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L-Amino acid derived pyridinium-based chiral compounds and their efficacy in chiral recognition of lactate†

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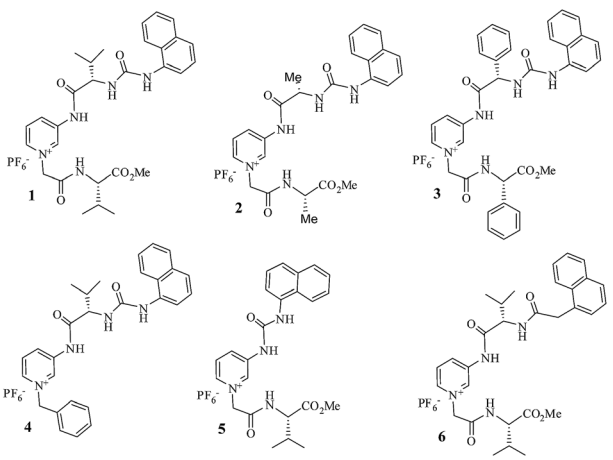
A series of pyridinium-based chiral compounds **1–6** have been designed and synthesized. L-Amino acids have been used as the chiral source in the molecules. Among the chiral compounds, an L-valine derived compound **1** was found to exhibit enantioselective recognition of D-lactate in fluorescence. Structural tuning of this derivative, either by replacing L-valine with L-alanine or L-phenylglycine or by reducing the number of chiral centres around the binding site, does not result in any significant change in enantioselectivity in the recognition process. Change of the urea site to amide introduces compound **6** that displays good enantiodiscrimination for lactate (enantiomeric fluorescence difference ratio ef = 28.33 for D-lactate), even better than that of the L-valine derived compound **1** and of other reported structures in the literature.

Introduction

Enantioselective recognition of chiral analytes is an important topic in chiral recognition.[1] Chiral recognition is unavoidably significant as chiral biomolecules such as proteins, nucleic acids and carbohydrates play a vital role in life. In this area, synthetic receptors that are capable of discriminating a particular isomer from its mirror image isomer through photophysical changes have attracted much attention. Of the different photophysical processes, fluorescence is noteworthy because of high sensitivity and thus its application in chiral recognition has been studied for several decades.[2] Chiral fluorescence-based sensors can be used in the rapid determination of enantiomeric composition as well as in high-throughput catalysis for asymmetric synthesis.[3] Thus the development of fluorescence-based enantioselective sensors for distinguishing chiral amines,[4a] amino alcohols,[4b–c] chiral acids,[4d] chiral amino acids[4e–h] and carbohydrates[4i–j] *etc.*, has begun to attract research attention. In past several years, enantioselective recognition of biologically significant α-hydroxycarboxylic acids[5] as well as of α-amino acids and their derivatives[4e–h] has been much explored. Of the different α-hydroxycarboxylates, lactate is a simple example which is biologically relevant. While the isomer L(+)-lactate is important in biological metabolism, D(−)-lactate is harmful to human metabolism and can result in acidosis and decalcification.[6] Thus the enantioselective binding of lactate or its derivatives is crucial, although there are few reports in the literature.[5g,7] Recently, we have reported L-valine derived pyridinium-based chiral receptor **1**, which shows enantioselective binding of lactate by exhibiting significant change in emission in the presence of D-lactate over L-lactate in CH_3CN.[8] In relation to this, we wish to report in this full account a series of pyridinium-based chiral hydrogen bonding receptors **2–6** and their chiral recognition properties towards hydroxycarboxylates in detail, emphasizing the importance of structural tuning to achieve good chiral discrimination.



It is to be pointed out that the exploration of 3-aminopyridine in devising chiral sensors for the enantioselective recognition of carboxylate-based substrates is unknown in the literature except for our recent example of structure **1**.[8]

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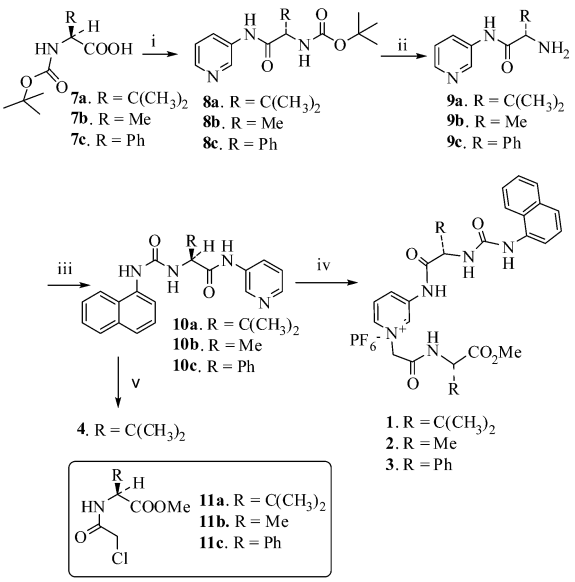
† Electronic supplementary information (ESI) available: Figures showing the change in fluorescence and UV-vis titrations of receptors **1–6** with various chiral anions, Job plot, binding constant table, ^{1}H NMR titration and other spectral data. See DOI: 10.1039/c5ra00017c

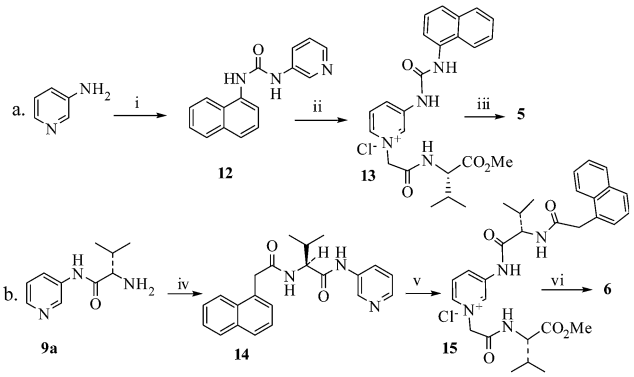
Results and discussion

Compounds **1–6** were synthesized according to Schemes 1 and 2. Following our reported reaction protocols for the synthesis of **1**,[8] compounds **2** and **3** were synthesized (Scheme 1). Boc protected L-amino acids such as valine **7a**, alanine **7b** and phenyl glycine **7c** were reacted with 3-aminopyridine in the presence of dicyclohexylcarbodiimide (DCC) to give the coupled products **8a–c**, respectively. Removal of the Boc-groups in **8a**, **8b** and **8c** using trifluoroacetic acid (TFA) gave the amines **9a**, **9b** and **9c**, respectively, which individually upon reaction with 1-naphthyl isocyanate, obtained from the reaction of 1-naphthylamine with triphosgene, yielded the respective urea derivatives **10a**, **10b** and **10c**. For quarternization of the pyridine ring nitrogens in **10a–c**, the chloroamides **11a–c**, which were obtained from the reactions of methyl esters of amino acids with chloroacetyl chloride, were used. Individual reflux of compounds **10a–c** in the presence of the corresponding chloroamides **11a–c** in dry CH_3CN for 4 days afforded the chloride salts of **1–3**. Next, anion exchange reactions of the chloride salts of **1–3** were pursued using NH_4PF_6 to give the desired compounds **1**, **2** and **3**. On the other hand, reaction of **10a** with benzyl bromide in dry CH_3CN followed by Br^- exchange with PF_6^- gave compound **4**.

Compounds **5** and **6** were synthesized according to Scheme 2. Triphosgene mediated reaction of 3-aminopyridine, followed by addition of 1-naphthylamine in Scheme 2a gave the urea **12**, which on further reaction with the chloroamide **11a**, gave the chloride salt **13**. Chloride exchange in **13** using NH_4PF_6 gave the desired compound **5**. On the other hand, the amine **9a** was coupled with 1-naphthylacetyl chloride to give the amide derivative **14**, which, under reflux in CH_3CN in the presence of chloroamide **11a**, gave the chloride salt **15**. Next, chloride exchange in **15** using NH_4PF_6 gave the desired compound **6** in appreciable yield. All the compounds were characterized by usual spectroscopic methods.



Scheme 1 (i) 3-Aminopyridine, DCC, CH_2Cl_2, 20 h; (ii) TFA, CH_2Cl_2, 3 h; (iii) 1-naphthylamine, triphosgene, Et_3N, CH_2Cl_2, 16 h; (iv) (a) **11a–c**, CH_3CN, reflux, 4 days; (b) NH_4PF_6, $CH_3OH–H_2O$; (v) (a) benzyl bromide, CH_3CN, reflux, 18 h; (b) NH_4PF_6, $CH_3OH–H_2O$.



Scheme 2 (a) (i) 1-Naphthylamine, triphosgene, Et_3N, CH_2Cl_2, 18 h; (ii) **11a**, CH_3CN, reflux, 4 days; (iii) NH_4PF_6, $CH_3OH–H_2O$; (b) (iv) 1-naphthylacetyl chloride, CH_2Cl_2, Et_3N, 12 h; (v) **11a**, CH_3CN, reflux, 3 days; (vi) NH_4PF_6, $CH_3OH–H_2O$.

Chiral recognition requires multiple-point interaction.[9] Analysis of the structures **1–6** reveals that the pyridinium cation is the principal binding site in all cases. Around this motif, other different functional groups have been considered in different ways to have diverse chiral receptor structures that are capable of attaining multiple-point interaction. Variation of the amino acid in the design strategy has been considered to account for the steric requirements in the binding site for good chiral discrimination. The naphthalene moiety has been used as the fluorescence signaling unit to assess the chiral recognition behavior of the molecules. It is to be pointed out that the 3-aminopyridinium motif is important in anion recognition as it provides hydrogen bond donors from different anchoring groups and also a polarized C–H bond at the *ortho* position to the anion and the complex is further stabilized by charge–charge interaction. Its widespread use in anion recognition by different researchers and also by us has recently been thoroughly reviewed.[10]

To study the chiral recognition properties of the receptor structures **1–6**, tetrabutylammonium salts of D- and L-hydroxy acids such as lactic and mandelic acids were used. In our earlier report[8] we showed that compound **1** selectively recognizes D-lactate over L-lactate with an ef [ef = $(I_D - I_0)/(I_L - I_0)$ where I_0 represents the fluorescence emission intensity in the absence of the chiral substrate, I_L and I_D are the fluorescence intensities in the presence of L- and D-lactates, respectively] of 5.32. To understand the structural role of L-valine (chiral source) in **1**, we studied compound **2**, which bears L-alanine instead of L-valine. The fluorescence study of **2** ($c = 3 \times 10^{-5}$ M) in CH_3CN revealed poor enantiodiscrimination. Upon gradual addition of guests to the solution of **2** in CH_3CN, the emission of **2** at 378 nm increased with a red shift of ~28 nm. But the change in emission for each pair occurred to nearly the same extent (Fig. S1, ESI†). Only in the case of D-lactate it was slightly more (ef = 1.16). Fig. 1, in this regard, shows the change in emission of **2** in the presence of 20 equiv. of D/L-lactates and mandelates in

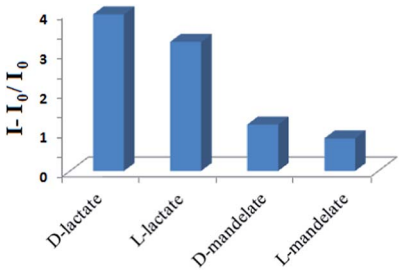


Fig. 1 Change in fluorescence ratio of **2** ($c = 3 \times 10^{-5}$ M) upon addition of 20 equiv. of guests in CH_3CN at 406 nm ($\lambda_{exc} = 300$ nm).

CH_3CN. As can be seen from Fig. 1, receptor structure **2** shows preferential binding to the isomers of lactates than to mandelate. But the enantioselection was insignificant. This was also true in the ground state. In a UV-vis study, no marked difference in absorption spectra of **2** during titration was observed (Fig. S2, ESI†).

Under identical conditions, a fluorescence study of **3** ($c = 3 \times 10^{-5}$ M), which contains L-phenyl glycine as the chiral source, also revealed poor enantiodiscrimination in CH_3CN. On addition of the guests to a solution of **3** in CH_3CN the emission of **3** at ~400 nm increased (Fig. S3, ESI†) to the same extent and in the case of L-lactate it was a little more (ef = 1.08). Fig. 2 represents the change in emission ratio of **3** in the presence of 6 equiv. of D/L-lactates and mandelates in CH_3CN. Further addition of guests to the receptor solution decreased the emission gradually (Fig. S3, ESI†). Similar to **2**, in UV titration no characteristic difference in the absorption spectra of **3** was observed in the presence of the guests (Fig. S4, ESI†).

Thus, these results corroborate that in the present study, valine with its steric isopropyl substituent at the α-carbon is superior to alanine and phenyl glycine with methyl and phenyl groups, respectively, in chiral recognition to discriminate the enantiomers of lactate.

After establishing L-valine as the suitable chiral source in the series, we moved further to understand its positional role around the pyridinium motif in the chiral discrimination of α-hydroxycarboxylate. For this, compounds **4** and **5** were synthesized. While in **4** the L-valine unit is present at the 3-position of the pyridinium motif, in compound **5** it is present on the pyridinium ring nitrogen. Fluorescence titrations of these two compounds in CH_3CN revealed that both **4** and **5** were unable to show chiral discrimination of the guests studied. In the case of receptor **4**, although the lactate-induced change in emission was greater than the cases with mandelates, the enantiomers of lactate were discriminated with ef = 1.65 (Fig. 3a). In comparison, chiral receptor **5** under identical conditions in CH_3CN did not exhibit any fluorescence selectivity between lactate and mandelate. But the enantiomers of lactate were poorly discriminated with an ef of 1.18 (Fig. 3b). These observations underline the fact that the presence of L-valine as a single unit either at the ring nitrogen or at the amine function of 3-aminopyridine does not do much to cause enantiodiscrimination of lactate.

To evaluate the potentiality of the urea functionality in the design, we then considered amide analogue **6**. A thorough fluorescence study of **6** ($c = 3 \times 10^{-5}$ M) was carried out in CH_3CN. Like urea analogue **1**, compound **6** selectively discriminated the stereoisomers of lactates. Upon gradual addition of D-lactate to a solution of **6** in CH_3CN, while the emission at 338 nm decreased to a small extent, a new emission at 425 nm appeared with significant intensity. In comparison, a small increase in emission at 425 nm with the addition of L-lactate was observed. Fig. 4 represents the titration spectra for **6** with both D- and L-lactates. Under identical conditions, titration experiments for **6** with D- and L-mandelates were performed and negligible changes in emission were found. No peak at 425 nm was noticed during interaction (Fig. S9, ESI†). It is thus presumed that the peak at 425 nm in the presence of the lactates is due to the formation of an intermolecular excimer between the naphthalenes.[11] Mandelate, being more bulky than lactate, is weakly involved in binding and thus is unable to participate in intermolecular chelation, responsible for excimer emission.

Fig. 5 shows the emission ratio of **6** in the presence of D/L-lactates and mandelates in CH_3CN. As can be seen from Fig. 5, while the receptor **6** shows sharp fluorometric discrimination between D- and L-lactates at 425 nm, enantiomers of mandelate are scarcely discriminated. The enantiomeric fluorescence difference ratio, ef, is determined to be 28.33, which is considerably greater than the case with **1**. Even, the ef value is significantly greater than that for the salen-based chiral fluorescent sensor reported by Song *et al.*[5g] It is further to be pointed out that the quantum yield[12] of **6** is much more enhanced upon interaction with D-lactate than with L-lactate. The increment is

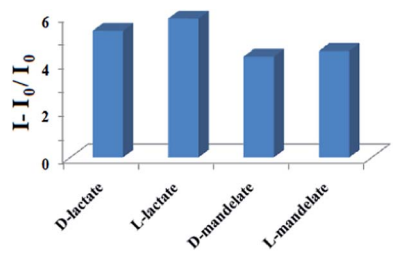


Fig. 2 Change in fluorescence ratio of **3** ($c = 3 \times 10^{-5}$ M) upon addition of 6 equiv. of guests in CH_3CN at 405 nm ($\lambda_{exc} = 300$ nm).

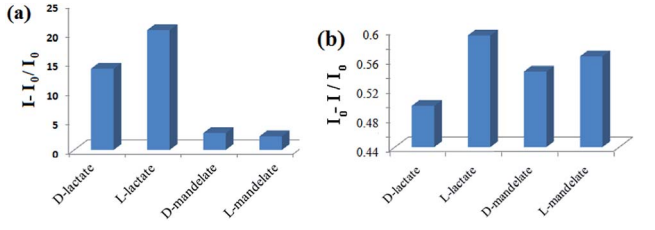


Fig. 3 Change in fluorescence ratio of (a) **4** ($c = 3 \times 10^{-5}$ M) upon addition of 13 equiv. of guests in CH_3CN at 402 nm ($\lambda_{exc} = 300$ nm), and (b) **5** ($c = 3 \times 10^{-5}$ M) upon addition of 19 equiv. of guests in CH_3CN at 401 nm ($\lambda_{exc} = 300$ nm).

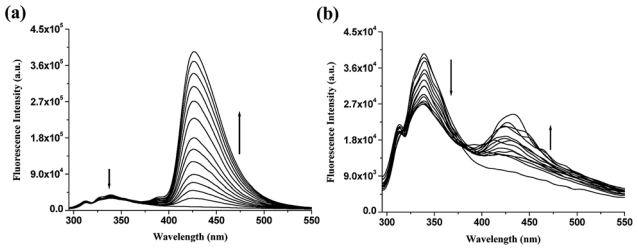


Fig. 4 Fluorescence titration spectra for **6** ($c = 3 \times 10^{-5}$ M) in CH_3CN with tetrabutylammonium salts of (a) D- and (b) L-lactic acids (in all cases 6×10^{-4} M is a maximal concentration of anion applied; λ_{exc} = 285 nm).

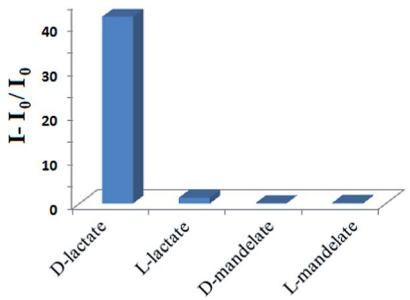


Fig. 5 Change in fluorescence ratio of **6** ($c = 3 \times 10^{-5}$ M)) upon addition of 17 equiv. of guests in CH_3CN at 425 nm.

considerable with respect to the receptor **1** (ESI, Table S1†). Thus the amide analogue **6** is established to be more efficient than **1** in the enantioselective recognition of lactate.

In the interaction process, the stoichiometry of the interaction of **6** with both D- and L-lactates was determined to be 1 : 1, as confirmed by Job plot[13] (Fig. S11, ESI†). In this context, it is to be pointed out that the appearance of the intermolecular excimer between the naphthalenes in Fig. 4 may originate from the equilibrium species with the stoichiometry of adducts 1 : 1 (polymeric assembly), 2 : 2 or others. However, the binding constant value[14] was determined from a nonlinear fit of the emission titration data and found to be $(1.55 \pm 0.19) \times 10^4$ M^{-1} for D-lactate (Fig. 6). For L-lactate, it was determined to be $(5.29 \pm 0.89) \times 10^3$ M^{-1} (Fig. S12, ESI†) and this is about three times less than the binding constant value for D-lactate. However, due to poor change in emission, we were unable to fit the titration data to a nonlinear equation to determine the binding constant values for both the stereoisomers of mandelates. A comparison of the binding constant values as shown in Table S2 (ESI†) shows that the receptor **6**, among the designs, exhibits stronger binding towards D-lactate.

However, the enantioselective response of **6** towards a particular stereoisomer of lactate was further realized from the change in emission of **6** in the presence of its mirror image isomer. Fig. 7, in this context, demonstrates these features. L-Lactate induced change in emission of **6** was further perturbed to a considerable extent upon addition of D-lactate (Fig. 7a). The reverse addition was observed to be insignificant (Fig. 7b).

For practical applications, we also investigated the chiral recognition behaviour of **6** with the same guests in aqueous CH_3CN ($CH_3CN : H_2O = 4 : 1$ v/v). Surprisingly, guest-induced minor change in emission indicated its inefficiency in chiral recognition in aqueous organic solvent (ESI, Fig. S13†).

Prior to studying the interaction of **6** with the lactate isomers *via* ^1H NMR, a NOESY spectrum of **6** was recorded in CD_3CN to identify the positions of the different protons (ESI, Fig. S14†). Among the different protons, the interacting protons of **6** were identified in the ^1H NMR spectrum by observing the positional movement of the signals in the presence of D- and L-lactates. In relation to this, Fig. 8 highlights the spectral changes of **6** in the presence of D-lactate. All the amide protons of types 'a', 'b' and 'c' underwent downfield chemical shifts in the presence of D-lactate. The amide proton of type 'a' became invisible in the presence of a small amount of the guest and this is presumed to be due to its strong participation in hydrogen bonding that makes the signal broaden. On the other hand, while the amide proton of type 'c' is significantly shifted downfield, the amide proton of type 'b' exhibits a small change in chemical shift upon complexation. The participation of the pyridinium motif in complexation was also recognized from the downfield chemical shifts of the *ortho* protons of types 'd' and 'e'. The plot in the inset of Fig. 8 shows the change in chemical shifts of the different interacting protons with guest concentration. It is of note that, during interaction, some signals for naphthalene ring protons (asterisks marked in Fig. 8; for details see Fig. S14†) in the regions 7.93 ppm and 7.50 ppm underwent an upfield chemical shift when D-lactate was gradually added. Guest-

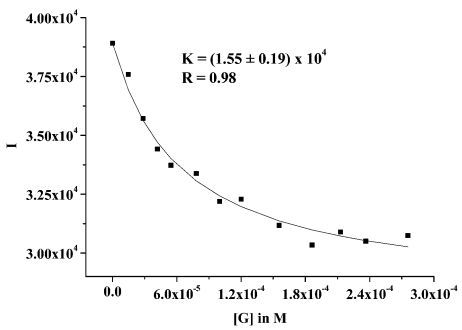


Fig. 6 Nonlinear curve fitting of the fluorescence titration data for **6** with D-lactate.

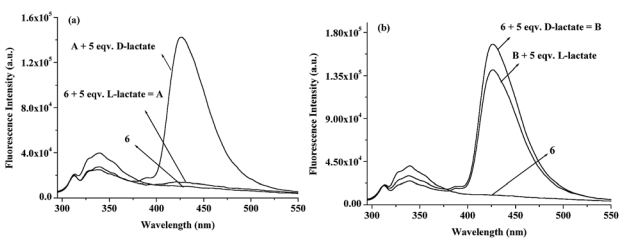


Fig. 7 Fluorescent response of **6** ($c = 3 \times 10^{-5}$ M) to (a) D-lactate ($c = 6 \times 10^{-4}$ M) in the presence of L-lactate ($c = 6 \times 10^{-4}$ M) and (b) L-lactate ($c = 6 \times 10^{-4}$ M) in the presence of D-lactate ($c = 6 \times 10^{-4}$ M) in CH_3CN.

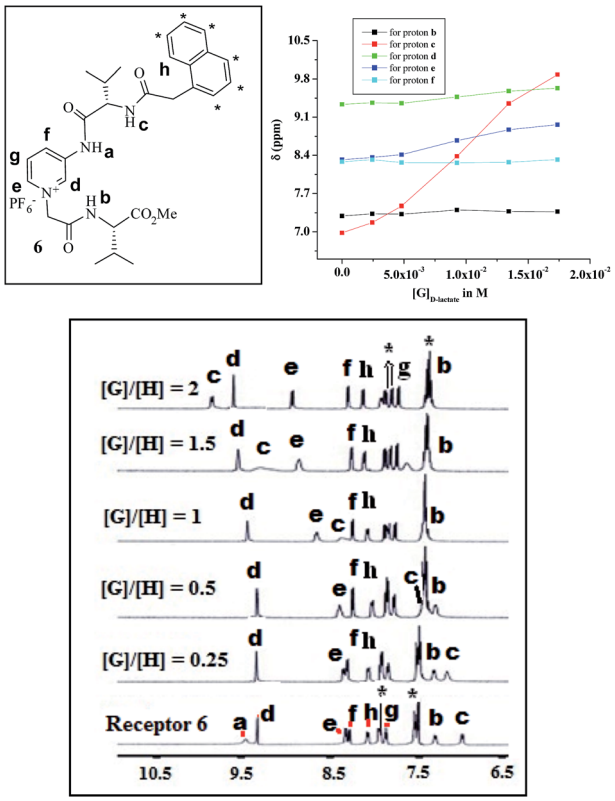


Fig. 8 Partial ^{1}H NMR (400 MHz, CD_3CN) spectra of **6** ($c = 1 \times 10^{-2}$ M) in the absence and presence of D-lactate [inset: change in chemical shift values for the interacting protons with guest concentration].

induced intermolecular chelation of the receptors in solution probably gives a situation where the naphthalene ring experiences π-stacking interaction. This is in accordance with the observation of an excimer emission peak[11] at 425 nm in fluorescence (see Fig. 4). A similar observation in the ^{1}H NMR spectra of **6** was noted upon gradual addition of L-lactate, although the changes in chemical shifts of the interacting protons were less compared to those in the case of D-lactate (Fig. S15, ESI†).

Generally the selectivity of a chiral environment towards the two enantiomers of a chiral species is due to the formation of transient diastereomeric adducts, which differ in both energetic and structural aspects. In the present case, in spite of the several possibilities of stoichiometries of the adducts (1 : 1, 2 : 2 or others) in solution, we became interested to study the hydrogen bonding features of the receptor **6** with the lactate isomers and also the corresponding stabilities of the discrete 1 : 1 adducts in the gas phase through DFT calculations. DFT optimization[15] was done in the gas phase using the B3LYP function and 3–21 basis set (Fig. 9). Like structure **1**,[8] receptor module **6** also showed a preference for D-lactate over its mirror image isomer. D-Lactate is observed to be complexed 4.56 kcal mol^{-1} more strongly than the L-isomer. Fig. 9 represents the DFT optimized structures in the gas phase with the hydrogen bonding schemes.

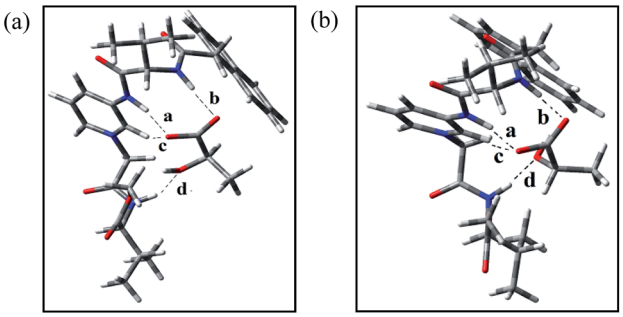


Fig. 9 DFT optimized geometries of the complexes of (a) **6** D-lactate (hydrogen bond distances in Å: $a = 1.60$, $b = 1.95$, $c = 2.19$ and $d = 1.78$); and (b) **6** L-lactate in the gas phase (hydrogen bond distances in Å: $a = 1.52$, $b = 1.92$, $c = 2.39$ and $d = 1.79$).

Conclusions

In summary, we have designed and synthesized a series of pyridinium-based chiral receptors **1–6** of which structures **1** and **6** have been established as chiral receptors for the enantioselective sensing of D-lactate over its mirror image. Both the structures contain an L-valine unit as the chiral source, which brings good enantioselectivity in the recognition process. Other amino acids such as L-alanine and L-phenyl glycine as the chiral source in the designed structures **4** and **5**, respectively, did not bring any enantioselectivity. The steric features of the side chain of the α-amino acid, hydrogen bonding effects and charge–charge interactions play important roles in the recognition process. It is further of note that between **1** and **6**, the receptor structure **6**, with an amide functionality at the site of the naphthalene instead of a urea, shows greater enantioselectivity (ef = 28.33) towards D-lactate and establishes its efficacy in the chiral recognition of lactates. Further insight along this direction is underway in our laboratory.

Experimental

Compounds **8a**, **10a**, **11a** and **1** were obtained according to our earlier reported procedure.[8] Synthetic procedures and characterization data of these compounds are further given in the ESI.† Compounds **2**, **3** and the intermediates such as **8b** and **c**, **10b** and **c** and **11b** and **c** were prepared according to the same procedure as followed for **1** (ESI†).[8]

Compound (4)

To a stirred solution of **10a** (0.1 g, 0.275 mmol) in CH_3CN (15 mL), was added benzyl bromide (0.06 g, 0.35 mmol) and the mixture was refluxed for 18 h. After completion of reaction, purification of the crude reaction mixture by preparative TLC using ethyl acetate as eluent gave the bromide salt of **4** as a gummy product (0.11 g, yield: 74%). In the next step, based on the procedure of anion exchange as followed in the case of **1**, the bromide ion was exchanged with the PF_6^- ion using NH_4PF_6 (0.1 g, 0.61 mmol) in MeOH–H_2O (20 mL) to give the desired compound **4** (0.115 g, yield: 93%), mp 120 °C, $[\alpha]_D^{25} = 19.41$ ($c =$

0.618 g/100 mL, CH_3CN), ^1H NMR (400 MHz, $CDCl_3$ containing two drops d_6-DMSO): δ 10.80 (s, 1H), 9.36 (s, 1H), 8.52 (s, 1H), 8.33 (d, 1H, $J = 5.20$ Hz), 8.23 (d, 1H, $J = 8$ Hz), 8.08 (d, 1H, $J = 4$ Hz), 7.84 (d, 1H, $J = 8$ Hz), 7.79–7.76 (m, 1H), 7.58–7.52 (m, 2H), 7.46–7.43 (m, 3H), 7.39–7.33 (m, 5H), 7.01 (d, 1H, $J = 8$ Hz), 5.51 (s, 2H), 4.47 (t, 1H, $J = 8$ Hz), 2.23–2.18 (m, 1H), 1.08–1.05 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$ containing two drops d_6-DMSO): δ 173.3, 156.7, 139.8, 138.1, 134.4, 134.06, 134.0, 133.9, 132.0, 130.0, 129.5, 129.0, 128.3, 128.1, 126.8, 125.8, 125.74, 125.70, 123.7, 121.5, 118.7, 65.2, 60.0, 30.9, 19.4, 18.0; FT-IR: ν cm^{-1} (KBr): 3631, 3367, 3095, 2966, 1707, 1655, 1595, 1547, 1504; HRMS (TOF MS ES^+): calcd for $(M - PF_6)^+$: 453.2285, found: 453.2233.

1-(Naphthalene-1-yl)-3-(pyridine-3-yl)urea (12)

To a stirred solution of triphosgene (0.5 g, 1.68 mmol) in dry CH_2Cl_2 (5 mL), was added 3-aminopyridine (0.16 g, 1.7 mmol) dissolved in dry CH_2Cl_2 (25 mL), dropwise using a dropping funnel for 30 min. After complete addition of 3-aminopyridine, triethylamine (0.62 mL, 2.5 equiv.) was added and the reaction mixture was stirred for another 40 min. Then 1-naphthylamine (0.27 g, 1.89 mmol) in dry CH_2Cl_2 (25 mL), was added to the reaction mixture. Stirring of the reaction mixture was continued for 16 h. After completion of reaction, CH_2Cl_2 was evaporated off and water was added to the residue. The aqueous layer was extracted with $CHCl_3$ (25 mL × 3) and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude mass was purified by silica gel column chromatography using petroleum ether–ethyl acetate (2 : 3, v/v) as eluent to give the compound **12** (0.3 g, yield: 68%), mp 221 °C, ^1H NMR (400 MHz, d_6-DMSO): δ 9.30 (s, 1H), 8.97 (s, 1H), 8.72 (s, 1H), 8.28 (d, 1H, $J = 4.80$ Hz), 8.19 (d, 1H, $J = 8$ Hz), 8.09–8.00 (m, 3H), 7.75 (d, 1H, $J = 8$ Hz), 7.69–7.60 (m, 2H), 7.55 (t, 1H, $J = 8$ Hz), 7.40 (dd, 1H, $J_1 = 8$ Hz, $J_2 = 4$ Hz); ^{13}C NMR (100 MHz, d_6-DMSO): δ 153.5, 143.3, 140.3, 137.0, 134.4, 134.1, 128.8, 126.7, 126.4, 126.3, 125.6, 124.1, 123.9, 121.8, 118.6 (one carbon is not resolved); FT-IR: ν cm^{-1} (KBr): 3263, 3013, 1642, 1587, 1555; mass: (LCMS) 264.0 $(M + 1)^+$.

Compound (5)

To a stirred solution of **12** (0.12 g, 0.455 mmol) in dry CH_3CN (15 mL), was added compound **11a** (0.12 g, 0.577 mmol) dissolved in dry CH_3CN (5 mL) and the reaction mixture was refluxed for 4 days. After completion of reaction, the crude product was purified by preparative TLC using ethyl acetate as eluent to give yellowish gummy compound **13** (0.15 g, yield: 70%). Finally, based on the procedure followed in the case of compound **1**, the chloride anion in **13** was exchanged with the PF_6^- ion using NH_4PF_6 (0.15 g, 0.92 mmol) in MeOH–H_2O (20 mL) to give the desired compound **5** (0.16 g, yield: 86%), mp 160 °C, $[\alpha]_D^{25} = -9.5$ ($c = 0.524$ g/100 mL, MeOH), ^1H NMR (400 MHz, $CDCl_3$ containing two drops d_6-DMSO): δ 9.91 (s, 1H), 9.31 (s, 1H), 8.79 (s, 1H), 8.69 (d, 1H, $J = 8$ Hz), 8.43 (d, 1H, $J = 8$ Hz), 8.31 (d, 1H, $J = 5.60$ Hz), 8.04 (d, 1H, $J = 8$ Hz), 7.91–7.88 (m, 3H), 7.69 (d, 1H, $J = 8$ Hz), 7.56–7.46 (m, 3H), 5.38 (s, 2H), 4.45–4.42 (m, 1H), 3.73 (s, 3H), 2.21–2.16 (m, 1H), 0.96 (d, 6H, $J = 6.40$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$ containing two drops d_6-DMSO): δ 171.5, 163.8, 152.6, 140.9, 137.8, 134.3, 133.9, 133.1, 132.5, 128.5, 127.4, 127.1, 125.9, 125.5, 125.0, 121.1, 119.7, 62.3, 58.0, 52.0, 30.6, 18.8, 17.8 (one carbon in the aromatic region is unresolved); FT-IR: ν cm^{-1} (KBr): 3379, 3286, 3099, 2967, 1736, 1703, 1656, 1598, 1533, 1504; HRMS (TOF MS ES^+): calcd for $(M - PF_6)^+$: 435.2027, found: 435.2032.

(*S*)-3-Methyl-2-(2-(naphthalene-1-yl)actamido)-*N*-(pyridine-3-yl)butanamide (14)

To a stirred solution of 1-naphthylacetic acid (0.2 g, 1.07 mmol) in dry CH_2Cl_2 (15 mL), was added oxalyl chloride (0.2 mL, 2 equiv.) and two drops of dry DMF and the stirring was continued for 6 h. Then solvent was evaporated off *in vacuo* to give the desired 1-naphthylacetyl chloride. This was directly used in the next step. 1-Naphthylacetyl chloride was dissolved in dry CH_2Cl_2 (10 mL) and to this solution amine **9a** (0.25 g, 1.2 mmol) in dry CH_2Cl_2 (10 mL) containing Et_3N (0.25 mL, 1.5 equiv.) was added. The reaction mixture was stirred for another 12 h. After completion of the reaction, the solvent was removed under reduced pressure, water was added to the residue, and the product was extracted with $CHCl_3$ (25 mL × 2) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product, which was purified by silica gel column chromatography using petroleum ether–ethyl acetate (1 : 9, v/v) as eluent to give the product **14** (0.25 g, yield: 64%), mp 196 °C, $[\alpha]_D^{25} = -1.99$ ($c = 0.502$ g/100 mL, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$): δ 9.05 (s, 1H), 8.55 (s, 1H), 8.30 (d, 1H, $J = 4$ Hz), 7.91 (d, 1H, $J = 8$ Hz), 7.86 (dd, 2H, $J_1 = 8$ Hz, $J_2 = 2$ Hz), 7.81 (d, 1H, $J = 8$ Hz), 7.50–7.39 (m, 4H), 7.15 (dd, 1H, $J_1 = 8$ Hz, $J_2 = 4$ Hz), 6.22 (d, 1H, $J = 8$ Hz), 4.47 (t, 1H, $J = 8$ Hz), 4.08 (dd, 2H $J_1 = 28$ Hz, $J_2 = 16$ Hz), 1.98–1.93 (m, 1H), 0.80 (d, 3H, $J = 6.80$ Hz), 0.62 (d, 3H, $J = 6.80$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 170.6, 145.0, 141.5, 134.7, 133.8, 131.8, 130.5, 128.8, 128.5, 128.3, 127.1, 126.6, 126.0, 125.6, 123.5, 123.4, 59.3, 41.3, 30.8, 19.1, 18.1; FT-IR: ν cm^{-1} (KBr): 3257, 3047, 2959, 1660, 1637, 1534; mass: (LCMS) 362.0 $(M + 1)^+$.

Compound (6)

To a stirred solution of **14** (0.15 g, 0.415 mmol) in dry CH_3CN (20 mL), was added compound **11a** (0.11 g, 0.529 mmol) in dry CH_3CN (5 mL) and the reaction mixture was refluxed for 3 days. The crude product was purified by preparative TLC using ethyl acetate as eluent to give yellowish gummy compound **15** (0.147 g, yield: 62%). Finally, according to the ion exchange procedure followed for the synthesis of **1**, the chloride anion in **15** was exchanged with the PF_6^- ion using NH_4PF_6 (0.14 g, 0.86 mmol) in MeOH–H_2O to give the desired compound **6** (0.15 g, yield: 85%), $[\alpha]_D^{25} = 16.33$ ($c = 0.612$ g/100 mL, CH_3CN), ^1H NMR (400 MHz, $CDCl_3$ containing two drops of d_6-DMSO): δ 10.68 (s, 1H), 9.19 (s, 1H), 8.41 (d, 1H, $J = 8$ Hz), 8.30 (t, 2H, $J = 8$ Hz), 7.99 (d, 1H, $J = 8$ Hz), 7.86–7.84 (m, 1H), 7.80 (d, 1H, $J = 8$ Hz), 7.75–7.71 (m, 1H), 7.50–7.44 (m, 4H), 6.86 (d, 1H, $J = 8$ Hz), 5.33 (s, 2H), 4.41–4.35 (m, 2H), 4.11 (d, 2H, $J = 16$ Hz), 3.73 (s, 3H), 2.21–2.16 (m, 1H), 1.99–1.97 (m, 1H), 0.96–0.94 (m, 6H), 0.80 (d, 3H, $J = 6.80$ Hz), 0.71 (d, 3H, $J = 6.80$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$ containing two drops of d_6-DMSO): δ 171.9, 171.7, 171.6, 163.9,

140.0, 138.9, 135.5, 134.5, 133.5, 131.9, 131.3, 128.5, 128.0, 127.9, 127.4, 126.3, 125.8, 125.5, 123.8, 62.3, 59.4, 58.2, 52.1, 30.8, 30.57, 30.50, 19.1, 18.8, 17.9, 17.8; FT-IR: ν cm^{-1} (KBr): 3631, 3406, 3103, 2968, 1740, 1693, 1656, 1596, 1537, 1508; HRMS (TOF MS ES$^+$): calcd for $(M - PF_6)^+$: 533.2758, found: 533.2750.

Preparation of anionic guests

All the tetrabutylammonium salts were prepared by adding 1 equivalent of tetrabutylammonium hydroxide in methanol to a solution of carboxylic acid (1 equivalent) in methanol. The mixture was stirred at room temperature for 3 h and evaporated to dryness under reduced pressure. The gummy mass was further dried under vacuum for 24 h.

Binding constant determination[14]

Binding constant values were determined using the fluorescence titration data. The nonlinear fit of the titration data was done using equation: $I = I_0 + (I_{lim} - I_0)/2C_H\{C_H + C_G + 1/K_a - [(C_H + C_G + 1/K_a)^2 - 4C_HC_G]^{1/2}\}$ where I represents the intensity; I_0 represents the intensity of pure host; C_H and C_G are the corresponding concentrations of host and anionic guest; K_a is the binding constant. The binding constant (K_a) and the correlation coefficient (R) were obtained from a nonlinear least-square analysis of I *vs.* C_H and C_G.

Quantum yield determination

Quantum yields of the compounds were determined in CH_3CN by the relative comparison procedure using naphthalene as standard ($\Phi_{Nap} = 0.23$ in cyclohexane).[12a] The general equation used in the determination of relative quantum yields is as follows:[12b–c]

$$\Phi_u = (\Phi_s \times F_u \times A_s \times \lambda_{exs} \times \eta_u^2)/(F_s \times A_u \times \lambda_{exu} \times \eta_s^2)$$

where Φ is the quantum yield, F is the integrated area under the corrected emission spectrum, A is the absorbance at the excitation wavelength, λ_{ex} is the excitation wavelength, η is the refractive index of the solution and the subscripts 'u' and 's' refer to the unknown and the standard, respectively.

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