 9.45	nd	nd
6	F^-	nd	nd	nd	5.75 ± 2.49
7	Cl^-	nd	3.81 ± 1.577	nd	15.41 ± 68.29
8	Br^-	5.850 ± 4.06	nd	nd	nd

nd: Not determined; *Anions were used as tetrabutylammonium salts form

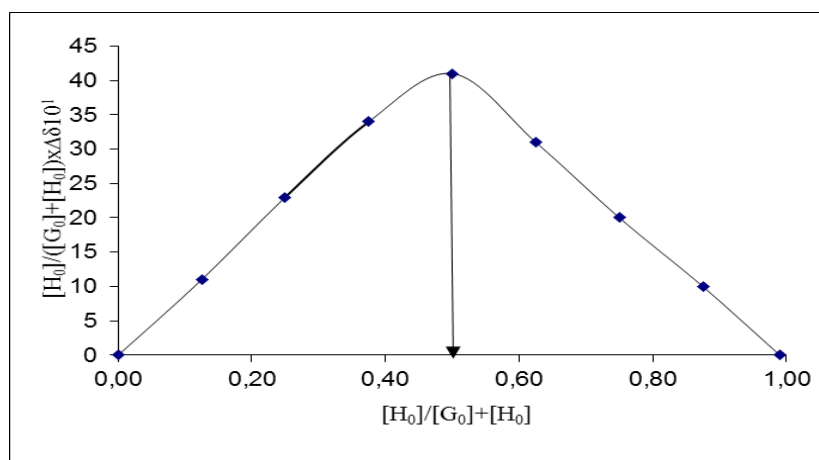


Figure 2. Job's Plots of tripodal receptor **3** with TBAH₂PO₄.

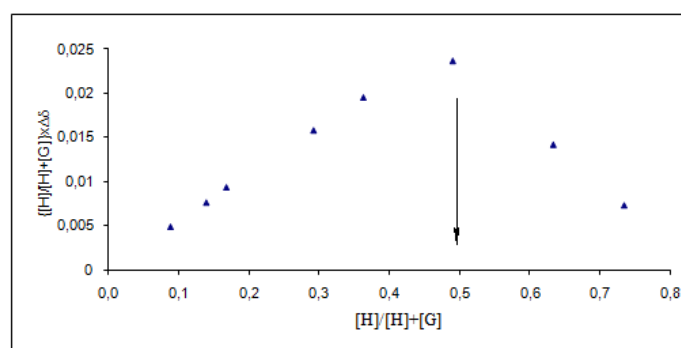


Figure 3. Job's Plots of tripodal receptor **3** with (S)-AM1.

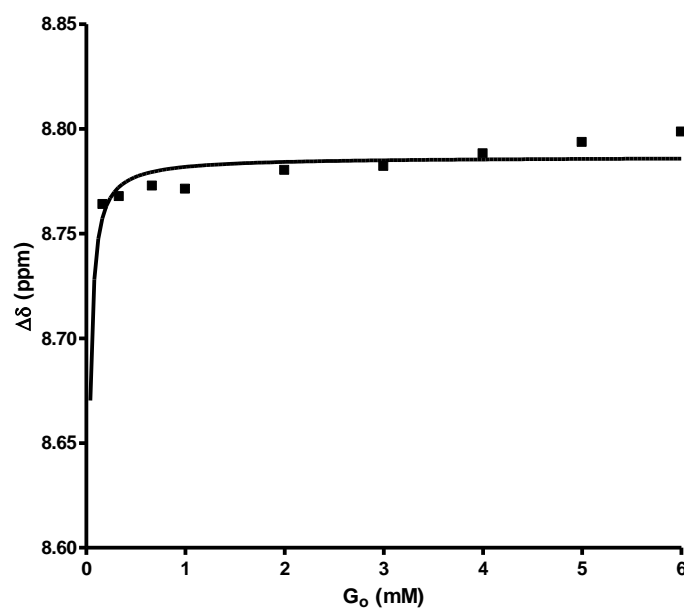


Figure 4. A nonlinear plot of $\Delta\delta$ versus G_0 for the complex of tripodal receptor **3** with TBAH₂PO₄ salt, serving as the source of H₂PO₄[−] guest.

The observed better affinity of a receptor towards the acetate anion may be associated with the presence of favorable π -CH interactions. In addition, acetate ion acts as a stronger base than benzoate anion. Therefore causes stronger binding. It is well established that compounds containing $-N(H)$ or $-O(H)$ hydrogen bond groups can undergo a deprotonation process upon the addition of an acetate anion. In summary, we have synthesized and characterized a simple tripodal receptor which binds fluoride, chloride, bromide, acetate, benzoate, dihydrogen phosphate, and hydrogen sulfate anions showing strong selectivity for the acetate and dihydrogen phosphate in $DMSO-d_6$. The host-guest affinity results from non-covalent interactions, including electrostatic interactions, hydrogen bonding, Van der Waals, coordination to a metal ion, and a combination of these interactions. As to the anions, their size, shape, hydrogen bonding capability, acid/base properties and the number of interaction sites available should also be considered.

Cation recognition

The design of amide-based tripodals for a cation requires a receptor unit that selectively interacts with organic ammonium salts. Owing to the special structure of their three flexible donor-atom-containing chains, tripodal receptors can form complexes with many organic ammonium cations.²⁹ Enantiomeric recognition studies of amine or protonated amine salts are considered important, because these molecules are basic building blocks of biological materials. Since, the tripodal receptors are highly symmetric and relatively rigid due to amide moieties, they are used in the enantioselective discrimination of phenylethylammonium [(*R*)-AM1 and (*S*)-AM1] and naphthylethylammonium [(*R*)-AM2 and (*S*)-AM2] salts by 1H NMR titration method. Extensive studies on molecular recognition by receptors have shown that an important characteristic of complexation is the simultaneous operation of several weak forces working between the guest and receptors, which determine how the size and shape of a guest molecule fit into the host cavity.

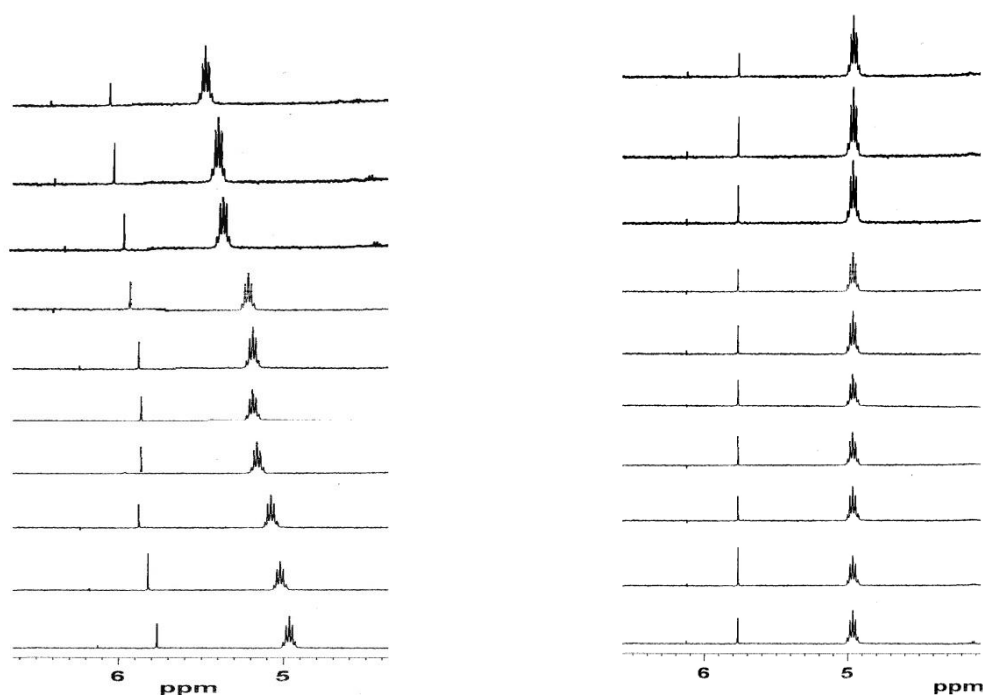


Figure 5. Stack plots of 1H -NMR titration spectra of corresponding chemical shift in chiral $-CH$ group in the guests from the complex between tripodal receptor **3** and the chiral ammonium cation guests: (*R*)-AM1(left) and (*S*)-AM1 (right).

The dissociation constants of the receptors (**1-4**) with an enantiomeric cation of organic ammonium salts are presented in Table 2. The data indicate that the tripodal receptors form modest stable complexes with all enantiomeric ammonium cation guests (except tripodal receptor **2** with (*R*)-AM-1 and tripodal receptor **3** with (*S*)-AM1) (Table 2). This may be attributed to the strict geometrical complementary relationship between the tripodal receptor cavity and organic ammonium cations.²²

In Table 2 the results demonstrate that the hosts **2** and **3** form stronger complexes with ammonium cation salts than those of hosts **1** and **4**, which is likely due to the naphthyl group being more aromatic favoring stronger π - π and cation- π interaction than the phenyl group. The highest enantioselectivity was observed in the tripodal receptor **2**. Tripodal receptor **2** prefers to bind *S*-enantiomer of AM1 with ERF of 91.74% ($K_d = 1.53$ mM, $K_d^R/K_d^S = 0.09$). Another striking point comes from the discrimination of AM1 salt by receptor **1**, which preferably bind to *S* enantiomer with ERF of 72.14% ($K_d = 1.53$ mM, $K_d^R/K_d^S = 2.59$).

Table 2. Enantiomeric recognition studies of tripodal receptors **1-4** towards organic ammonium salts in DMSO-*d*₆ at 25 ± 0.1 °C

Tripodal Receptor	Cation	K_d (mM)	K_d^R/K_d^S	ERF %
1	(<i>R</i>)-AM-1	3.7±0.32	2.59	72.14 (<i>R</i>)
	(<i>S</i>)-AM1	1.43±0.07		
	(<i>R</i>)-AM-2	2.52±0.27	1.56	39.06 (<i>S</i>)
			0.64 (K_d^S/K_d^R)	
2	(<i>S</i>)-AM2	1.6±0.17		
	(<i>R</i>)-AM-1	0.14±0.08	0.09	91.74 (<i>S</i>)
	(<i>S</i>)-AM1	1.53±0.21		
	(<i>R</i>)-AM-2	1.02±0.37	1.01	49.75 (<i>S</i>)
3	(<i>S</i>)-AM2	1.01±0.38		
	(<i>R</i>)-AM-1	2.61±0.38	2.55	71.83 (<i>R</i>)
			0.39 (K_d^S/K_d^R)	
	(<i>S</i>)-AM1	1.02±0.005		
4	(<i>R</i>)-AM-2	1.98±0.10	0.92	52.08 (<i>S</i>)
	(<i>S</i>)-AM2	2.14±0.29		
	(<i>R</i>)-AM-1	3.92±0.15	0.92	52.08 (<i>S</i>)
	(<i>S</i>)-AM1	21.72±1.66		
	(<i>R</i>)-AM-2	3.92±0.32	2.58	72.07 (<i>R</i>)
	(<i>S</i>)-AM-2	1.52±1.01		

*AM1: Phenylethylammoniumperchlorate; AM2: Naphthylethylammoniumperchlorate

ERF: Enantiomer Recognition Factor: Calculated from $K_d^R + K_d^S = 100$ and K_d^R/K_d^S ratio

On the other hand **4** shows better enantioselectivity for naphthylethylammonium cation compared with **1**, **2**, **3** particularly for (*R*)-AM-2 ($K_d^R/K_d^S = 2.58$ Table 2). It was found that both hosts bind and discriminate organic ammonium cations, possibly due to stronger π - π and π -cation interactions between tripodal receptors (hosts) and ammonium cations (guests) molecules in addition to weaker non-covalent interactions (hydrogen

bonding, Van der Waals, dipole-dipole etc.). This indicates that increased π - π interaction and the phenyl-naphthyl state are the best fit between the tripodal receptor cavity and organic ammonium cations (Fig. 6).

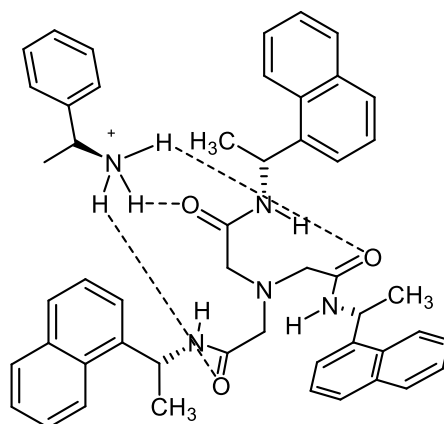


Figure 6. Proposed mechanism of tripodal receptor **3** and (S)-AM1.

Considering the values in Table 1, it can be noted that (S)-configured tripodal receptors show better selectivity for the (R)-, while the (R)- configurable tripodal receptors exhibit better selectivity for the (S)- ammonium salts. It seems that the size and shape of the guest molecule and the structural change of the host molecule administrate the complexation phenomena to some extent. Hence, the induced fit and the geometrical complement between the host and the guest play a crucial role in the chiral recognition of organic ammonium cations.

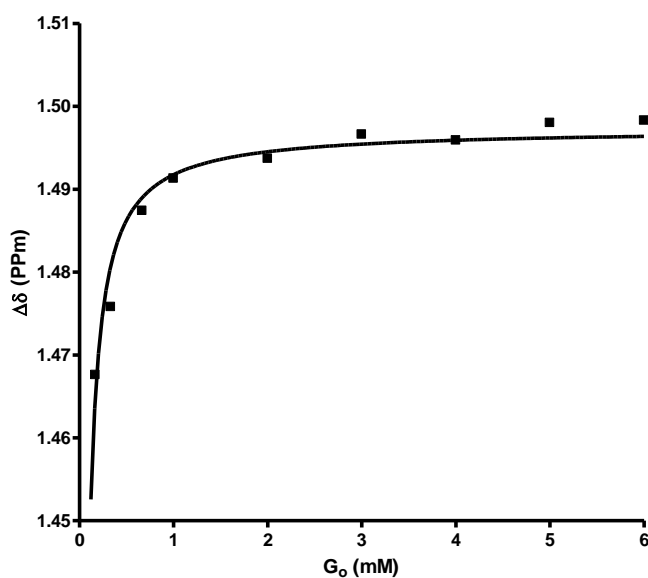


Figure 7. Nonlinear plots of δ versus G_0 for the complex of tripodal receptor **3** with (S)-AM1.

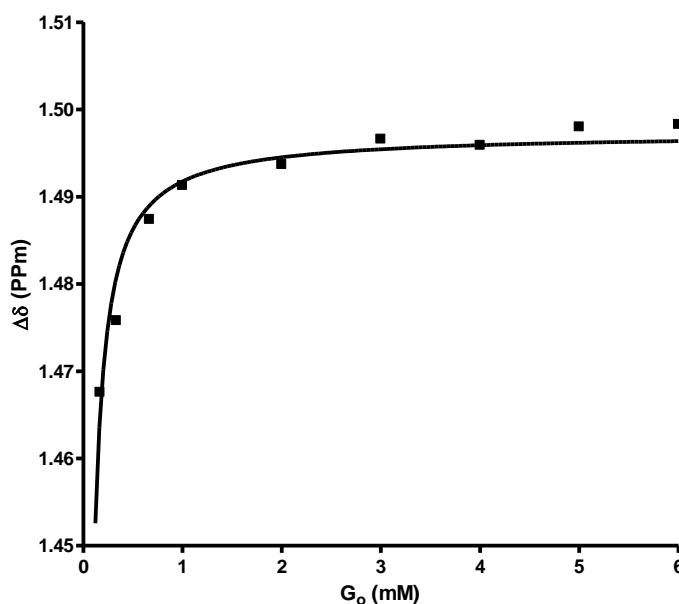


Figure 8. Nonlinear plots of $\Delta\delta$ versus G_0 for the complex of tripodal receptor **3** with (*R*)-AM1

Conclusions

Four receptors possess high affinity for dihydrogenphosphate, benzoate and acetate anions. The tripodal receptors **1** and **2** show a relatively weak affinity towards all anions, while tripodal receptor **3** and **4** do not bind to ClO_4^- and Br^- anions at all. The results also show that receptors can discriminate between the enantiomers of AM1 and AM2 salts. The data may be relevant in the understanding of the main driving forces in anion and cation recognition in living cells. They may also be used in the development of anion and cation sensors.

Experimental Section

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. Elemental analyses were obtained with CARLO-ERBA Model 1108 apparatus. Optical rotations were taken on a Perkin-Elmer 341 Model polarimeter. ^1H (400.1 MHz), ^{13}C (100.6 MHz) and 2D NMR (DEPT, COSY, HETCOR, HMQC, HMBC) spectra were recorded on a BRUKER AV400 NMR spectrometer in the indicated solvents. Chemical shifts are expressed in part per million (δ) using residual solvent protons as internal standards.

Synthesis of the tripodal receptors

The synthesis of tripodal receptors were carried out at optimum reaction conditions (temperature, time and power). The determination of optimization reaction conditions were given our previous paper. The best yields of tripodal receptors were found between 76%- 84% at 900 W, 25 minutes, atmospheric pressure and 150 °C.

(*R*)-Tripodal Receptor 1: Nitrilotriacetic acid (0.52 g, 2.6 mmol) and (0.95 g, 7.9 mmol) (*R*)-(+)-1-Phenylethylamine were activated by irradiation with microwave. The crude product was crystallized with

EtOAc:hexane (3:1) to obtain **1** as a white solid (1.02 g, 78%). Mp. 156-157 °C, $[\alpha]_D^{21} = +72^0$ (c 1.0, CHCl₃); IR (KBr, cm⁻¹) v 3282 (N-H), 3083 (Ar-H), 3028 (Ar-H), 1657 (amide first band), 1554 (amide second band). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 1.44 (d, 9H, *J* 6.8 Hz), 3.13 (s, 6H), 5.09 (pentet, 3H, *J* 6.8 Hz), 7.23-7.30 (m, 15H), 7.95 (d, 3H, *J* 8.0 Hz); ¹³C NMR (100 Hz, CDCl₃) δ (ppm): 22.14, 49.05, 60.86, 126.19, 127.35, 128.67, 143.29, 169.53; Anal. Calcd for C₃₀H₃₆N₄O₃: C, 71.97; N, 11.19; H, 7.26; Found: C, 71.82; N, 11.12; H, 7.28.

(S)-Tripodal receptor 2. Nitrilotriacetic acid (0.51g, 2.6 mmol) and (0.95 g, 7.9 mmol) (S)-(-)-1-phenylethylamine were activated by irradiation with microwave. The crude product was crystallized with EtOAc:hexane (3:1) to obtain **2** as a white solid (1.05g, 80%). Mp. 157-158 °C, $[\alpha]_D^{21} = -76^0$ (c 1.0, CHCl₃); IR (KBr, cm⁻¹) v 3282 (N-H), 3083 (Ar-H), 3028 (Ar-H), 1656 (amide first band), 1555 (amide second band), ¹H NMR (400 MHz, CDCl₃) δ (ppm): 1.31 (d, 9H, *J* 7.2 Hz), 3.24 (s, 6H), 5.09 (pentet, 3H, *J* 7.2 Hz), 7.24-7.32 (m, 15H), 7.61 (d, 3H, *J* 8.0 Hz); ¹³C NMR (100 Hz, CDCl₃): δ 22.06, 49.02, 60.74, 126.18, 127.40, 128.71, 143.14, 169.34; Anal. Calcd for C₃₀H₃₆N₄O₃: C, 71.97; N, 11.19; H, 7.25. Found: C, 71.84; N, 11.13; H, 7.24.

(R)-Tripodal receptor 3. Nitrilotriacetic acid (0.50 g, 2.6 mmol) and (1.34 g, 7.9 mmol) (R)-(+)-1-(1-Naphthyl)ethylamine were activated by irradiation with microwave. The crude product was purified by flash column chromatography on silica gel using with EtOAc:hexane (8:1) to obtain for tripodal receptor **3** as a white solid (1.29 g, 76%). Mp. 114-115 °C, $[\alpha]_D^{21} = +23.7^0$ (c 1.0, CHCl₃); IR (KBr, cm⁻¹) v 3267 (N-H), 3054 (Ar-H), 2973 (Ar-H), 1648 (amide first band), 1539 (amide second band), ¹H NMR (400 MHz, CDCl₃) δ (ppm): 1.44 (d, 9H, *J* 6.8 Hz), 3.34 (s, 6H), 5.74 (pentet, 3H, *J* 6.8 Hz), 7.35-7.82 (m, 15H), 7.93-8.11 (m, 6H) 8.76 (d, 3H, *J* 8.0 Hz); ¹³C NMR (100 Hz, CDCl₃): δ (ppm) 22.11, 44.35, 58.23, 122.79, 123.48, 125.88, 126.08, 126.67, 127.72, 129.12, 130.74, 133.80, 169.88, 140.43; Anal. Calcd for C₄₂H₄₂N₄O₃: C, 77.51; N, 8.60; H, 6.50. Found: C, 77.57; N, 8.56; H, 6.53.

(S)-Tripodal receptor 4. Nitrilotriacetic acid (0.50 g, 2.6 mmol) and (1.34 g, 7.9 mmol) (S)-(-)-1-(1-Naphthyl)ethylamine were activated by irradiation with microwave. The crude product was purified by flash column chromatography on silica gel using with EtOAc:hexane (8:1) to obtain for tripodal receptor **4** as a white solid (1.29 g, 76%). Mp. 113-115 °C, $[\alpha]_D^{21} = +23.0^0$ (c 1.0, CHCl₃); IR (KBr, cm⁻¹) v 3277 (N-H), 3056 (Ar-H), 2971 (Ar-H), 1650 (amide first band), 1542 (amide second band), ¹H NMR (400 MHz, CDCl₃): δ (ppm): 1.45 (d, 9H, *J* 6.8 Hz), 3.10 (s, 6H), 5.84 (pentet, 3H, *J* 6.8 Hz), 7.28-7.44 (m, 15H), 7.70-7.80 (m, 6H) 7.82 (d, 3H, *J* 8 Hz); ¹³C NMR (100 Hz, CDCl₃), δ (ppm): 21.07, 44.48, 59.81, 122.57, 123.03, 125.33, 125.81, 126.46, 128.14, 128.85, 130.79, 133.83, 138.42, 169.00; Anal. Calcd for: C₄₂H₄₂N₄O₃: C, 77.51; N, 8.60; H, 6.50. Found: C, 77.48; N, 8.53; H, 6.55.

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Supplementary Material

IR, ¹H (400 MHz), ¹³C (100 MHz), ¹H-¹H (COSY) and ¹H-¹³C (HETCOR) and DEPT NMR spectrums of tripodal receptors in DMSO-*d*₆ are given in the Supplementary Data file.

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