Cholic acid-based fluorescent probes for enantioselective recognition of trifunctional amino acids†‡

Hao Wang, Wing-Hong Chan* and Albert W. M. Lee

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The ditopic fluorescent photoinduced electron transfer (PET) amino acid sensory probes **1a** and **1c** were designed and synthesized from cholic acid. To confer the probes with specific binding ability, an amidothiourea moiety and a cyclic diamino-chiral receptive site were introduced on the C17 side chain and the C7 and C12 hydroxyl pendants, respectively. In acetonitrile, the probes demonstrated differential binding toward trifunctional amino acids like serine, lysine, threonine and tyrosine against other simple amino acids. Enantioselectivities (K_D/K_L) of up to 8.9 and sensitivities in the micromolar range with the probes were observed for trifunctional amino acids.

Introduction

The design and development of molecule-based fluorescent sensing probes targeted at biologically important substrates such as amino acids and α-hydroxyacids have been attracting much research interest recently since it can provide valuable information for understanding the mechanism of molecular recognition in biological systems.[1] By introducing chirality into the binding site, the resulting fluorescent host molecule could carry out enantioselective recognition of chiral organic molecules. In connection with this, a number of fluorescent probes based on azacrown, binaphthol, crown ether, cyclodextrin, calixarene, cyclic (thio)urea, cyclophane, 1,8-diacridylnaphthalene, guanidinium salt and terpyridine macrocycle have been developed for enantiomeric recognition of amino acids and their derivatives.[2] Pioneered by the seminal works of Davis and others, cholic acid has proven to be a promising molecular scaffold to prepare supramolecular systems for molecular recognition.[3] Recently, we have discovered for the first time that the flexible side chain attached to C17 of cholic acid can be exploited to introduce a ligating group onto the C24 as an additional binding site for binding multi-functional small molecules.[4] To continue our interests in chemosensor development, in this study, we have exploited cholic acid as the chiral molecular framework to prepare fluorescent sensing probes for the enantioselective detection of trifunctional amino acids.

At the outset of the investigation, to construct cholic acid based enantioselective amino acid probes, we envisage that two synthetic strategies ought to be considered: (1) at least two binding sites must be incorporated into the host to ascertain a sufficiently strong interaction with guest analytes; and (2) an additional chiral moiety must be introduced onto the cholic acid scaffold close to the binding cavity so as to enhance the enantioselectivity ability of the probe toward chiral guests. Our previous studies revealed that the appendage of amidothiourea as a carboxylate binding site and an anthracene moiety as the fluorescent display unit can be achieved through the manipulation of the C17 side chain of cholic acid. The two axial hydroxyl groups at C7 and C12 could be utilized as useful pendants to append the second binding site and at the same time an additional chiral moiety could be introduced. To execute this strategy, chiral *trans*-1,2-diaminocyclohexane (DACH) would be a judicious choice to be incorporated onto the cholic acid scaffold to enhance enantioselectivity of the host. DACH is a widely used building block in asymmetric organocatalyst development,[5] after its appendage onto the backbone of cholic acid, the vicinal diamino groups could reorganize to provide a semi-rigid enantioselective receptive site to bind amino or hydroxyl functionality.

Results and discussion

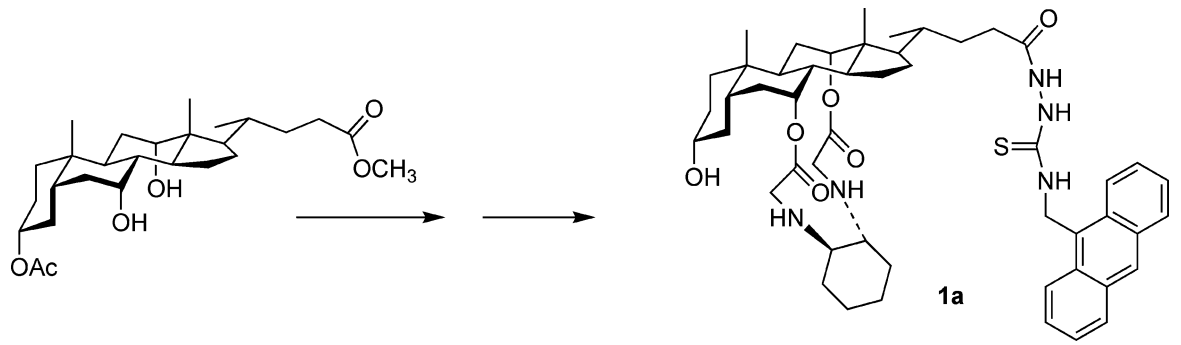
To execute the aforementioned strategy, starting from methyl 3-acetoxycholate, ditopic probe **1a** (Fig. 1) was constructed *via* a 5-step reaction sequence outlined in Scheme 1. The probe was recently exploited by us as a sensitive chemosensor for the detection of ATP.[6] To fully utilize the chirality inherited from both cholic acid and *trans*-1,2,-diaminocyclohexane as viable enantioselective probes, we envision that **1a** would display a high degree of enantioselectivity toward complementary guest molecules. The ditopic nature of the host would confer it with binding affinity to poly-functional guest molecules. For instance, the flexible C24 side chain bearing an amidothiourea group would bind strongly with carboxylate while the cyclic vicinal amino groups attached to the C7 and C12 could work cooperatively to provide an additional binding site for hydroxyl and amino groups. We anticipate that a number of trifunctional amino acids such as serine, threonine, lysine and tyrosine would be good candidates for the binding study. To shed light on the binding mechanism, the control compound **1b**, lacking the cyclic diamino chiral receptive site, was synthesized from methyl cholate in a two-step sequence.[4]

To investigate the binding characteristics and the enantioselectivity of host **1a** in molecular recognition, L-serine was first

Department of Chemistry, Hong Kong Baptist University, Kowloon Tong, Hong Kong SAR, China. E-mail: whchan@hkbu.edu.hk; Fax: +86 852 34117348; Tel: +86 852 34117076

† This paper is dedicated to Professor H. J. Liu on the occasion of his 65th birthday.

‡ Electronic supplementary information (ESI) available: Binding saturation curves based on ^{1}H NMR titrations of probe **1a** with antipodal forms of serine; binding free energy differences of diastereomeric complexes between amino acids and chiral hosts; molecular modeling studies of **1a**–serine complexes; solvent effect on the binding properties of **1a**. See DOI: 10.1039/b717544b



Scheme 1 Synthetic route for fluorescent chemosensor **1a**.[6]

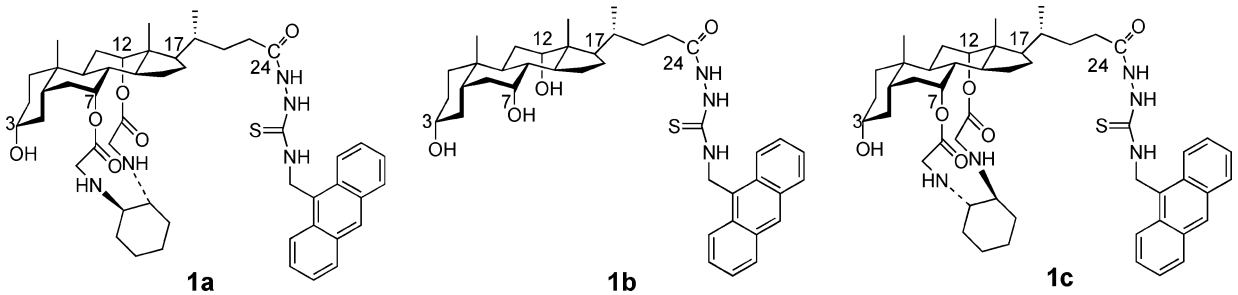


Fig. 1 Structures of fluorescent sensors **1a**, **1b**, **1c**.

selected as the guest. To evaluate the binding affinity of the host to the guest, fluorometric titration experiments were carried out with the concentration of **1a** fixed at 1.0×10^{-6} M in acetonitrile and the guest concentration (as tetrabutylammonium salt) was varied from 2.0×10^{-7} M to 7.0×10^{-5} M in acetonitrile. When the solution was excited at 366 nm, **1a** gave a characteristic emission spectrum with a monomeric anthracene maximum at *ca.* 413 nm. As shown in Fig. 2a, the fluorescent emission band at 413 nm was quenched gradually upon the addition of the guest. The complexation of the carboxylate of serine to the amidothiourea group of the host can enhance its electron density favoring the photo-induced electron transfer (PET) to the anthracene moiety. Consequently, the fluorescence of the probe decreases as the concentration of serine is increased.[4]

On the basis of Job's plot, a 1 : 1 complex between the host and the guest was confirmed (Fig. 3). When the same experiment was performed on D-serine, the 1 : 1 stoichiometry of the complex was maintained, yet a greater extent of quenching was observed.

The emission spectrum of **1a** was quenched by as much as 80% with the addition of 10 equivalents of D-serine (Fig. 2b). On the basis of the change of fluorescent intensity associated with the gradual addition of the guest molecule, the association constants of the two diastereomeric complexes (K_{ass}) were calculated using nonlinear least-squares curve fitting (entries 1 and 2, Table 1).[7] It is apparent that the respective association constant of the host to L- and D-serine differs by 6.7 fold, indicating the high enantioselectivity of the host toward the guests.[8]

On the other hand, the ^{1}H NMR spectroscopic studies were also employed to evaluate the binding interaction of the host and serine. The results corroborated with the findings of the fluorometric experiments (*vide infra*). To simplify the NMR titration results, by eliminating the proton signals of the counter-cation (*i.e.* tetrabutylammonium), **1a** was allowed to titrate directly with serine in dried CD_3CN. As shown in Fig. 4, when the probe was individually mixed with 1 equivalent of L-serine and D-serine anion in CD_3CN, a substantial upfield shift of the methylene protons (labeled with ★) adjacent to the anthracene moiety was observed. An upfield shift of anthracenylmethylene protons from δ5.51 of the pure **1a** to δ5.26 and 4.78 was observed in the corresponding diastereomeric serine–host complex, respectively (labeled with ★ in Fig. 4a, b, c). At the same time, in the presence of chiral **1a**, the α-H of L-serine and D-serine centered at δ3.92 underwent an upfield shift to δ3.32 and 3.13, respectively (labeled with ☆ in Fig. 4b, c, e). Most importantly, when a racemic mixture of serine was mixed with 1 equivalent of **1a**, the α-proton of each enantiomer of serine centered at δ3.90 resolved clearly into two distinctive multipets at δ3.32 and 3.10, respectively. Consistent with the fluorometric measurements, in contrast to the **1a**–L-serine complex, the stronger binding between host **1a** and D-serine induced a larger upfield shift for both the anthracenylmethylene protons of the host (0.73 ppm *vs.* 0.25 ppm) and the α-hydrogen of serine (0.72 ppm *vs.* 0.60 ppm). To probe the binding mode of the host–guest complex, molecular modeling studies were conducted by using SPARTAN 04. Interestingly, revealed by the modeling, in the stable conformation of the **1a**–D-serine complex, the amino group of D-serine can form a H-bond with the C12 pendant ester oxygen atom. On the other hand, in the stable conformation of the **1a**–L-serine complex, the amino group of L-serine oriented away from the cholic acid core and precluded the formation of H-bonding (S-Fig. 2, ESI‡). Such a binding mode was further substantiated by investigating the binding of **1a** with the control compound *N*-acetyl D-serine. By transforming the amino group of serine into an *N*-acetyl group, the possibility of forming an additional H-bond was eliminated. As expected, the binding

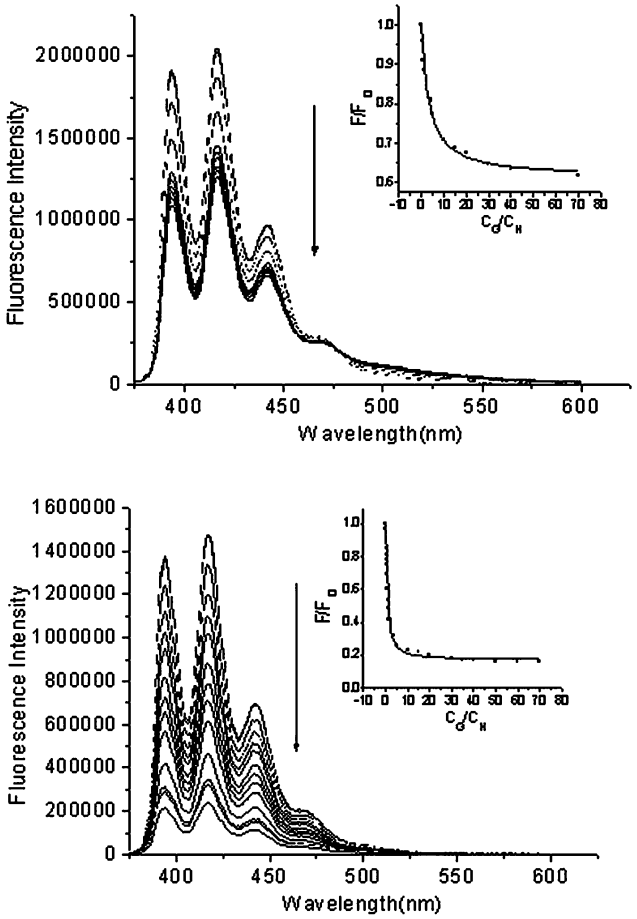


Fig. 2 (a) Fluorescence spectra of **1a** (1.0 μM) upon addition of L-serine in CH_3CN. Excitation wavelength was 366 nm. (b) Fluorescence spectra of **1a** (1.0 μM) upon addition of D-serine in CH_3CN. Excitation wavelength was 366 nm. Inset is the titration data point and the nonlinear least-squares fitting curve.

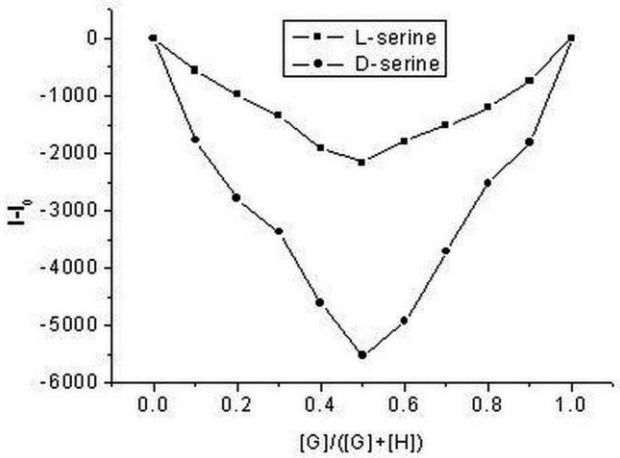


Fig. 3 Job's plot of **1a** with L- and D-serine anions in CH_3CN.

constant of **1a** and *N*-acetyl D-serine decreased to $2.84 \pm 0.38 \times 10^4$, which is very close to the binding constant of **1a** and L-serine (*i.e.* $3.36 \pm 0.23 \times 10^4$). On the basis of the NMR data and the molecular modeling, the binding mode of the host and D-serine is depicted in Fig. 5.

Detailed ^1H NMR titration of **1a** toward antipodal forms of serine in CD_3CN was undertaken. By monitoring the complexation induced chemical shift (CIS) of the anthracenylmethylene protons of the host, the binding constant of **1a** and L-serine, D-serine was found to be $(3.18 \pm 0.21) \times 10^4$, $(2.44 \pm 0.06) \times 10^5$, respectively (S-Fig. 1 and S-Table 1, ESI‡).[9] The binding constants obtained are in good agreement with those obtained from the fluorescent titrations (Table 1).

To define the scope of application of the host, we also extended our study to include the interaction of **1a** with other trifunctional amino acids. As reflected by the observed values of the association constants of the complexes shown in Table 1, the binding interaction of the host to serine is slightly stronger than that of the host to threonine, lysine and tyrosine. Apparently, the steric hindrance of the substituent present in threonine, lysine and tyrosine did not preclude its strong interaction with the host. Conceivably, the two proximal amino groups of the host could reorganize in such a manner to effectively interact with hydroxyl group, amino

Table 1 Association constants K_{ass} (M^{-1}) and relative coefficients (R) of sensors **1a**, **1b** and **1c** with various amino acids (as their tetrabutylammonium salts) in CH_3CN

	Host **1a**			Host **1b**		Host **1c**		
Guests	K_{ass}[a]	R[a]	K_D/K_L	K_{ass}[a]	R[a]	K_{ass}[a]	R[a]	K_L/K_D
L-serine	$(3.36 \pm 0.23) \times 10^4$	0.9951		$(1.75 \pm 0.16) \times 10^3$	0.9942	$(1.97 \pm 0.12) \times 10^5$	0.9935	6.2
D-serine	$(2.26 \pm 0.17) \times 10^5$	0.9966	6.7	$(1.77 \pm 0.17) \times 10^3$	0.9944	$(3.18 \pm 0.19) \times 10^4$	0.9971	
L-threonine	$(2.05 \pm 0.03) \times 10^4$	0.9985		$(1.37 \pm 0.09) \times 10^3$	0.9951	$(1.54 \pm 0.09) \times 10^5$	0.9977	8.1
D-threonine	$(1.82 \pm 0.14) \times 10^5$	0.9954	8.9	$(1.36 \pm 0.09) \times 10^3$	0.9953	$(1.90 \pm 0.13) \times 10^4$	0.9963	
L-lysine	$(1.70 \pm 0.12) \times 10^4$	0.9933		$(1.28 \pm 0.11) \times 10^3$	0.9970	$(0.98 \pm 0.16) \times 10^5$	0.9948	7.4
D-lysine	$(1.37 \pm 0.11) \times 10^5$	0.9970	8.1	$(1.25 \pm 0.12) \times 10^3$	0.9967	$(1.31 \pm 0.08) \times 10^4$	0.9925	
GABA	$(1.22 \pm 0.09) \times 10^4$	0.9968		$(1.05 \pm 0.07) \times 10^3$	0.9971	$(1.21 \pm 0.09) \times 10^4$	0.9946	
L-tyrosine	$(2.57 \pm 0.18) \times 10^4$	0.9981		$(1.52 \pm 0.12) \times 10^3$	0.9962	$(1.77 \pm 0.05) \times 10^5$	0.9913	7.2
D-tyrosine	$(1.94 \pm 0.09) \times 10^5$	0.9936	7.5	$(1.53 \pm 0.13) \times 10^3$	0.9959	$(2.44 \pm 0.16) \times 10^4$	0.9930	
L-cysteine	$(1.22 \pm 0.11) \times 10^3$	0.9962		982 ± 12	0.9928	$(4.36 \pm 0.12) \times 10^3$	0.9918	
L-glycine	863 ± 29	0.9947		827 ± 14	0.9948	$(2.19 \pm 0.05) \times 10^3$	0.9944	
L-alanine	525 ± 17	0.9978		503 ± 10	0.9956	$(1.27 \pm 0.11) \times 10^3$	0.9939	
L-valine	—[b]	—[b]		—[b]	—[b]	—[b]	—[b]	
L-phenylalanine	—[b]	—[b]		—[b]	—[b]	—[b]	—[b]	

[a] The values were calculated from the change in the fluorescence spectra. [b] The value is too small to be calculated.

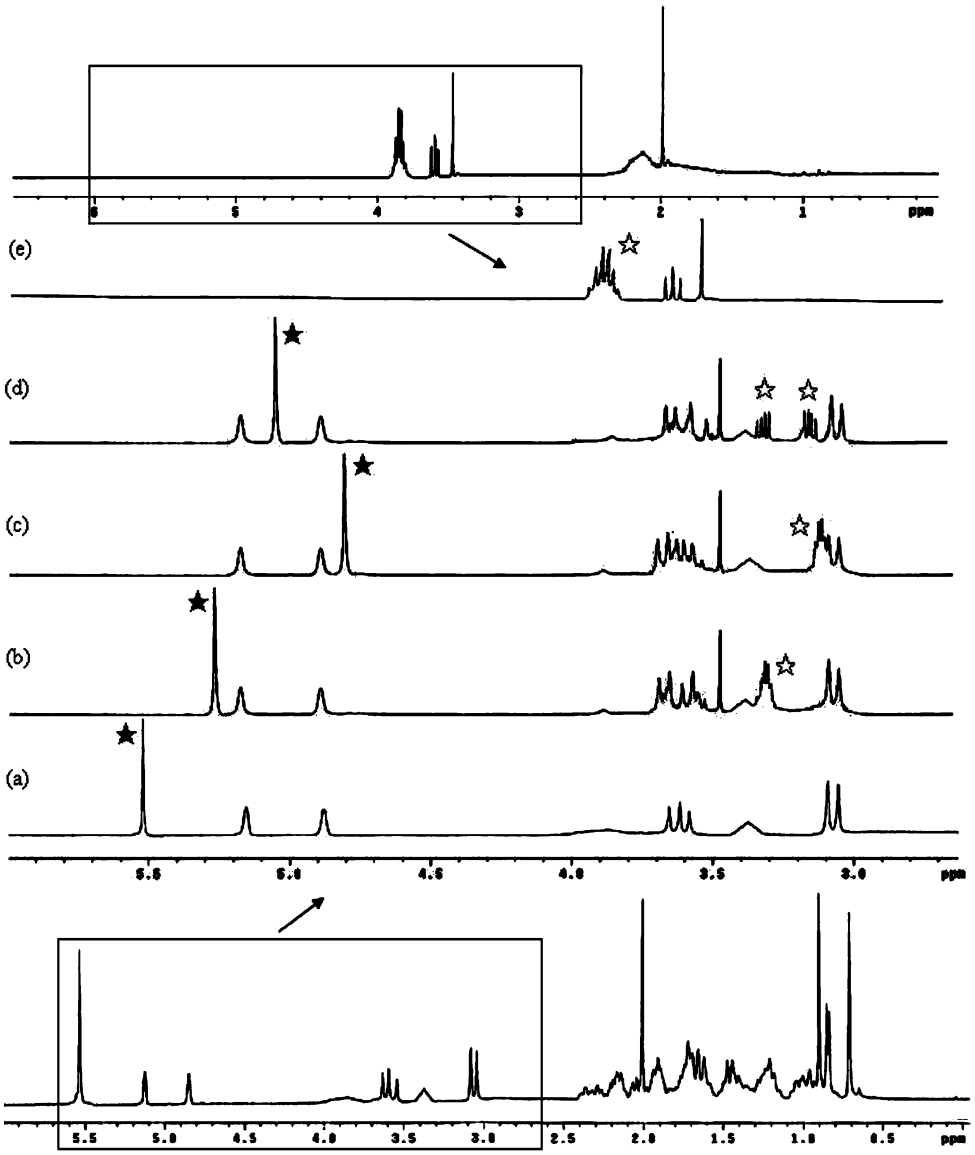


Fig. 4 Partial ^{1}H NMR spectra for (a) probe (free), (b) probe + L-serine (1 equiv.), (c) probe + D-serine (1 equiv.), (d) probe + racemic serine (1 equiv.), (e) serine in CD_3CN. [probe] = [serine] = 2×10^{-2} M.

group or phenolic group *via* hydrogen bonding. Furthermore, the importance of this hydrogen bonding in the host–guest interaction

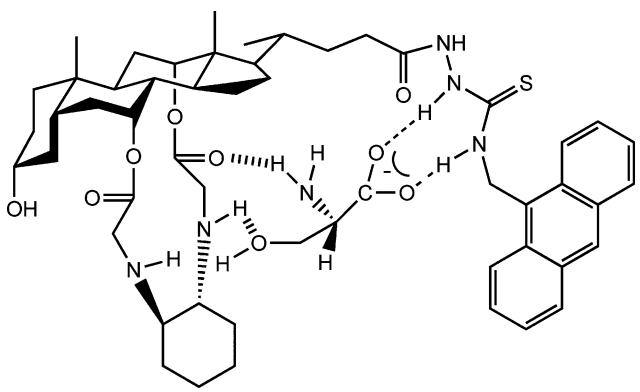


Fig. 5 Proposed binding mode of host **1a** with D-serine.

is evident by comparing the complex between the host and serine to that between the host and cysteine. The inability of the thiol group to form a strong hydrogen bond with the chiral receptor reduced the corresponding association constant by a factor of 25 fold. Among the four pairs of enantiomeric amino acids, the host showed a consistent bias for the D-amino acids with high K_D/K_L values from 6.7 to 8.9. The relative free energy differences of the four pairs of diastereomeric complexes of **1a** and trifunctional amino acids were found to be fairly substantial values ranging from 1.11 to 1.27 kcal mol^{-1} (S-Table 2, ESI‡). To provide more insight into the host–guest interaction, fluorescent titration experiments of the control compound **1b** and various amino acids were carried out. By removal of the receptive site located in the core of the host, the association constants of host **1b** and each of the trifunctional amino acid guests are 110 to 130 times lower than that of the ditopic probe **1a** and the respective guest. Interestingly, host **1b** failed to impart any

chiral discrimination ability toward the D- and L-series of serine, threonine and lysine. Evidently, the semi-rigid chiral receptive site of **1a** conferred by *trans*-1,2-diaminocyclohexane not only provided an additional binding site for binding guests but also played a crucial role in manifesting the enantioselective properties of the host. Furthermore, in contrast to our reported cholic acid based dicarboxylate chemosensor, the more rigid chiral receptor stretching out from the C7 and C12 hydroxyl pendants must be responsible for the high enantioselectivity exhibited by the present probe.[10] With regard to the size of the binding cavity, a much longer chain length between the terminal amino and carboxylate group of lysine and GABA did not preclude their strong binding with host **1a**. Apparently, the flexible C24 side chain possessing a carboxylate receptive site could accommodate guests of different chain length equally well. It is noteworthy that simple steric free α-amino acids like glycine and alanine bind only marginally with both host **1a** and the control compound **1b** with an association constant of similar value. Presumably, the molecular length defined by the amino and carboxylate group of these compounds is not long enough to reach the minimum distance separating the two receptors of host **1a**. The results strongly suggested that only the C24 amidothiourea receptive site of both hosts can interact with the carboxylate group of glycine and alanine. By increasing the bulkiness of the α substituent of the amino acids, as exemplified by valine and phenylalanine, no host–guest interaction was observed between both hosts **1a** and **1b** and the amino acid guests. To address the "match/mismatch" effect on enantioselective recognition, using the same synthetic protocol described in Scheme 1, the corresponding diastereomeric sensor **1c** was assembled by attachment of the (*S*,*S*)-1,2-diaminocyclohexane moiety onto the C7 and C12 pendant groups of cholic acid. Subsequently, the binding interaction of host **1c** with the same series of amino acids (as tetrabutylammonium salt) was investigated by fluorescent titrations. The association constants of each of the complexes are compiled in Table 1. Interestingly, in contrast to host **1a**, opposite enantioselectivity toward serine, threonine, lysine and tyrosine was displayed by host **1c**. The extent of enantioselectivity exhibited by the two diastereomeric hosts is comparable with each other. This implies that the chiral discrimination power of hosts **1a** and **1c** may be due to the 1,2-diaminocyclohexane moiety.

To demonstrate the enantioselectivity of sensors **1a** and **1c**, sample solutions of serine with various enantiomeric compositions were prepared and their interaction with **1a** and **1c** was studied separately. As shown in Fig. 6, an excellent linear relationship between the fluorescence response of each host and the enantiomeric compositions of serine was found. The graph can be used to determine the enantiomeric excess (ee) of a mixture of D- and L-serine.

To explore the potential of using **1a** as a sensing probe applicable to aqueous solution,[11] fluorescent titration experiments of **1a** with D-serine and L-serine were carried out in various compositions of aqueous acetonitrile solutions. With increasing content of water, the corresponding binding constants were reduced accordingly. When 1 : 1 aqueous acetonitrile was used, the binding constants of **1a** and D, L-serine were determined to be $(3.57 \pm 0.26) \times 10^4$, $(8.71 \pm 0.42) \times 10^3$, respectively. Even under such a highly competing solvent system, the enantioselectivity displayed by **1a** towards the antipodal forms of serine was quite respectable (*i.e.* $K_D/K_L = 4.1$) (S-Table3, ESI‡).

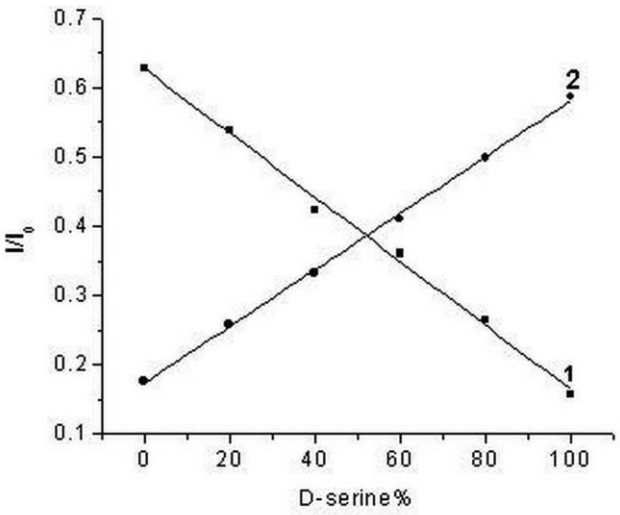


Fig. 6 Fluorescence response of **1a** (1.0 μM) (line 1, slope = −0.462) and **1c** (1.0 μM) (line 2, slope = 0.407) with serine (50 equiv.) at various D-composition in CH_3CN. Excitation wavelength was 366 nm.

Conclusion

In summary, the chiral fluorescent probes **1a** and **1c**, readily accessible from cholic acid, were found to be highly sensitive, chemoselective and enantioselective to amino acids. The two receptive binding sites of the sensors could provide multi-point interactions through hydrogen bonding with trifunctional amino acids such as serine, lysine, threonine and tyrosine. The cooperative influence of the chirality of cholic acid and 1,2-*trans*-diaminocyclohexane renders the sensor highly enantioselective. The results should assist further development and application of enantioselective chemical sensing.

Experimental

1 General methods

The melting point was determined with a MEL-TEMPII melting point apparatus (uncorrected). ^1H and ^{13}C NMR spectra were recorded on a JOEL AL 270 spectrometer (at 270 and 67.8 MHz, respectively) or VARIAN INOVA 400 spectrometer (at 400 and 100 MHz, respectively) in $CDCl_3$. High resolution mass spectra were recorded on a Bruker Autoflex mass spectrometer (MALDI-TOF) or electrospray ionization high-resolution mass spectra on an API Qstar Pulsari mass spectrometer. Fluorescent emission spectra were collected on a PTI luminescence lifetime spectrometer. Unless specified, all fine chemicals were used as received.

2 Synthesis of probes 1a and 1c

2.1 Synthesis of probe 1a. The preparation of probe **1a** was reported in full elsewhere.[6]

2.2 Synthesis of probe 1c. This diastereomer of sensor **1a** was obtained using the same procedure described elsewhere[6] by substituting (*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt with (*S*,*S*)-1,2-diammoniumcyclohexane mono-(−)-tartrate salt in step two. Sensor **1c** was obtained as a pale yellow

solid. Mp: 173–175 °C, $[\alpha]_D^{26} = 42.4°$ ($c = 1$, CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.72 (s, 3H), 0.83 (d, 3H, $J = 6.2$ Hz), 0.94 (s, 3H), 3.20–3.32 (m, 2H), 3.63 (s, 1H), 3.74–3.78 (m, 2H), 5.09 (s, 1H), 5.28 (s, 1H), 5.64 (s, 2H), 7.27 (s, 1H), 7.41–7.50 (m, 4H), 7.94 (d, 2H, $J = 8.1$ Hz), 8.24 (d, 2H, $J = 8.1$ Hz), 8.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.38, 17.72, 22.73, 24.04, 24.07, 24.14, 25.06, 27.36, 27.36, 29.19, 30.96, 31.38, 31.42, 34.42, 34.81, 35.23, 38.50, 39.46, 41.24, 41.33, 45.24, 45.51, 47.56, 50.41, 51.37, 51.66, 62.75, 64.23, 71.04, 72.33, 76.49, 124.45, 125.46, 126.85, 127.39, 129.21, 130.67, 131.64, 134.22, 169.85, 170.26, 174.59. MALDI TOF HRMS: calcd for $C_{50}H_{67}N_5O_6SNa$, 888.4816; found, 888.4828.

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