Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Journal Name

RSCPublishing

ARTICLE

Application of optically active chiral bis(imidazolium) salts as potential receptors of chiral dicarboxylate salts of biological relevance

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Laura González-Mendoza,[a] Jorge Escorihuela,[b] Belén Altava,*[,a] M. Isabel Burguete,[a] and Santiago V. Luis*[,a]

A family of chiral bis(imidazolium) salts derived from natural amino acids has been synthesized by a simple synthetic approach and the corresponding bis(trifluoromethylsulfonyl)imide salts have shown to be room temperature chiral ionic liquids (RTCILs). The structures and self-assembling properties of the resulting salts have been studied by ^{1}HNMR, ATR-FTIR, DSC, SEM and theoretical calculations. Moreover, these receptors have been applied to the enantiomeric recognition of dicarboxylic amino acids. The supramolecular complexes formed have been studied by ^{1}HNMR titration experiments, ATR-FTIR and DSC.

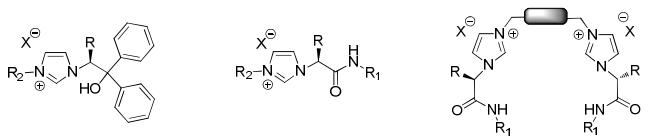
Introduction

The study of the self-assembly of organic salts has been recently the topic of several papers.[1] One of the main reasons for this interest lies in the very simple synthetic procedures leading to them and their high level of modularity for the wide range of cations and anions available. Regarding potential applications, self-assembly of organic salts can afford conductive materials that can find different applications.[2]

On the other side, chirality plays a critical role in organic chemistry, both in terms of self-organization properties and in terms of selective recognition. Recognition of chiral carboxylic acids by synthetic receptors is one important research topic due to their biological importance and its potential applications in drug discovery.[3] Chiral carboxylic acids are ubiquitous architectural units of natural products and drug molecules as well as versatile functional synthons.[4] In this regard, dicarboxylates are particularly important targets as they are implicated in different biomolecular processes.[5]

From the different available organic salts, imidazolium based species have been extensively investigated in the last years and have been studied as sensors,[6] receptors and devices for halides, or other inorganic anions,[7] for organic carboxylates[8] and phosphates[9] or even for nucleic acids.[10] Imidazolium groups provide both a positive charge and relatively acidic C–H groups to bind anionic species. In particular the C2-H hydrogen bond donor of the imidazolium heterocycle has been exploited extensively as a binding site for carboxylates.[11] Besides, the properties of imidazolium ionic liquids (ILs) are being extensively analyzed in different field as they possess low vapor pressure and flammability in addition to a high thermal stability and conductivity, which can be easily tuned by small changes in the cation or anion structure.[12]

In this context, our research group has been recently involved in the preparation and study of different imidazolium receptors prepared from racemic mixtures,[13] or from enantiomerically pure materials obtained from the chiral pool.[14, 8e] Thus, imidazolium based receptors **1** and **2** have been described as chiral shift agents (CSAs) for the enantiodiscrimination of racemic mandelate and other chiral carboxylic acids.[8e] In the light of the former results, it seems reasonable to assume that bis(imidazolium) receptors could be appropriate targets for the development of CSAs for dicarboxylic acids.[15]



1
R: $CH(CH_3)_2$; CH_2Ph; $CH_2CH(CH_3)_2$
R_2: CH_2Ar

2
R: $CH(CH_3)_2$; CH_2Ph; $CH_2CH(CH_3)_2$
R_1: CH_2Ph; But
R_2: CH_2Ph; Me; But; Non

3
R: $CH(CH_3)_2$, CH_2Ph
R_1: CH_2Ph; n-Non

Fig. 1 The structures of chiral ionic liquids used as CSAs for chiral carboxylates.

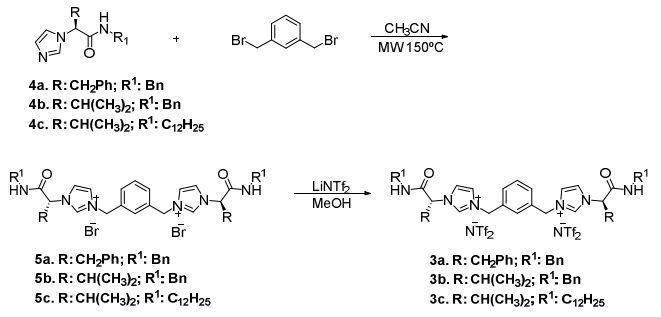
Here we report on the preparation of a new family of chiral ionic liquids (CILs) with the general structure **3** using natural amino acids as the source of chirality. The structures and properties of the resulting salts have been studied in the solid state and in solution, and they have been investigated as chiral receptors for dicarboxylic amino acid derivatives.

Results and discussion

Synthesis and characterization of the bis(imidazolium) compounds.

Different chiral bis(imidazolium) compounds (CILs **3a-c**) derived from several amino acids and with variable N-amide substitution were prepared (Scheme 1). For this purpose, enantiopure imidazoles **4a-c**, described previously by our group,[8e, 16] were used as precursors for the synthesis of chiral imidazolium salts **3a-c**. Thus, a mixture of the corresponding imidazole derivative (**4a**, **4b** or **4c**) and α,α′-dibromo-m-xylene in CH_3CN was heated under microwave irradiation (150 °C, 120 W, 250 psi). After 30 min, the mixture was cooled down to room temperature, the solvent was evaporated under reduced pressure and the solid was washed with hexane/diethyl ether (2:1) to obtain the pure corresponding bis(imidazolium) halide salts **5a**, **5b** and **5c** in high yield. Finally, the bis(imidazolium) compounds **5** were converted into the corresponding CILs **3** by anion exchange using lithium bis(trifluoromethylsulfonyl)imide (X = NTf_2^-). All the compounds were liquid at room temperature with melting points of 28, 15 and –6 °C for CILs **3a**, **3b**, and **3c**, respectively. The anion exchange was confirmed by elemental analysis and was accompanied by a significant upfield shift of the signal for the proton of the C2 of the imidazolium ring in ^{1}H NMR. Thus, for the bis(imidazolium) compound **3a** this signal shifted from 9.65 ppm for **5a** to 8.75 ppm for **3a** (in $CDCl_3$, 500 MHz, 303 K, 10 mM). The structures of the new CILs were fully characterized by ^{1}H NMR, ^{13}C NMR, IR, MS, DSC, TGA and elemental analysis.

As has been observed in other systems,[13d] the strong interaction between the bis(imidazolium) cation and the corresponding anion through electrostatic forces and hydrogen bonding can provide tightly associated ion pairs with well-defined ion-pair and supramolecular structures in the solid/liquid states and in solution. In this regard, initial attenuated total reflectance (ATR)-FTIR and ^{1}H NMR data obtained for this family of bis(imidazolium) compounds strongly supported the presence of strong amide NH-anion hydrogen-bonding interactions. However, it is important to note that other secondary interactions such as additional H bonding involving the hydrogen atoms at C2, C4 or C5, π-stacking or C–H–π bonding involving benzyl aromatic rings, can also be present.



Scheme 1. Synthesis of chiral bis(imidazolium) salts.

The phase transition temperatures (melting points, Tm) of the newly synthesized salts were determined by differential scanning calorimetry (DSC). As shown in Table 1, all salts (**3** and **5**) are ionic liquids, showing Tm values ranging from 90 °C for **5a** to -6 °C for **3c**, and a thermal stability above 250 °C. It is remarkable that even bromide salts **5** present an IL behaviour, with mps below 100 ºC, in particular taking into account that they are ditopic systems.[17] As expected, substituting the halide anion for the less coordinating NTf_2^- anion, is accompanied by a decrease in the melting point. This change in the anion also gives a clear increment in the thermal stability with values of Td > 300 °C. Indeed, organic salts containing NTf_2^- anion are RTILs for all the cases studied with Tm < 28 °C, showing phase transition temperatures ranging from 28 °C for **3a** to -6 °C for **3c**.

Table 1. Phase transition temperature (*T*m) and decomposition temperature (*T*d) for CILs **3** and **5**.

Entry	CIL	X^{-} [c]	*T*m (°C)[a]	*T*d (°C)[b]
1	**5a**	Br	90	274
2	**5b**	Br	82	285
3	**5c**	Br	78	305
4	**3a**	NTf_2	28	350
5	**3b**	NTf_2	15	365
6	**3c**	NTf_2	-6	378

[a] Data obtained from DSC in the second heating cycle. [b] Data obtained from TGA. [c] charges omitted for clarity.

To obtain a more clear insight into the relative importance of these interactions, preliminary computational calculations were carried out for compound **5a** using the Monte Carlo conformational search available in Spartan'14.[18] The resulting minimum energy conformer was optimized at a semi empirical level (PM6) using the Gaussian 09 software.[19] The optimized structure obtained for **5a** is shown in Fig. 2, revealing the presence of a predominant hydrogen bonding interaction between the amide NH and the bromide anion (NH - anion distance 2.207 and 2.208 Å). Additionally, hydrogen-bonds interactions between the imidazolium Ha protons (C2-H) and the anion are also present (distances 2.407 and 2.418 Å). The anion is also located at a very short distance from the H_d proton at the stereogenic carbon (2.541 and 2.598 Å) and the Hg proton of the central aromatic ring (2.573 and 2.596 Å) (for the labelling of protons, see Fig. 4). Thus, a cleft-like folded structure in which the aromatic rings of the N-benzyl groups occupy the final section of the cleft seems to be the most stable disposition for the ion pair when a strongly coordinating anion is involved.[20]

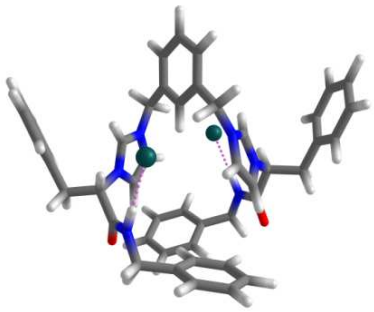


Fig. 2 Most stable conformer obtained for **5a** using Gaussian 09 (semiempiric level PM6). Hydrogen bonds are denoted by dotted lines.

The supramolecular structure at room temperature of the CILs was initially studied by ATR-FTIR spectroscopy, as this technique gives separate vibrational bands for distinct species.[21] In the ATR-FTIR spectra of **5a-c** and **3a-c**, the bands between

3150 and 3000 cm^{-1} are diagnostic of the C–H stretching modes of the aromatic rings (Fig. 3). In this region, for the imidazolium aromatic ring, the C4-H (Hb) and C5-H (Hc) stretching modes appear at higher wavenumbers, whereas vibrational bands corresponding to the C2-H (Ha) stretching mode are present at lower wavenumbers.[22] In the partial ATR-FTIR spectra for **5c**, shown in Fig. 3, vibrational bands observed at 3120 cm^{-1} for **5c** and 3143 cm^{-1} for **3c** can be assigned to C-H imidazolium (Hb and Hc) stretching modes, whereas the vibrational band corresponding to Ha overlaps with the aromatic signals corresponding to the meta-substituted spacer appearing at 3065 cm^{-1} for **5c** and 3060 cm^{-1} for **3c**. Additional vibrational bands observed at higher wavenumbers (over 3200 cm^{-1}) can be assigned to N–H stretching modes (3280 and 3224 for **3c** and 3217 cm^{-1} for **5c**). For compound **5c** with a more basic Brønsted anion, the NH and imidazolium C-H stretching modes are observed at lower frequencies. Interestingly, two different NH stretching modes are observed for **3c**, which suggests the presence of amide groups H-bonded at a different extent. Therefore, the amide NH is the hydrogen atom more strongly involved in the bonding with the anion, according to the experimental ATR-FTIR data. Also in the case of the bands for the C-H imidazolium bands the ATR-FTIR data indicate a stronger involvement in hydrogen bonding in the case of the system containing the more basic anion **5c**.

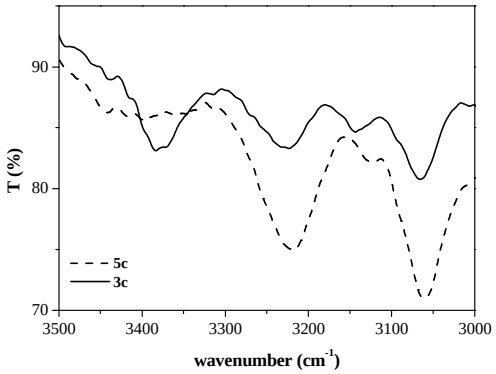


Fig. 3 Partial ATR-FTIR spectra for **3c** (continuous line) and **5c** (dotted line) at 25 °C.

Additional structural information was obtained by the use of ^{1}H-NMR and 1D-NOESY experiments. All the experiments were performed in $CDCl_3$ at 10 mM concentrations. As expected, the presence of the more basic Br^- anion provides a much stronger H-bonding interaction with the acidic hydrogen atoms, which is reflected in the appearance of the corresponding signals at lower fields (see ESI†). This is particularly relevant for the amide and Ha signals appearing in **5c** more than 1 ppm shifted relative to those in **3c**. Interestingly, appreciable shifts are also observed for Hg from the central benzene spacer, for Hb from the imidazolium fragment and for Hd and He corresponding to the proton of the stereogenic carbon and to those of the benzylic position. As shown in Fig. 4, very different NOE effects were observed for the bis(imidazolium) salts **5c** and **3c**, indicating the prevalence of clearly different conformations, in particular involving the rotation of the imidazolium ring relative to the benzene moiety. Thus, for example, a NOE effect was observed for **5c** between Hg and Ha protons, while for **3c** the NOE effect was observed between Hg and Hb protons. In the same way, while in **5c** a NOE effect is present between Hb and He, in **3c** the observed NOE with He involves Ha. A very rigid conformation seems to be prevalent in **5c**, most likely involving a cyclic intramolecular H-bonding structure of the anion and the acidic H atoms, as evidenced by the strong non-equivalence observed for the signals of the He atoms. This should be in good agreement with the preliminary structure calculated for the ion pair for **5a**.

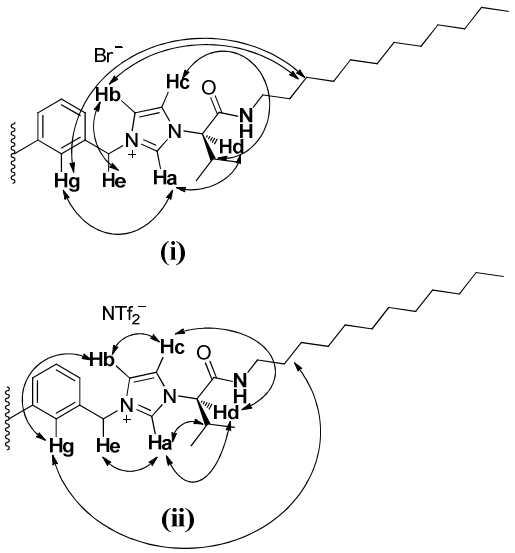


Fig. 4 Partial structure of the bis(imidazolium) salts **5c** (i) and **3c** (ii) where NOE peaks have been assigned with double-headed arrows (NOESY spectrum 500 MHz, at 303 K in $CDCl_3$).

More detailed molecular modelling studies were performed for compounds **5c** and **3c** at the B3LYP/6-31+G*//B3LYP/3-21G* level of theory and the optimized structures were found to be different in accordance with the results derived from 1D-NOESY experiments. For compound **5c**, a more compact structure was found, again defining a cleft structure formed by the spacer, the imidazolium rings and the amide fragments associated to the anion. In this case, however, the aliphatic amide N-substituents are folded back leaving open access to the cleft. On the contrary, **3c** adopts an open conformation with the bigger NTf_2^- anions located in the outer section and interacting only with one of the amide fragments.

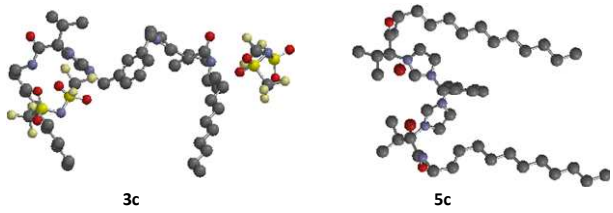


Fig. 5 Optimized structures for compounds **5c** and **3c** at the B3LYP/6-31+G*//B3LYP/3-21G* level of theory. Hydrogen atoms have been omitted for clarity.

The potential formation of supramolecular aggregates in solution was studied by obtaining the ^{1}H NMR spectra of the CILs at various concentrations in $CDCl_3$. Small concentration dependence was observed for salts **3a-c** in the ^{1}H NMR chemical shifts for the aromatic protons and for the amide NH proton signals (see ESI†). This suggests that intermolecular interactions are also weak when the NTf_2^- anion is present. However, strong concentration dependence was observed for the analogous halide salts **5a-c** (see ESI†). Thus, for example,

when increasing the concentration of **5c** from 2 to 80 mM, the corresponding ^{1}H NMR spectra showed significant upfield shifts for the signals of the acidic Ha from the imidazolium moiety ($\Delta\delta$ = -0.293 ppm), the Hg proton ($\Delta\delta$ = -0.134 ppm), whereas a downfield shift is observed for Hb ($\Delta\delta$ = 0.28 ppm). Slight variations were observed for the signals of N-H, He and the chiral proton (Hd) (Fig. 6). These data are consistent with a situation in which the low polarity of the solvent favours, for diluted solutions, a very strong intramolecular association of the ion pair in which the hydrogen bonding between the bromide anion and the Ha and amide hydrogen is prevalent. Upon increasing the concentration, intermolecular interactions become more important, weakening some of the initially observed intramolecular H-bonds. In particular, the intramolecular anion-cation H-bonding seems to preferentially involve Ha, while the intermolecular association seems to involve preferentially Hb. Moreover, this is in agreement with the differences observed with the concentration in the splitting observed for the He,e´ protons ($\Delta\delta$ = 0.45 and 0.11 ppm at 2 and 80 mM respectively).

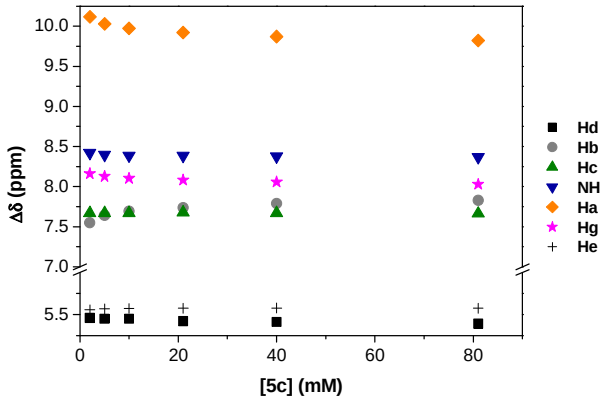


Fig. 6 Observed chemical shift changes with concentration for different proton signals in the ^{1}H NMR spectra of **5c** in $CDCl_3$.

Although compounds **3a-c** are liquid at room temperature, salts **5a-c** can form distinct microstructures in the solid state at room temperature. The morphologies of the aggregated formed by the halide salts were studied by using SEM techniques. In Fig. 7, the SEM images obtained from water/MeOH (5 %) solutions of **5a-c** (1 mM) evidence the presence of different morphologies significantly affected by the structure and the nature of the salt (Fig. 7). In this regard, compound **5a** forms a well-defined fractal structure with small spheres organized in rows growing perpendicularly from the precursor row. On the other hand **5b** and **5c** tend to form spherical aggregates, although the structures are better defined for **5c**.

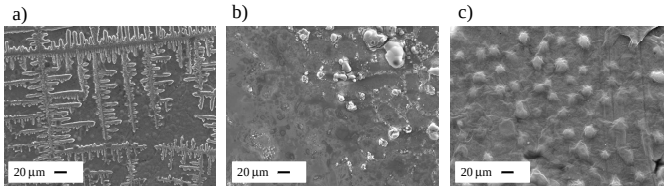


Fig. 7 SEM images of salts a) **5a**; b) **5b** and c) **5c**

Molecular recognition studies.

To explore the potential of the new chiral ionic liquids for chiral recognition, the binding between the imidazolium-based chiral ionic receptors and the selected carboxylate substrates was studied by ^{1}H NMR titration experiments at 303 K. We used bis(trifluoromethylsulfonyl)imide (NTf_2^-) as the anion for the imidazolium compounds and tetraethylammonium (TEA) counterions for the carboxylate substrates. As for related monotopic systems,[8e] and according to the former results, these two low coordinating counterions were selected for this study in order to reduce to maximize the interaction of the selected guests with the dicationic receptors.

Thus, the prepared CILs **3a-c** were tested as chiral receptors for aspartate and glutamate TEA salts. Aspartate and glutamate participate within the neurotransmitter family of substances. Aspartate has been considered to be a neurotransmitter, whereas GABA and glycine are thought to be major inhibitory transmitters. Excitatory transmitters such as aspartate lead to depolarization of the nerves; on the other hand, inhibitory transmitters cause hyperpolarization, apparently by increasing the permeability within the nerve of potassium and chloride.[23]

Initially, ^{1}H NMR spectroscopy was used to investigate the recognition ability of compound **3a**. For this purpose, 1:1 mixtures of the corresponding CIL and the L-aspartate or L-glutamate TEA salts were examined. All experiments were performed using a mixture of $CDCl_3$/DMSO-d_6 (5%), as this was found to be the more suitable medium for the experiments, since it allows a good solubility of the different species. As shown in Fig. 8, after the addition of the guest, the amide NH and the Ha proton signals from **3a** moved downfield, revealing the formation of supramolecular complexes between this CIL and the TEA salts. Thus, for example, by addition of 1 equiv of the L-glutamate TEA salt to a 8 mM solution of **3a** in $CDCl_3$, a significant downfield shift variation was observed for the amide NH, the imidazolium Ha, the chiral Hd proton signals ($\Delta\delta$ = 1.57, 0.74 and 0.6 ppm, respectively). This indicates the strong involvement of the amide and Ha protons in the hydrogen bonding interactions between the TEA salt and **3a**. On the other hand, smaller chemical shift variations were observed for the Hg proton signal, moving downfield ($\Delta\delta$ = 0.14 ppm), whereas most aromatic signals are shifted upfield, suggesting a specific involvement of this hydrogen atom of the aromatic spacer in the supramolecular complex.

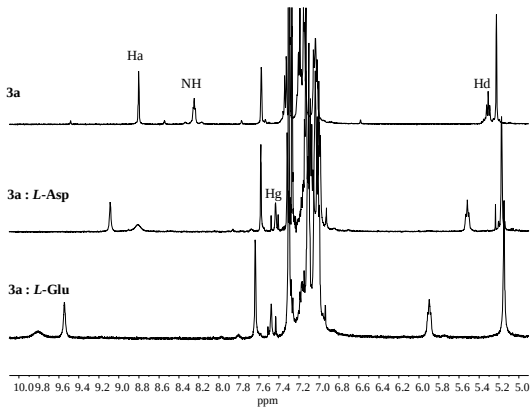


Fig. 8 Partial ^{1}H NMR spectra (500 MHz, 303 K, in $CDCl_3$ 5% DMSO-d_6) of **3a** (8 mM) in the presence of 1eq. of L-AspTEA (8 mM) and L-GluTEA (8 mM).

Titration experiments using **3a-c** and L- and D-aspartic and L- and D-glutamic TEA salts in a mixture of $CDCl_3$/DMSO-d_6 (5%) were also carried out (see ESI†). The corresponding complexation curves,

using the Hd proton signal of **3a-c** in the presence of TEA L- and D-aspartate, are gathered in Fig. 9. Similar complexation curves are observed for the Ha proton signal. Some enantiorecognition can be observed for the host **3a**, with larger $\Delta\delta/\Delta\delta_{max}$ values being observed for the L-enantiomer. However, no enantioselective recognition was observed when **3c** or **3d** were used as the receptors. These data suggest that the selectivity for aspartate follows the order **3b** > **3a** ≈ **3c**. Finally, none of the assayed receptors (**3a-c**) showed enantiodiscrimination for the glutamate salt (see ESI†). Receptors **3a** and **3c** are selective for glutamate, while receptor **3b** displays a relatively similar behaviour with both salts.

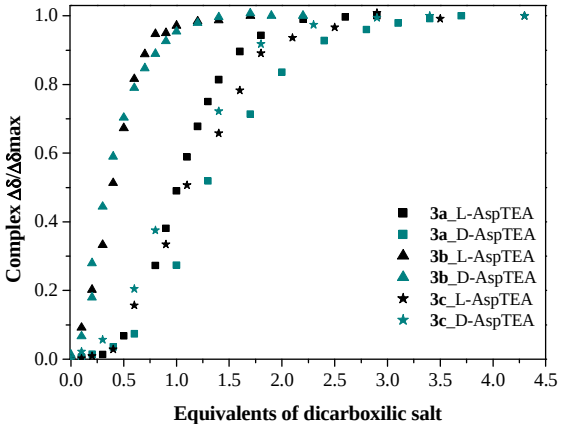


Fig. 9 Complexation curves for the receptors **3a-c** (8mM in $CDCl_3$ 5% DMSO-d_6) in the presence of L- or D- AspTEA. ($\Delta\delta = \delta - \delta_0$; $\Delta\delta_{max} = \delta_{max} - \delta_0$)

The stoichiometry of the resulting D- and L-aspartate-**3a** adducts was determined by ^{1}H NMR spectroscopy using Job's plots (also known as the continuous variation method).[24] Keeping the total concentration at 8 mM, the plot of $\Delta\delta$ versus the mole fraction of **3a** showed a maximum at $X_{3a} = 0.5$ for L- and D-AspTEA, indicative of a 1:1 stoichiometry for the complexes formed in solution by both enantiomers (see ESI†). At higher concentrations, the corresponding Job's plots for the different receptors tend to show complex patterns indicative of the formation of host-guest aggregates with variable stoichiometries.

Stability constants could not be accurately measured for the interaction between the receptors and the dicarboxylates assuming a 1:1 complexation (host:guest) using the HYPNMR and other fitting programs, using the variation of the chemical shifts of the Ha, Hd and NH proton signals. Besides, when titrations were carried out using CD_3CN as the solvent, a precipitate was formed during the titration until a stoiquiometric amount of the guest was added, observing then a clear solution in the NMR tube. This observation, along with the data from Job's plots at different concentrations and the sigmoidal nature of some of titration curves support the participation of more complex and nonspecific aggregates implicating several molecules of both host and guest. In this regard, we attempted to improve the fitting by manually adding additional equilibria and we observed (graphically) that the fitting was more accurate considering these additional binding modes. However, the automatic fitting option failed due to a large number of variables to be optimized (see ESI†). Nevertheless, this approach, considering the formation of other competing supramolecular species, allowed a rough estimation of the binding constants for the 1:1 complexes receptor:AspTEA. The corresponding values are given in table 2 (for the binding with GluTEA see ESI†).

Table 1. Binding Constants obtained by ^{1}H NMR Titration at 308 K (500 MHz, $CDCl_3$:5% DMSO-d_6).

Entry	receptor	substrate	log β^a
1	**3a**	L-AspTEA	~3.73
2	**3a**	D-AspTEA	~3.32
3	**3b**	L-AspTEA	~4.42
4	**3b**	D-AspTEA	~4.45
5	**3c**	L-AspTEA	~3.52
6	**3c**	D-AspTEA	~3,62

[a] estimated values, taking into consideration the formation of other species with complex stoichiometries.

Additional information about the nature of the complexes was obtained from ATR-FTIR and DSC experiments. While host **3a** and the guest (TEA salts of L and D-aspartate) are liquid at room temperature, the mixtures formed for a 1:1 CIL **3a** : AspTEA ratio are yellowish solids.

The partial ATR-FTIR spectra for **3a**, L-AspTEA and the 1:1 mixture are shown in Fig. 10. As can be observed, the NH and C-H imidazolium stretching bands for **3a** moved to lower wavenumbers in the presence of L-aspartate, indicating the participation of these groups in hydrogen bond interactions (Fig. 10a). Moreover, big differences were observed in the 1700-600 cm^{-1} region; the signals from the guest associated to the COO^- stretching bands at 1571 and 1458 cm^{-1} changed significantly and the N-H out of the plane bending at 880 cm^{-1} is not observed in the complex. Slight differences were observed for the signals corresponding to the C=C deformation of the imidazolium at ca. 1497 cm^{-1} that shift to lower wavenumbers (Fig. 10b).

In accordance with the enantioselective recognition detected by ^{1}H NMR, slight differences were observed for the two 1:1 mixtures formed by the TEA salts of both enantiomers of aspartate with **3a**, in particular for the C=C bending deformation, appearing at slightly lower wavenumbers for the L-aspartate complex, and for the C=O stretching bands from the carboxylate group. It must be noted that for the system derived from L-AspTEA no changes were observed in the spectrum when the temperature was increased, while small differences were observed for the D-AspTEA complex (Fig. 11). Interestingly, the corresponding ATR-FTIR spectra were identical after melting.

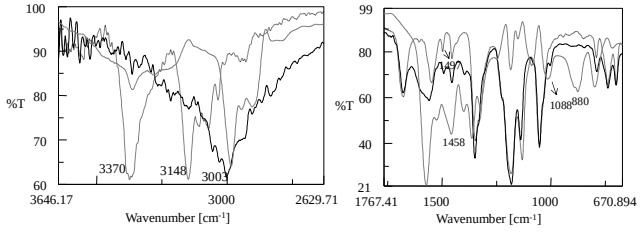


Fig. 10 Partial ATR-FTIR spectra of **3a** (dotted grey); L-AspTEA (grey line) and the 1:1 mixture **3a**:L-AspTEA (black line).

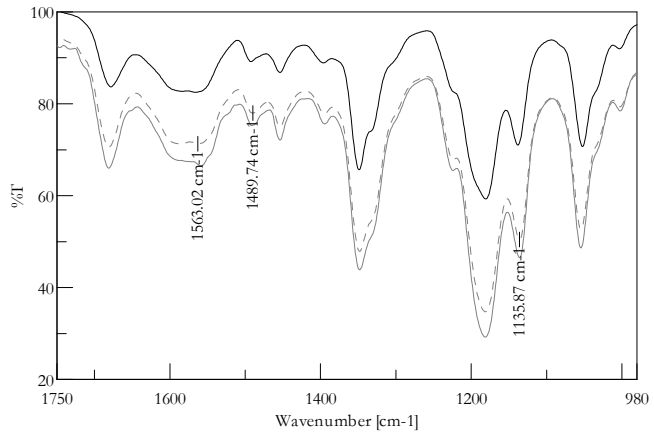


Fig. 11 Partial ATR-FTIR spectra of the 1:1 mixture **3a**:D-AspTEA at 25 °C (black line); **3a**:D-AspTEA at 94 °C (dotted grey line) and **3a**:L-AspTEA at 94 °C (grey line).

Finally, the corresponding DSC thermograms (from 20 to 120 °C and a heating rate of 1 °C/min) for these 1:1 mixtures showed a very broad exotermic peak in the second dynamic heating cycle associated to the crystallization and a broad endotermic peak at 86 °C associated to the complexes melting (m.p for L-Aspartate = 50 °C, m.p for **3a** = 28 °C). Both transitions were also confirmed by optical microscopy with cross polarizers using a heating plate. As can be seen in the ESI†, the transitions are slightly better defined for the system derived from L-Aspartate.

Conclusions

In conclusion, we have developed a family of C_2-symmetric chiral bis(imidazolium) compounds, with CILs properties, that are easily synthesized by simple reactions from commercially available amino acids. Different studies have been carried out in order to establish the influence of the nature of the side chain as well as the presence of additional functional groups in the final CILs on their intrinsic properties. These new ditopic CILs, have been shown to form supramolecular complexes, in solution and in the solid state, with different dicarboxylic amino acids (as their TEA salts). Significant guest-induced chemical shifts can be observed for the NMR signals of receptor upon addition of the corresponding dicarboxylate. ^{1}H NMR shifts and NOE experiments, along with ATR-FTIR data, provided important information on the structural elements associated to the formation of the corresponding complexes. H-bonding of the carboxylate groups with the amide NH and the acidic protons of the imidazolium ring are essential in this regard, although other intermolecular interactions seem also to be present. Although in dilute solutions 1:1 complexes are prevalent, the formation of higher order aggregates is also suggested by some data. A selective recognition of the glutamate derivative takes place for **3a** and **3c**, while no selectivity is observed for **3b**. Some enantioselectivity has been detected for the interaction between **3a** and the aspartate salts, favouring the recognition of the L-derivative. Further studies towards the sustainable application of these chiral ionic liquids as receptors and transporters for anions are in progress.

General Experimental Methods. All reagents were purchased from commercial suppliers and used as received. Chiral imidazoles (**4a-b**) were synthesized as described previously by ou group[8e] starting from N-protected amino acids commercially available. The NMR spectroscopic experiments were carried out at 500 or 125 MHz for ^{1}H and ^{13}C NMR, respectively. The chemical shifts are reported using the residual solvent signal as the internal standard. FTIR spectra were acquired with a MIRacle single-reflection ATR diamond/ZnSe accessory. Melting points were measured by using a differential scanning calorimeter (DSC). The instrument was calibrated for temperature and heat flow with zinc and indium reference samples. Samples were placed in a 40 mL, hermetically sealed aluminium pan with a pinhole in the top. An empty aluminium pan was used as the reference. Samples were exposed to a flowing N_2 atmosphere. Before the DSC test, each sample was dried at 60 °C in a vacuum oven for 12 h, and was further dried *in situ* in the differential scanning calorimeter by holding the sample at 100 °C for 60 min because the presence of volatiles, especially water, can affect the melting temperatures. Melting transition temperatures of compounds **3a-c** were determined by using multiple cycles (typically three) involving heating the sample from –70 to 125 °C followed by cooling from 125 to –70 °C, both at a rate of 5 °C/min. Melting transition temperatures of compounds **5a-c** were determined by using multiple cycles (typically three) involving heating the sample from 30 to 150 °C followed by cooling from 150 to 30 °C, both at a rate of 5 °C/min. The melting temperatures were determined at the peak of the transition. Decomposition temperatures were measured using a TG-STDA, heating samples from 20 to 600 °C at a rate of 10 °C/min. The reactions under microwave conditions were carried out using a CEM Discover System Microwave, model 908010, using a surface infrared sensor for temperature control.

General Procedure for the Synthesis of Bis(imidazolium) Salts 5a, 5b and 5c: The corresponding imidazole derivative (2.2 equiv) and α,α′-dibromo-m-xylene (1 equiv.) in CH_3CN were stirred under microwave irradiation (power = 120 W; pressure = 250 psi; T = 150 °C) during 30 min. After reaction, the solvent was evaporated under reduced pressure and the resulting product was washed with hexane/diethyl ether (2:1) to obtain the corresponding bis(imidazolium) halide salts **5a**, **5b** and **5c**.

1-[(1*R*)-1-(benzylcarbamoyl)–2–phenylethyl]-3-{[3-({1-[(1*S*)-1-(benzylcarbamoyl)-2-phenylethyl]-1H-imidazol-3-ium-3-yl}methyl)phenyl]methyl}-1H-imidazol-3-ium dibromide (**5a**). The reaction between **4a** and α,α′-dibromo-*m*-xylene in CH_3CN gave a brown solid (0.49 g, 78 %). mp 90 °C; $[\alpha]_D^{25}$ = -22.6 (c= 0.01, $CHCl_3$); IR (ATR) 3447, 3262, 3136, 3063, 2969, 2937, 2877, 1679, 1551, 1454, 1357, 1226, 1167, 1037 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 9.65 (s, 2H), 9.00 (t, J = 5.8 Hz, 2H), 7.76 (s, 1H), 7.66 (s, 2H), 7.53 (s, 2H), 7.19 – 7.11 (m, 19H), 7.05 (d, J = 3.3 Hz, 4H), 6.28 (t, J = 8.0 Hz, 2H), 5.30 (q, J = 14.5 Hz, 4H), 4.45 (δδ, J = 14.9, 6.4 Hz, 2H), 4.19 (dd, J = 14.9, 5.3 Hz, 2H), 3.44 (dd, J = 13.6, 7.5 Hz, 2H), 3.27 (dd, J = 13.7, 8.6 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 166.8, 137.6, 136.4, 134.4, 134.2, 130.5, 130.1, 129.7, 129.3, 129.19, 129.0, 128.6, 127.5, 127.3, 122.5, 121.5, 62.8, 52.9, 43.5, 39.0; HRMS (ESI-TOF) calcd for ($C_{46}H_{46}N_6O_2$/2) $[M]^{2+}$ 357.1841, found 357.1836; calcd for ($C_{46}H_{46}BrN_6O_2$) $[M + Br]^+$ 793.2866, found 793.2866; Anal. Calcd. (%) for $C_{46}H_{46}Br_2N_6O_2$: C, 63.16; H, 5.30; N, 9.61. Found: C, 63.34; H, 5.40; N, 9.54.

1-[(1*R*)-1-(benzylcarbamoyl)-2-methylpropyl]-3-{[3-({1-[(1*S*)-1-(benzylcarbamoyl)-2-methylpropyl]-1H-imidazol-3-ium-3-yl}methyl)phenyl]methyl}-1H-imidazol-3-ium dibromide (**5b**). The reaction between **4b** and α,α′-dibromo-*m*-xylene in CH_3CN, gave an orange solid (0.31 g, 96 %). mp 82

°C. $[\alpha]_D^{25}$ =-16.6 (c= 0.01, $CHCl_3$); IR (ATR) 3410, 3213, 3059, 2967, 2937, 2876, 1674, 1549, 1495, 1453, 1225, 1153,1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 10.06 (s, 2H), 8.97 (t, *J* = 5.9 Hz, 2H), 8.07 (s, 1H), 7.61 (s, 4H), 7.42 (s, 3H), 7.24 (d, *J* = 7.4 Hz, 4H), 7.23 – 7.17 (m, 6H), 5.68 (d, *J* = 14.4 Hz, 2H), 5.53 (d, *J* = 10.6 Hz, 2H), 5.36 (d, *J* = 14.4 Hz, 2H), 4.52 (dd, *J* = 14.9, 6.6 Hz, 2H), 4.23 (dd, *J* = 14.9, 5.4 Hz, 2H), 2.49 – 2.44 (m, 2H), 1.02 (d, *J* = 6.5 Hz, 6H), 0.80 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm):167.1, 137.9, 136.3, 134.3, 130.4, 130.0, 128.6, 127.7, 127.4, 122.8, 121.0, 68.13, 53.1, 43.6, 31.3, 18.9, 18.6; HRMS (ESI-TOF) calcd for ($C_{38}H_{46}N_6O_2$/2) $[M]^{2+}$ 309.1841, found 309.1839; calcd for ($C_{38}H_{46}BrN_6O_2$) $[M + Br]^+$ 697.2866, found 697.2872; Anal. Calcd. (%) for $C_{38}H_{46}Br_2N_6O_2 \cdot 2H_2O$: C, 56.02; H, 6.19; N, 10.32. Found: C, 56.02; H, 6.03; N, 10.07.

1-[(1*R*)-1-(dodecylcarbamoyl)-2-methylpropyl]-3-{[3-({1-[(1*S*)-1-(dodecylcarbamoyl)-2-methylpropyl]-1H-imidazol-3-ium-3-yl}methyl)phenyl]methyl}-1H-imidazol-3-ium methane dibromide (**5c**). The reaction between **4c** and α,α′-dibromo-*m*-xylene in CH_3CN gave an orange solid (0.47 g, 91 %). mp 68 °C; $[\alpha]_D^{25}$ =-8.6 (c= 0.01, $CHCl_3$); IR (ATR) 3416, 3218, 3060, 2959, 2923, 2853, 1679, 1550, 1464, 1371, 1223, 1155 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 10.08 (s, 2H), 8.41 (s, 2H), 8.15 (s, 1H), 7.67 (s, 2H), 7.59 (s, 2H), 7.42 (dd, *J* = 12.7, 6.0 Hz, 3H), 5.77 (d, *J* = 14.3 Hz, 2H), 5.47 (d, *J* = 10.6 Hz, 2H), 5.36 (d, *J* = 14.3 Hz, 2H), 3.47 – 3.27 (m, 2H), 3.11 – 2.98 (m, 2H), 2.51 – 2.41 (m, 2H), 1.52 (d, *J* = 6.5 Hz, 4H), 1.24 (s, 36H), 1.07 (d, *J* = 6.5 Hz, 6H), 0.93 – 0.81 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 166.8, 136.5, 136.4, 134.2, 130.8, 130.0, 122.7, 122.6, 121.0, 120.8, 68.2, 53.3, 40.0, 32.0, 31.3, 29.8, 29.5, 29.3, 29.13, 27.1, 22.8, 19.0, 18.6, 14.2; HRMS (ESI-TOF) calcd for ($C_{48}H_{82}N_6O_2$/2) $[M]^{2+}$ 387.3250, found 387.3249; calcd for ($C_{48}H_{82}BrN_6O_2$) $[M + Br]^+$ 853.5683, found 853.5687; Anal. Calcd. (%) for $C_{48}H_{82}Br_2N_6O_2 \cdot H_2O$: C, 60.49; H, 8.88; N, 8.82. Found: C, 60.35; H, 8.61; N, 8.43.

General Procedure for the Synthesis of Bis(imidazolium) Salts 3a, 3b and 3c. A solution of $LiNTf_2$ (2.2 equiv.) in MeOH was added to a solution of the corresponding halide salt (1 equiv) in MeOH, and the resulting mixture stirred for 48 h. The solvent was then evaporated at reduced pressure, further H_2O added, and the mixture extracted with CH_2Cl_2 (3×20 mL). The organic phases were combined, dried with $MgSO_4$, and the solvent evaporated under reduced pressure to afford the corresponding bis(imidazolium) salt **3a**, **3b** or **3c**.

1-[(1*R*)-1-(benzylcarbamoyl)-2-phenylethyl]-3-{[3-({1-[(1*S*)-1-(benzylcarbamoyl)-2-phenylethyl]-1H-imidazol-3-ium-3-yl}methyl)phenyl]methyl}-1H-imidazol-3-ium; bis(trifluoro[(trifluoromethanesulfonylazanidyl)sulfonyl]methane) (**3a**). The reaction between **5a** and $LiNTf_2$ gave a brown liquid (0.45 g, 93 %). mp 28 °C; $[\alpha]_D^{25}$ = - 7.8 (c= 0.01, $CHCl_3$); IR (ATR) 3434, 3263, 3135, 3063, 2968, 2936, 2877, 1679, 1554, 1454, 1355, 1166 ,1036, cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.75 (s, 2H), 8.17 (t, *J* = 5.3 Hz, 2H), 7.57 (s, 2H), 7.32 (s, 1H), 7.31 (s, 2H), 7.15 (dt, J = 12.3, 7.0 Hz, 16H), 7.04 – 6.99 (m, 7H), 5.30 (t, *J* = 7.9 Hz, 2H), 4.36 (dd, *J* = 14.8, 6.1 Hz, 2H), 4.13 (dd, *J* = 14.8, 4.8 Hz, 2H), 3.40 (dd, *J* = 13.6, 7.2 Hz, 2H), 3.13 (dd, *J* = 13.6, 8.7 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 166.3, 136.8, 135.3, 133.7, 133.5, 131.0, 129.9, 129.2, 129.0, 128.9, 128.8, 127.9, 127.7, 122.5, 122.1, 121.0, 118.5, 63.8, 53.2, 44.0, 40.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ 78.7; HRMS (ESI-TOF) calcd for ($C_{46}H_{46}N_6O_2$/2) $[M]^{2+}$=357.1841, found 357.1839; calcd for ($C_{48}H_{46}F_6N_7O_6S_2$) $[M + NTf_2]^+$ 994.2855, found 994.2852; Anal. Calcd. (%) for $C_{50}H_{46}F_{12}N_8O_{10}S_4 \cdot H_2O$: C, 46.44; H, 3.74; N, 8.66; S, 9.92. Found: C, 46.35; H, 3.53; N, 8.28; S, 10.08.

1-[(1*R*)-1-(benzylcarbamoyl)-2-methylpropyl]-3-{[3-({1-[(1*S*)-1-(benzylcarbamoyl)-2-methylpropyl]-1H-imidazol-3-ium-3-yl}methyl)phenyl]methyl}-1H-imidazol-3-ium;bis(trifluoro[(trifluoromethanesulfonylazanidyl)sulfonyl]methane) (**3b**). The reaction between **5b** and $LiNTf_2$ gave a yellow liquid (0.19 g, 73 %). mp 15 °C; $[\alpha]_D^{25}$ = -2.9 (c= 0.01, $CHCl_3$); IR (ATR) 3376, 3146, 3072, 2973, 2880, 1679, 1548, 1454, 1347, 1330, 1183, 1132, 1052 cm^{-1}1; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.99 (s, 2H), 8.24 (s, 2H), 7.51 (s, 2H), 7.46 (s, 1H), 7.37 (s, 2H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.26 (s, 2H), 7.15 (dt, *J* = 18.6, 7.1 Hz, 10H), 5.33 – 5.24 (m, 4H), 4.57 (d, *J* = 9.8 Hz, 2H), 4.34 (dd, *J* = 14.7, 5.9 Hz, 2H), 4.13 (dd, *J* = 14.7, 4.8 Hz, 2H), 2.38 – 2.17 (m, 2H), 0.87 (d, *J* = 6.5 Hz, 6H), 0.66 (d, *J* = 6.5 Hz, 6H): ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 166.7, 137.1, 135.2, 133.9, 131.1, 130.1, 129.7, 128.8, 127.9, 127.8, 122.6, 122.4, 121.0, 118.5, 68.9, 53.4, 44.0, 32.5, 18.7, 18.2; ^{19}F NMR (470 MHz, CD_3CN) δ 80.2; HRMS (ESI-TOF) calcd for ($C_{38}H_{46}N_6O_2$/2) $[M]^{2+}$ 309.1841, found 309.1837; found 357.1839; calcd for ($C_{40}H_{46}F_6N_7O_6S_2$) $[M + NTf_2]^+$ 898.2855, found 898.2852; Anal. Calcd. (%) for $C_{42}H_{46}F_{12}N_8O_{10}S_4$: C, 42.78; H, 3.93; N, 9.50; S, 10.88. Found: C, 42.41; H, 4.22; N, 9.12; S, 10.59.

1-[(1*R*)-1-(dodecylcarbamoyl)-2-methylpropyl]-3-{[3-({1-[(1*S*)-1-(dodecylcarbamoyl)-2-methylpropyl]-1H-imidazol-3-ium-3-yl}methyl)phenyl]methyl}-1H-imidazol-3-ium;bis(trifluoro[(trifluoromethanesulfonylazanidyl)sulfonyl]methane (3c). The reaction between **5c** and $LiNTf_2$ gave a brown liquid (0.20 g, 72 %). mp -6 °C; $[\alpha]_D^{25}$ = -34.3 (c= 0.01, $CHCl_3$); IR (ATR) 3384, 3223, 3143, 3065, 2958, 2924, 2854, 1677, 1549, 1464, 1351, 1193, 1150,1057 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.83 (s, 2H), 7.78 (s, 2H), 7.57 (s, 1H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.40 (d, *J* = 11.7 Hz, 4H), 7.00 (t, *J* = 5.3 Hz, 2H), 5.36 (dd, *J* = 33.3, 14.6 Hz, 4H), 4.60 (d, *J* = 10.2 Hz, 2H), 3.32 (dt, *J* = 13.7, 6.8 Hz, 2H), 3.12 – 3.01 (m, 2H), 2.42 – 2.25 (m, 2H), 1.63 – 1.41 (m, 4H), 1.27 – 1.23 (m, 36H), 1.05 (t, *J* = 8.2 Hz, 6H), 0.87 (t, *J* = 6.8 Hz, 6H), 0.76 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 166.7, 135.1, 133.9, 131.1, 130.1, 129.8, 122.6, 122.4, 121.1, 118.5, 69.1, 53.3, 40.2, 32.4, 32.0, 29.7, 29.7, 29.6, 29.5, 29.3, 28.9, 26.9, 22.8, 18.7, 18.1, 14.2; ^{19}F NMR (470 MHz, CD_3CN) δ 80.2; HRMS (ESI-TOF) calcd for ($C_{48}H_{82}N_6O_2$/2) $[M]^{2+}$ 387.3250, found 387.3239; ; calcd for ($C_{50}H_{82}F_6N_7O_6S_2$) $[M + NTf_2]^+$ 1054.5672, found 1054.5673; Anal. Calcd. (%) for $C_{52}H_{82}F_{12}N_8O_{10}S_4 \cdot H_2O$: C, 46.14; H, 6.26; N, 8.28. Found: C, 45.90; H, 5.88; N, 8.01.

NMR titration procedures. The titrations were performed with the bis(imidazolium) compounds as their bis(trifluoromethylsulfonyl)imide salts (**3a-c**). Stock solutions of the bis(imidazolium) salts were prepared by weighting the corresponding amount of the compound (**3a-c)** and reaching a final concentration around 8−12 mM. The solvent used was 95:5 $CDCl_3$:DMSO-d_6 since this mixture allowed a good solubility during the whole titration experiment. Additionally, a stock solution of the titrant containing 100 mM tetraethylammonium salt of each carboxylate was prepared by dissolving the salt in the stock solution of the bis(imidazolium), maintaining the concentration of the bis(imidazolium) salts constant during the titration experiment. The stock solution of

the bis(imidazolium) salt was introduced in a NMR tube and the ^{1}H NMR spectrum (500 MHz, 303 K) was acquired, then successive aliquots of the stock solution of the carboxylate were added and the ^{1}H NMR spectrum recorded after each addition.

Theoretical studies. The supramolecular complexes between **3a** and the guests were generated manually and submitted to conformational analysis by Monte Carlo conformational searches as implemented in Spartan'14 software. To this aim, 10000 structures were stochastically generated and minimized with the MMFF molecular force field. Then, the lowest 100 minima were analysed and ordered attending to their relative energies. Different starting geometries and anion-cation dispositions were used in order to verify that the systems converged to the same final minima. The obtained minima were subsequently fully minimized at the B3LYP/6-31+G*//B3LYP/3-21G* level of theory.

Acknowledgements

Financial support from Ministerio de Economía y Competitividad (CTQ2011-28903-C02-01 and CTQ2012-38543-C03-01), Generalitat Valenciana (PROMETEO 2012/020 and ACCOMP/2014/275) and Universitat Jaume I (P1·1B2013-38) is acknowledged. Technical support from the SCIC-UJI for instrumentation is acknowledged.

Notes and references

[a] Department of Inorganic and Organic Chemistry, Universitat Jaume I, Av. de Vicent Sos Baynat s/n, 12071 Castellón, Spain.
E-mail: luiss@uji.es
[b] Laboratory of Organic Chemistry, Wageningen University, Dreijenplein 8, 6703 HB, Wageningen, the Netherlands.

† Electronic Supplementary Information (ESI) available: NMR spectra, ATR-FTIR, DSC, Jobplot, complexation curves and theoretical calculations. See DOI: 10.1039/b000000x/

1 (a) S. Das, S. L. de Rooy, A. N. Jordan, L. Chandler, I. I. Negulescu, B. El-Zahab, I. M. Warner, *Langmuir*, 2012, **28**, 757; (b) P. Koley, M. G. Drew, A. Pramanik, *J. Nanosci. Nanotechnol*., 2011, **11**, 6747; (c) V. A. Mallia, H.-I. Seo, R. G. Weiss, *Langmuir*, 2013, **29**, 6476; (d) D. Wu, R. Liu, W. Pisula, X. Feng, K. M¨ullen, *Angew. Chem., Int. Ed*., 2011, **50**, 2791.

2 (a) Z. Guo, N. R. Song, J. H. Moon, M. Kim, E. *J*. Jun, *J*. Choi, *J*. Y. Lee, C. W. Bielawski, J. L. Sessler, *J*. Yoon, *J. Am. Chem. Soc*., 2012, **134**, 17846; (b) T. S. Jo, J. J. Koh, H. Han, P. K. Bhowmik, *Mater. Chem.Phys*., 2013, **139**, 901. A. K. Nedeltchev, H. Han, P. K. Bhowmik, *J. Mater. Chem*., 2011, **21**, 12717; (c) A. P. Kulkarni, C. J. Tonzola, A. Babel, S. A. Jenekhe, *Chem. Mater*., 2004, **16**, 4556; (d) U. Mitschke, P. Bauerle, *J. Mater. Chem.*, 2000, **10**, 1471; (e) Francesca D'Anna, Carla Rizzo, Paola Vitale, Giuseppe Lazzara, Renato Noto, *Soft. Matter*., 2014, **10**, 9281.

3 (a) T. H. Webb, C. S. Wilcox, *Chem. Soc. Rev*. 1993, **22**, 383; (b) L. Pu, *Chem. Rev*. 2004, **104**, 1687.

4 Q. Ren, K. Ruth, L. Thöny-Meyer, M. Zinn, *Appl. Microbiol. Biotechnol*. 2010, **87**, 41.

5 Patrick, G. L. An Introduction to Medicinal Chemistry; Oxford University Press, Inc.: New York, 2013.

6 (a) E. K. Bollough, C. A. Kilner, M. A. Little, C. E. Willans, *Org. Biomol. Chem*. 2012, **10**, 2824; (b) C-L. Do-Thanh, N. Khanal, Z. Lu, S. A. Cramer, D. M. Jenkins, M. D. Best, *Tetrahedron* 2012, **68**, 1669; (c) E. *J*. Jun, Z. Xu, M. Lee, *J*. Yoon, *Tetrahedron Lett*. 2013, **54**, 2755; (d) S. H. Mashraqui, R. Betkar, M. Chandiramani, D. Quinonero, A. Frontera, *Tetrahedron Lett*. 2010, **51**, 596; (e) Z.-M. Su, H.-M. Ye, X.-X. Zhu, L.-L. Xie, S. Bai, Y.-F. Yuan, *J. Organomet. Chem*. 2014, **750**, 162; (f) V. Suresh, N. Ahmed, I. S. Youn, K. S. Kim. *Chem. Asian J*. 2012, **7**, 658; (g) Y. Chun, N. Jiten Singh, I.-C. Hwang, J. Woo Lee, S. U. Yu, K. S. Kim, *Nat. Commun*. 2013, **4**, 1797; (h) *J*. S. García, L. Rodríguez, P. Gamez, A. Robertazzi, *J. Phys. Chem. A* 2012, **116**, 9110.

7 (a) H. Zhou, Y. Zhao, G. Gao, S. Li, J. Lan, J. You, *J. Am. Chem. Soc*. 2013, **135**, 14908; (b) V. Amendola, M. Boiocchi, B. Colasson, L. Fabbrizzi, M.-J. Douton-Rodriquez, F. Ugozzoli, *Angew. Chem., Int. Ed*. 2006, **45**, 6920.

8 (a) S. K. Kim, B.-G. Kang, H. S. Koh, Y.-J. Yoon, S. J. Jung, B. Jeong, K.-D. Lee, J. Yoon, *Org. Lett*. 2004, **6**, 4655; (b) A. L. Koner, J. Schatz, W. M. Nau, U. Pischel, *J. Org. Chem*. 2007, **72**, 3889; (c) L. Yang, S. Qin, X. Su, F. Yang, J. You, C. Hu, R. Xie, J. Lan, *Org. Biomol. Chem*. 2010, **8**, 339; (d) Md. W. Ahmad, S. H. Kim, H.-S. Kim, *Tetrahedron Lett.* 2011, **52**, 6743; (e) L. González, B. Altava, B. M. Bolte, M. I. Burguete, E. García-Verdugo, S. V. Luis, *Eur. J. Org. Chem*. 2012, **26**, 4996; (f) B. Roy, A. K. Bar, B. Gole, J. Mukheriee, *Org. Chem*. 2013, **78**, 1306; (g) L. Casal-Dujat, P. C. Griffiths, C. Rodríguez-Abreu, C. Solans, S. Rogers, L. J. Pérez-García, *Mater. Chem. B* 2013, **1**, 4963; (h) F. Wang, R. Nandhakumar, Y. Hu, D. Kim, K. M. Kim, J. Yoon, *J. Org. Chem*. 2013, **78**, 11571; (i) Q. Lu, *J*. Hou, J. Wang, B. Xu, J. Zhang, X. Yu, *Chin. J. Chem*. 2013, **31**, 641.

9 (a) S. K. Kim, N. J. Singh, S. J. Kim, H. G. Kim, J. K. Kim, J. W. Lee, K. S. Kim, J. Yoon, *Org. Lett*. 2003, **5**, 2083; (b) J. Yoon, S. K. Kim, N. J. Singh, J. W. Lee, Y. J. Yang, K. Chellappan, K. S. Kim, *J. Org. Chem*. 2004, **69**, 581; (c) J. Y. Kwon, N. J. Singh, H. Kim, S. K. Kim, K. S. Kim, J. Yoon, *J. Am. Chem. Soc*. 2004, **126**, 8892; (d) Z. Xu, N. J. Singh, J. Lim, J. Pan, H. N. Kim, S. Park, K. S. Kim, J. Yoon, *J. Am. Chem. Soc*. 2009, **131**, 15528; (e) N. Ahmed, B. Shirinfar, I. Geronimo, K. S. Kim, *Org. Lett*. 2011, **13**, 5476; (f) H. N. Kim, J. H. Moon, S. K. Kim, J. Y. Kwon, Y. J. Jang, J. Y. Lee, J. Yoon, *J. Org. Chem*. 2011, **76**, 3805; (g) J. R. Jadhav, C. H. Bae, H.-S. Kim, *Tetrahedron Lett.* 2011, **52**, 1623; (h) J. Y. Jung, E. J. Jun, Y.- U. Kwon, J. Yoon, *Chem. Commun*. 2012, **48**, 7928; (i) N. Wu, J. Lan, L. Yan, J. You, *Chem. Commun*. 2014, **50**, 4438.

10 (a) P. P. Neelakandan, D. Ramaiah, *Angew. Chem., Int. Ed*. 2008, **47**, 8407; (b) Q.-L. Li, J. Huang, Q. Wang, N. Jiang, C.-Q. Xia, H.-H. Lin, J. Wu, X.-Q. Yu, *Bioorg. Med. Chem*. 2006, **14**, 4151; (c) B. Shirinfar, N. Ahmed, Y. S. Park, G.-S. Cho, I. S. Youn, J.-K. H. G. Nam, K. S. Kim, *J. Am. Chem. Soc*. 2013, **135**, 90; (d) M.-Q. Wang, K. Li, H.-R. Xu, X.-Q. Yu, *Anal. Methods* 2013, **5**, 5903.

11 S. Marullo, F. D'Anna, M. Cascino, R. Noto, *J. Org. Chem*. 2013, **78**, 10203.

12 (a) Kokorin, A., Ionic Liquids: Theory, Properties, New Approaches. InTech: 2011 ; (b) H. Niedermeyer, J. P. Hallett, I. J. Villar-Garcia, P. A. Hunt, T. Welton, *Chem. Soc. Rev*. 2012, **41**, 7780.

13 (a) N. Ríos-Lombardía, E. Busto, V. Gotor-Fernández, V. Gotor, R. Porcar, E. García-Verdugo, S. V. Luis, I. Alfonso, S. García-Granda,

A. Menéndez-Velázquez, *Chem. Eur. J*. 2010, **16**, 836; (b) N. Ríos-Lombardía, R. Porcar, E. Busto, I. Alfonso, J. Montejo-Bernardo, S. García-Granda, V. Gotor, S. V. Luis, E. Garcia-Verdugo, V. Gotor-Fernández, *ChemCatChem*, 2011, **3**, 1921; (c) R. Porcar, V. Sans, N. Ríos-Lombardía, V. Gotor-Fernández, V. Gotor, M. I. Burguete, E. García-Verdugo, S. V. Luis, *ACS Catalysis*, 2012, **2**, 1976; (d) E. Faggi, R. Porcar, M. Bolte, S. V. Luis, E. García-Verdugo, I. Alfonso *J. Org. Chem*. 2014, **79**, 9141.

14 (a) B. Altava, D. S. Barbosa, M. Isabel Burguete, J. Escorihuela, S. V. Luis, *Tetrahedron: Asymmetry* 2009, **20,** 999; (b) L. González, J. Escorihuela, B. Altava, M. I. Burguete, S. V. Luis, *Eur. J. Org. Chem*. 2014, **24**, 5356.

15 M. L. Patil, C. V. L. Rao, S. Takizawa, K. Takenaka, K. Onitsuka, H. Sasai, *Tetrahedron*, 2007, **63**, 12702.

16 (a) M. I. Burguete, M. Collado, J. Escorihuela, F. Galindo, E. García-Verdugo, S. V. Luis, M. J. Vicent, *Tetrahedron Lett*. 2003, **44**, 6891; (b) M. I. Burguete, M. Collado, J. Escorihuela, S. V. Luis, *Angew. Chem. Int. Ed.* 2007, **46**, 9002; (c) J. Escorihuela, M. I. Burguete, S. V. Luis, *Tetrahedron Lett*. 2008, **49**, 6885; (d) J. Escorihuela, B. Altava, M. I. Burguete, S. V. Luis, *Tetrahedron* 2013, **69**, 551; (e) J. Escorihuela, L. González, B. Altava, M. I. Burguete, S. V. Luis, *Appl. Catal. A*, 2013, **462–463**, 23. (f) J. Escorihuela, B. Altava, M. I. Burguete, S. V. Luis, *RSC Advances* 2015, **5**, 14653.

17 (a) H. Shirota, T. Mandai, H. Fukazawa, T. Kato, *J. Chem. Eng. Data* 2011, **56**, 2453; (b) C. Maton, N. De Vos, C. V. Stevens, *Chem. Soc. Rev.* 2013, **42**, 5963

18 Spartan '14, version 1.1.0 (Sept 27 2013), Wavefunction Inc.: Irvine CA, 2014.

19 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, GAUSSIAN 09 (Revision D.1), Gaussian, Inc., Wallingford CT, 2009.

20 J. Rebek Jr, *Acc. Chem. Res*. 1999, **32**, 278.

21 E. R. Talaty, S. Raja, V. J. Storhaug, A. Dölle, W. R. Carper, *J. Phys. Chem. B* 2004, **108**, 13177.

22 K. Fumino, A. Wulf and R. Ludwig, *Angew. Chem. Int. Ed*. 2008, **47**, 8731.

23 (a) W. E. Childers Jr, R. B. Baudy, *J. Med. Chem*. 2007, **50**, 2557; (b) J. M. Schkeryantz, A. E. Kingston, M. P. Johnson, *J. Med. Chem.* 2007, **50**, 2563; (c) S. F. Traynelis, L. P. Wollmuth, C. J. McBain, F. S. Menniti, F. S.; Vance, K. M.; Ogden, K. K.; Hansen, K. B.; Yuan, H.; Myers, R. Dingledine, *Pharmacological Reviews* 2010, **62**, 405; (d) D. Lemoine, R. Jiang, A. Taly, T. Chataigneau, A. Specht, T. Grutter, *Chem. Rev*. 2012, **112**, 6285

24 (a) P. Job, *Ann. Chim. Fr*. 1928, **9**, 113. (b) V. M. S. Gil, N. C. Oliveira, *J. Chem. Educ*., 1990, **67**, 473.