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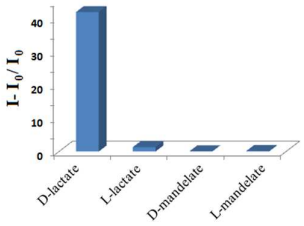
GRAPHICAL ABSTRACT

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

Kumaresh Ghosh*, and Anupam Majumdar

A series of L-amino acid derived pyridinium-based chiral compounds **1**-**6** have been designed and synthesized. Among the chiral compounds, compound **1** shows enantioselective recognition of D-lactate in fluorescence. Structural tuning of **1** introduces compound **6** that displays good enantioselectivity of lactate (*ef* = 28.33 for D-lactate).



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ARTICLE TYPE

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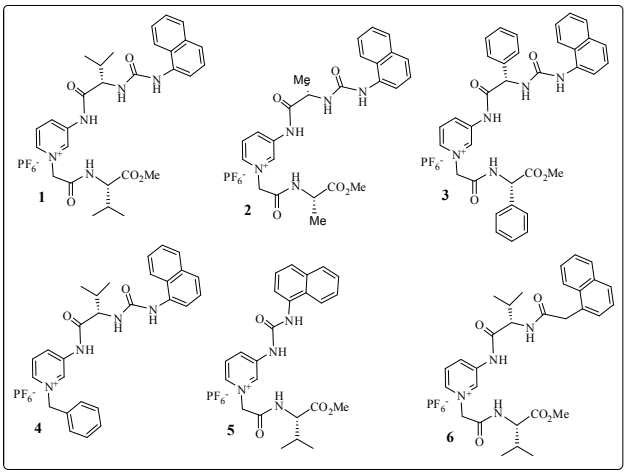
A series of pyridinium-based chiral compounds **1-6** have been designed and synthesized. L-Amino acid has been used as the chiral source in the molecules. Among the chiral compounds, L-valine derived compound **1** has been found to exhibit enantioselective recognition of D-lactate in fluorescence. Structural tuning of **1** either by replacing L-valine with L-alanine or L-phenylglycine or by reducing the number of chiral centre around the binding site does not show any significant enantioselectivity in the recognition process. Change of urea site by amide in **1** introduces compound **6** that displays good enantioselectivity of lactate (enantiomeric fluorescence difference ratio *ef* = 28.33 for D-lactate); even better than compound **1** and 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 which 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 over few decades.[2] Chiral fluorescence-based sensor can be used in rapid determination of enantiomeric composition as well as high-throughput catalysts 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 last 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** that 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 details emphasizing on 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 enantioselective recognition of carboxylate-based substrates is unknown in the literature except our recent example on structure **1**.[8]

Results and discussion

Compounds **1-6** were synthesized according to the Schemes 1 and 2. Following our reported reaction protocols for the synthesis of **1**,[8] compounds **2** and **3** were synthesized (Scheme 1). Boc

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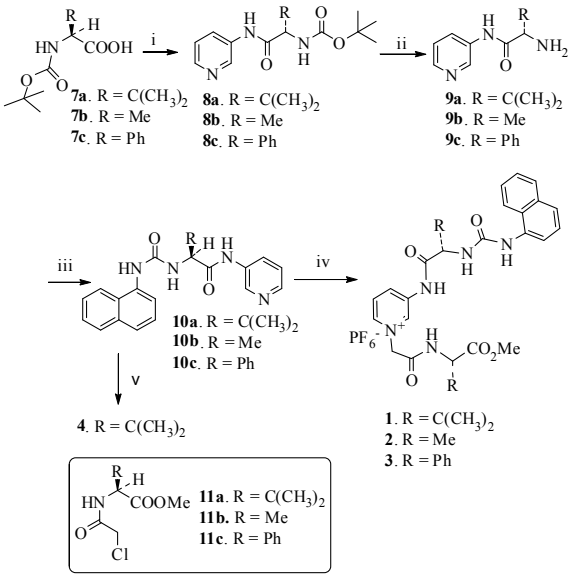
†Electronic Supplementary Information (ESI) available Figures showing the change in fluorescence and UV-vis titrations of receptors **1**-6 with various chiral anions, Job plot, binding constant table, ^{1}H NMR titration and other spectral data. See http://dx.doi.org/10.1039/b000000x/

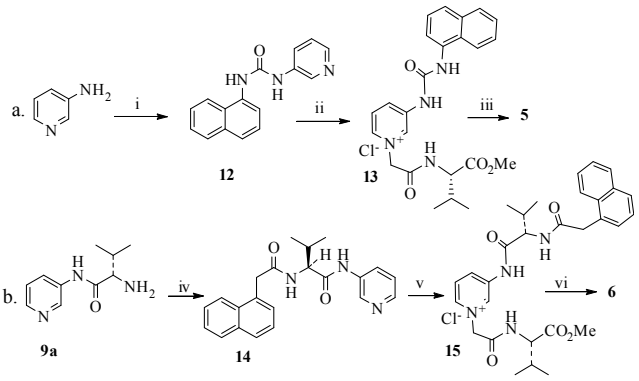
protected L-amino acids such as valine **7a**, alanine **7b** and phenyl glycine **7c** were reacted with 3-aminopyridine in the presence of dicyclohexylcarbodiimide (DCC) to have the coupled products **8a-c**, respectively. Removal of the Boc-groups in **8a**, **8b** and **8c** using trifluoroacetic 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 undertaken. Individual reflux of compounds **10a-c** in 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 have 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 the compound **4**.



Scheme 1. i. 3-Aminopyridine, DCC, CH_2Cl_2, 20 h; ii. TFA, CH_2Cl_2, 3 h; iii. 1-naphthyl amine, triphosgene, Et_3N, CH_2Cl_2, 16 h, iv. a. **10a**/**10b**/**10b**, 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.

Compounds **5** and **6** were synthesized according to the 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** introduced 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.

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



Scheme 2. a. i. 1-Naphthylamine, triphosgene, Et_3N, CH_2Cl_2, 18 h; ii. **10a**, 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.

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 undertaken. In our earlier report[8] it has been shown that compound **1** selectively recognizes D-lactate over L-lactate with *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. For understanding the structural role of L-valine (chiral source) in **1**, we studied compound **2** which bears L-alanine instead of L-valine. Fluorescence study of **2** (c = 3 x 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

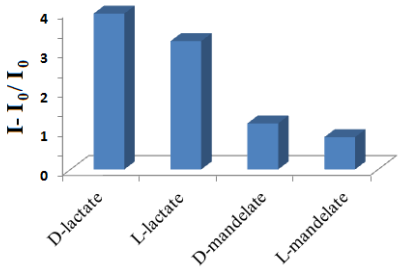


Figure 1. Change in fluorescence ratio of **2** (c = 3 x 10^{-5} M) upon addition of 20 equiv. amounts of guests in CH_3CN at 406 nm (λ_{exc} = 300 nm).

2 at 378 nm was increased with a red shift of ~28 nm. But the change in emission for each pair occurred nearly to the same extent (Fig. S1, ESI). Only in case of D-lactate it was slightly

more (*ef* = 1.16). Figure 1, in this regard, shows the change in emission of **2** in the presence of 20 equiv. amounts of D/L-lactates and mandelates in CH_3CN. As can be seen from Fig. 1, receptor structure **2** shows preferential binding to the isomers of lactates than mandelate. But the enantioselection was insignificant. This was also true in the ground state. In UV-vis study, no marked difference in absorption spectra of **2** during titration was observed (Fig. S2, ESI).

Under identical conditions fluorescence study of **3** (c = 3 x 10^{-5} M) which contains L-phenyl glycine as the chiral source also revealed poor enantio discrimination in CH_3CN. On addition of the guests to the solution of **3** in CH_3CN the emission of **3** at ~ 400 nm was increased (Fig. S3, ESI) to the same extents and in case of L-lactate it was little more (*ef* = 1.08). Figure 2 represents the change in emission ratio of **3** in the presence of 6 equiv. amounts 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 absorption spectra of **3** was observed in presence of the guests (Fig. S4, ESI).

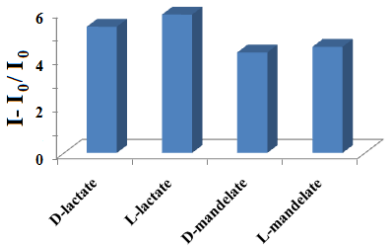


Figure 2. Change in fluorescence ratio of **3** (c = 3 x 10^{-5} M)) upon addition of 6 equiv. amounts of guests in CH_3CN at 405 nm (λ_{exc} = 300 nm).

Thus, this study corroborates that in the present study, valine with steric isopropyl substituent at the [alpha]- 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 chiral discrimination of [alpha]-hydroxycarboxylate. For this, compounds **4** and **5** were synthesized. While in **4** the L-valine unit is present at the 3-position of 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 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 *ef* of 1.18 (Fig. 3b). These observations underline the fact that the presence of L-valine as a single unit either at ring nitrogen or at amine function of 3-aminopyridine does not draw much attention to cause enatiodiscrimination of lactate.

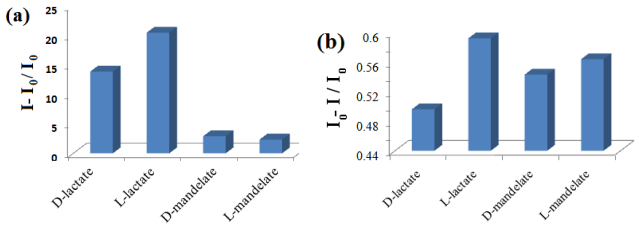


Figure 3. Change in fluorescence ratio of (a) **4** (c = 3 x 10^{-5} M)) upon addition of 13 equiv. amounts of guests in CH_3CN at 402 nm (λ_{exc} = 300 nm).and (b) **5** (c = 3 x 10^{-5} M)) upon addition of 19 equiv. amounts of guests in CH_3CN at 401 nm (λ_{exc} = 300 nm).

Now to evaluate the potentiality of urea functionality in the design, we then considered amide analogue **6**. A thorough fluorescence study of **6** (c = 3 x 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 the solution of **6** in CH_3CN while the emission at 338 nm was decreased to the 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. Figure 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 change in emission was found. No peak at 425 nm was noticed during interaction (Fig. S9, ESI). It is thus presumed that the peak at 425 nm in presence of the lactates is due to the formation of intermolecular excimer between the naphthalenes.[11] Mandelate being more steric than lactate is weakly involved in binding and thus is unable to form intermolecular chelation, responsible for excimer emission.

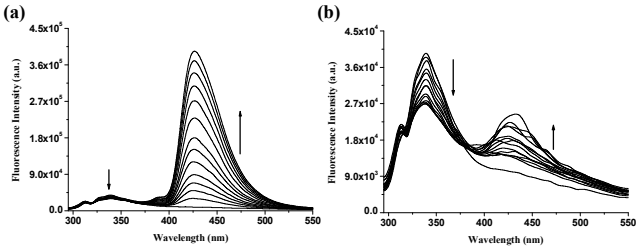


Figure 4. Fluorescence titration spectra for **6** (c = 3 x 10^{-5} M) in CH_3CN with tetrabutylammonium salts of (a) D - and (b) L - lactic acids (in all cases 6 x 10^{-4} M is a maximal concentration of anion applied; λ_{exc}= 285 nm).

Figure 5 shows the emission ratio of **6** in the presence of D/L-lactates and mandelates in CH_3CN. As can be seen from Figure 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 the salen-based chiral fluorescent sensor reported by Song *et. al.*[5g] It is further to be pointed out that quantum yield[12] of **6** is much enhanced upon interaction with D-lactate than L-lactate. The increment is considerable with respect to the receptor **1** (ESI, Table S1). Thus the amide analogue **6** is

established to be efficient than **1** in enantioselective recognition of lactate.

In the interaction process, the stoichiometry of interaction of **6** with both D- and L-lactates was determined to be 1:1 as confirmed by Job's plot[13] (Fig. S11, ESI). In this context, it is to be pointed out that the appearance of intermolecular excimer between the naphthalenes in Fig. 4 may be originated from the equilibrium species with stoichiometry of adducts 1:1 (polymeric assembly), 2:2 or others. However, the binding constant value[14]

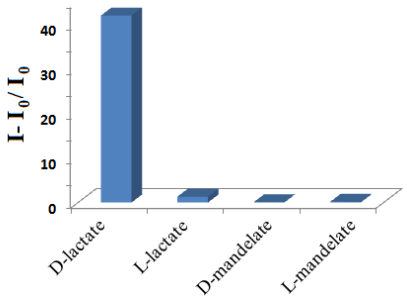


Figure 5. Change in fluorescence ratio of **6** (c = 3 x 10^{-5} M)) upon addition of 17 equiv. amounts of guests in CH_3CN at 425 nm.

was determined from non linear fit of the emission titration data and it was found to be (1.55 ± 0.19) x 10^4 M^{-1} for D-lactate (Figure 6). For L-lactate, it was determined to be (5.29 ± 0.89) x 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 in non linear equation to determine the binding constant values for both the stereoisomers of mandelates. A comparison of the binding constant values as shown in the Table S2 (ESI) represents that the receptor **6** among the designs exhibits stronger binding towards D-lactate.

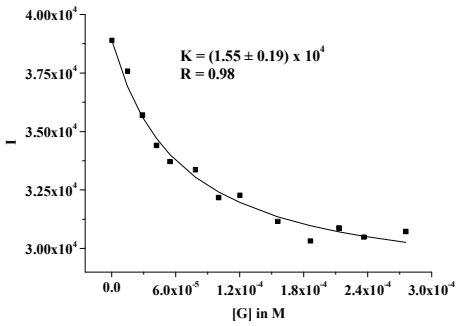


Figure 6. Nonlinear curve fitting of the fluorescence titration data for **6** with D – lactate.

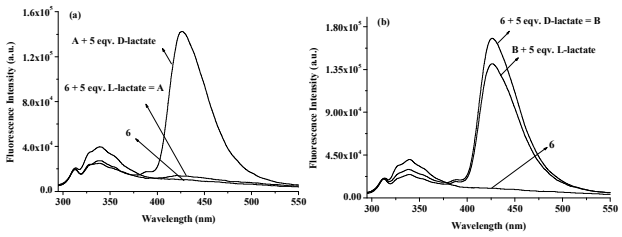
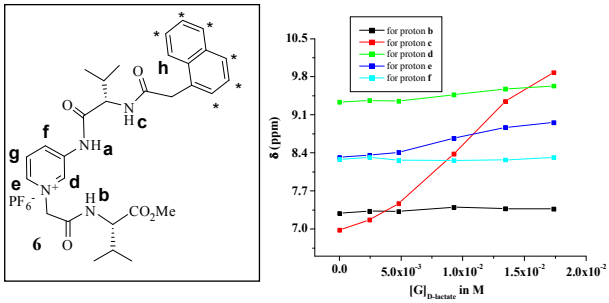


Figure 7. Fluorescent response of **6** (c = 3 x 10^{-5} M) to (a) D- lactate (c = 6 x 10^{-4} M) in the presence of L-lactate (c = 6 x 10^{-4} M) and (b) L -lactate (c = 6 x 10^{-4} M) in presence of D -lactate (c = 6 x 10^{-4} M) in CH_3CN.

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. Figure 7, in this context, demonstrates these features. L-lactate induced change in emission of **6** was further perturbed to the considerable extent upon addition of D-lactate (Fig. 7a). The reverse one was observed to be insignificant (Fig. 7b).

For practical application, 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 study the interaction of **6** with the lactate isomers in ^1H NMR, 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 ^1H NMR 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. Amide proton of type 'a' became invisible in the presence of 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 small change in chemical shift upon complexation. The participation of the pyridinium motif in complexation was also



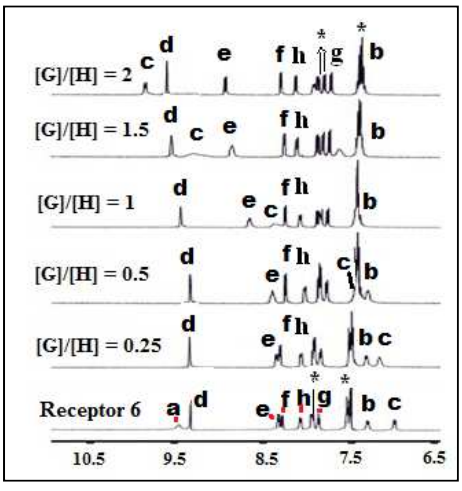


Figure 8. Partial ^1H NMR (400 MHz, CD_3CN) of **6** (c = 1 x 10^{-2} M) in the absence and presence of *D*-lactate [Inset: Change in chemical shift values for the interacting protons with guest concentration].

recognized from the downfield chemical shifts of the *ortho* protons of types'd' and 'e'. Plot in the inset of Fig. 8 represents the change in chemical shifts of the different interacting protons with guest concentrations. It is to note that during interaction some signals for naphthalene ring protons (asterisk marked in Fig. 8; for details see Fig. S14) in the regions 7.93 ppm and 7.50 ppm underwent upfield chemical shift when D-lactate was gradually added. Guest-induced intermolecular chelation of the receptors in solution probably gives a situation where 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 ^{1}H NMR of **6** was noted upon gradual addition of L-lactate although the change in chemical shift of the interacting protons was less compared to 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 realize the hydrogen bonding features of the receptor **6** with the lactate isomers and also the corresponding stabilities of the discrete 1:1 adducts in gas phase through DFT calculation . DFT optimization[15] was done in gas phase using 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 by 4.56 kcal/mol more strongly than L-isomer. Figure 9 represents the DFT optimized structures in gas phase with hydrogen bonding scheme.

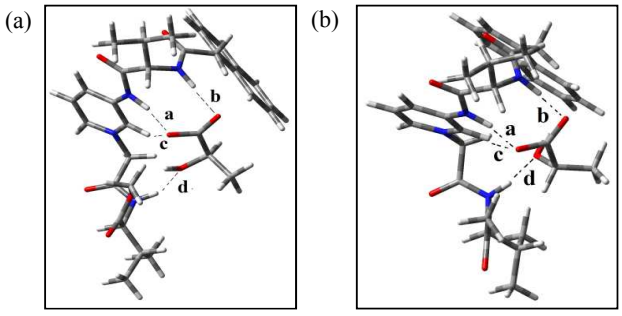


Figure 9. DFT optimized geometries of the complexes of (a) **6**.D-lactate (Hydrogen bond distances in Å: a = 1.60, b = 1.95, c = 2.19 and d = 1.78); and (b) **6**.L-lactate in gas phase (Hydrogen bond distances in Å: a = 1.52, b = 1.92, c = 2.39 and d = 1.79).

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 enantioselective sensing of D-lactate over its mirror image. Both the structures contain L-valine unit as the chiral source that brings good enantioselectivity in the recognition process. Other amino acids such as L-alanine and L-phenyl glycine as 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 effect and charge-charge interactions play important role in the recognition process. It is further mentionable that between **1** and **6**, the receptor structure **6** with the amide functionality at the site of naphthalene instead of 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 supporting information (ESI). Compounds **2**, **3** and the intermediates such as **8b-c**, **10b-c** and **11b-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), benzyl bromide (0.06 g, 0.35 mmol) was added 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 gummy product (0.11 g, yield: 74%). In the next step, based on the procedure of anion exchange as followed in case of **1**, the bromide ion was exchanged with 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 ^{0}C, $[\alpha]_D^{25}$ = 19.41 (c = 0.618 gm/100 mL, CH_3CN), ^{1}H 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 $(M\text{-}PF_6)^+$: 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), 3-aminopyridine (0.16 g, 1.7 mmol) dissolved in dry CH_2Cl_2 (25 mL) was added 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 x 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 ^{0}C, ^{1}H 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 unresolved); 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), compound **10a** (0.12 g, 0.577 mmol) dissolved in dry CH_3CN (5 mL) was added 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 case of compound **1**, the chloride anion in **13** was exchanged with 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 ^{0}C, $[\alpha]_D^{25}$ = - 9.5 (c = 0.524 gm/100 mL, MeOH), ^{1}H 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 (0ne 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-naphthyl acetic acid (0.2 g, 1.07 mmol), in dry CH_2Cl_2 (15 mL), oxalyl chloride (0.2 ml, 2 equiv.) and two drops of dry DMF was added and the stirring was continued for 6 h. Then solvent was evaporated off *in vacuo* to give the desired 1-naphthyl acetyl chloride. This was directly used in the next step. 1-Naphthyl acetyl chloride was dissolved in dry CH_2Cl_2 (10 mL) and to this solution amine **9a** (0.25 g, 1.2 mmol) taken 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 reaction, solvent was removed under reduced pressure, water was added to the residue, and the product was extracted with $CHCl_3$ (25 mL x 2), dried over anhydrous Na_2SO_4. Evaporation of 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 ^{0}C, $[\alpha]_D^{25}$ = -1.99 (c = 0.502 gm/100 mL, $CHCl_3$), ^{1}H 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), compound **11a** (0.11 g, 0.529 mmol) in dry CH_3CN (5 mL) was added and the reaction mixture was refluxed for 3 days. The crude 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 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 gm/100 mL, CH_3CN), ^{1}H 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: $I = I_0 + (I_{lim} - I_0) / 2C_H \{C_H + C_G + 1/Ka - [(C_H + C_G + 1/Ka)^2 - 4C_HC_G]^{1/2}\}$ where I represents the intensity; I_0 represents the intensity of pure host; C_H and C_G are corresponding concentration 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 yield of the compounds was determined in CH_3CN by the relative comparison procedure using naphthalene as standard (Φ_{Nap} = 0.23 in cyclohexane).[12a] The general equation used in the determination of relative quantum yields is as follows.[12b-c]

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

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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