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A BINOL-based chiral polyammonium receptor for highly enantioselective recognition and fluorescence sensing of (*S*,*S*)-tartaric acid in aqueous solution†

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A chiral ditopic polyammonium receptor featuring two [9]aneN$_3$ moieties separated by a (*S*)-BINOL linker is able to selectively bind and sense in water (*S*,*S*)-tartaric acid over its (*R*,*R*)/*meso* forms.

Enantiomeric recognition and sensing of chiral anions in water by fluorescent receptors is a challenging issue[1–5] in modern biological chemistry.[1] This goal is particularly difficult in aqueous solutions due to strong solvation of anions that effectively competes with binding by synthetic receptors. Accordingly, selective abiotic chemosensors for chiral anions in aqueous media are rare, enantioselective sensing being generally obtained in organic solvents[3,4] or in water-containing solvent mixtures.[5,6] Polyammonium receptors offer the chance to achieve selective anion recognition in water.[7] Nevertheless, the use of fluorescent polyammonium systems for enantiomeric recognition of chiral anions remains a scarcely explored field. We recently reported that ligands featuring two facing [9]aneN$_3$ units ([9]aneN$_3$ = 1,4,7-triazacyclononane) separated by heteroaromatic spacers can act as efficient and selective receptors/sensors for inorganic anions in water, based on a geometrical size/cavity fitting and binding complementarity in the host–guest interaction.[8]

We have now synthesized the chiral ligand **L** (Fig. 1),† coupling within the same receptor structure two [9]aneN$_3$ moieties and the (*S*) enantiomer of BINOL (1,1′-bi-2-naphthol), a synthon largely used to achieve chiral receptors for anions but scarcely soluble in water.[3,5] We thought that the presence of the two [9]aneN$_3$ units in **L** could ensure high solubility in pure water to the receptor itself, *via* the formation of polyammonium cations, and to the corresponding complexes with chiral anions,

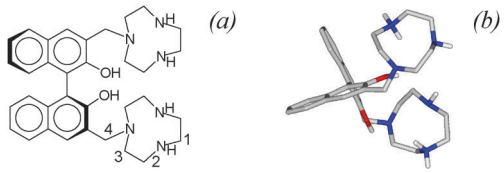

Fig. 1 (a) Drawing of ligand **L**; (b) minimized structure of the $(H_2\mathbf{L})^{2+}$ cation (hydrogens linked to carbon atoms not shown).

in particular α-hydroxydicarboxylates. Indeed, **L** features a good solubility in water in the pH range 2–12. Potentiometric titrations indicate the formation of polyammonium cations of the type $(H_x\mathbf{L})^{x+}$ (x = 1–5), with protonation constants ranging between 10.14 and 3.9 log units (Table S1).† Molecular modelling on the dication $(H_2\mathbf{L})^{2+}$ (see below) shows the BINOL unit in a cisoid conformation with the dihedral angle between the two naphthalene rings being *ca.* 81°;† the two [9]aneN$_3$ units lie on almost parallel planes, shifted *ca.* 6 Å and rotated *ca* 70° relative to each other (Fig. 1b).

Polyamine compounds containing phenolic functions are often found in zwitterionic forms,[9] containing negatively charged –OH functions. For **L**, the UV-vis spectrum shows a marked pH dependence. In fact, the absorption band of the (*s*)-BINOL moiety at 228 nm displays a 15 nm red-shift on increasing the pH from 7 to 12 (Fig. 2), accompanied by the formation of a new band at 370 nm. Superimposition of the absorbance at 228 and 248 nm with the distribution curves of the protonated species of **L** shows that the observed spectral changes, attributable to deprotonation of naphthol units, occur upon deprotonation of the $(H_2\mathbf{L})^{2+}$ cation to give at alkaline pH values the uncharged receptor **L**, which is, therefore, present in solution in its bis-zwitterionic form (Fig. 2). A similar result is also obtained by CD measurements: **L** features a dichroic band at 235 nm, which is 15 nm red-shifted in the alkaline pH region upon bisnaphthol deprotonation (Fig. S1).†

The fluorescence emission of **L** shows a different pH dependence. In fact, a marked decrease of the typical band at 365 nm of BINOL is noted on increasing the pH from 2 to 12. This behavior, often found in polyamine-based fluorescent receptors, can be attributed to the progressive deprotonation of the ammonium groups that makes the resulting lone pairs available to quench the

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† Electronic supplementary information (ESI) available: Details of all experimental procedures; stability constants and distribution diagrams of the complexes; emission spectra of **L** in the presence of different anions; NMR titrations data. See DOI: 10.1039/c2cc35383k

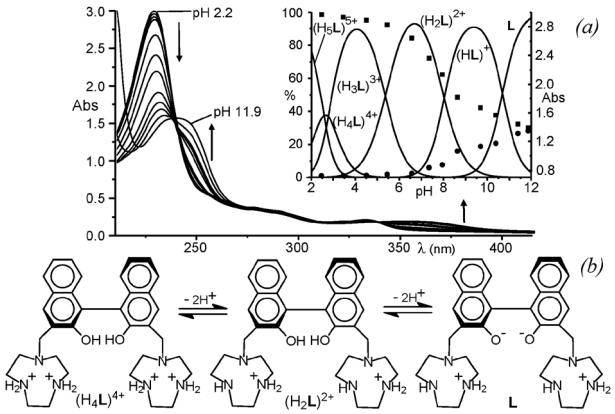

Fig. 2 (a) UV-vis spectra of **L** and absorbance at 228 (■) and 248 (●) nm (inset) at different pH values; (b) proposed localization of acidic protons in **L**, $(H_2L)^{2+}$ and $(H_4L)^{4+}$.

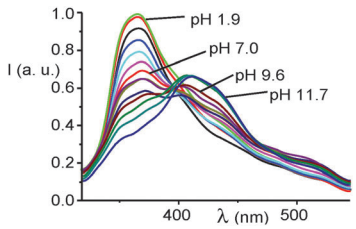

Fig. 3 Fluorescence spectra of **L** at different pH values (λ_{exc} = 279 nm).

emission of the fluorophore *via* a PET mechanism. In the present case, however, this process is accompanied, at alkaline pH values (Fig. 3), by the formation of a new emission band at 415 nm, which can be ascribed to deprotonation of the –OH functions in the (*s*)-BINOL unit.[10]

Potentiometric titrations in aqueous solutions show that the protonated forms of **L** bind the A^{2-} and HA^{-} forms of (*S*,*S*)/(*R*,*R*)/*meso*-tartaric, (*S*)/(*R*)-malic, maleic, fumaric and succinic acid to afford 1 : 1 complexes (see Fig. S2–S9 and Table S2 for a list of all species formed in the pH range investigated and their stability constants).† However, at pH 7 the receptor and the carboxylic acids are mainly present in solution in their $(H_2\mathbf{L})^{2+}$ and A^{2-} forms, respectively. Among the different anions, (*S*,*S*)-tartrate gives the highest constant for the relevant $(H_2\mathbf{L})^{2+} + A^{2-} = H_2\mathbf{L}A$ equilibrium ($\log K$ = 5.8). Remarkably less stable $H_2\mathbf{L}A$ complexes are formed by the other hydroxydicarboxylate anions, including *meso*-tartrate ($\log K$ = 3.8) and (*R*,*R*)-tartrate ($\log K$ = 3.3(1)). Maleate gives a more stable $H_2\mathbf{L}A$ complex ($\log K$ = 3.8(1)) than succinate ($\log K$ = 3.5(1)) and, overall, fumarate ($\log K$ = 2.7(1)). Conversely, no interaction is detected with (*S*)/(*R*)-lactate. The enantioselectivity displayed by **L** for (*S*,*S*)-tartrate is among the highest reported so far, the stability constant of the corresponding $H_2\mathbf{L}A$ adduct being almost three orders of magnitude higher than that found for the analogous adduct with (*R*,*R*)-tartrate.

Interestingly, the fact that (*S*)/(*R*)-lactate anions are not bound may be related to the presence of a single carboxylate function in them, which enables these anions to interact only with one protonated [9]aneN$_3$ unit, an interaction mode not strong enough to ensure the formation of stable complexes in water. Instead, for the other dicarboxylate anions, a binding mode involving their encapsulation within the cleft between

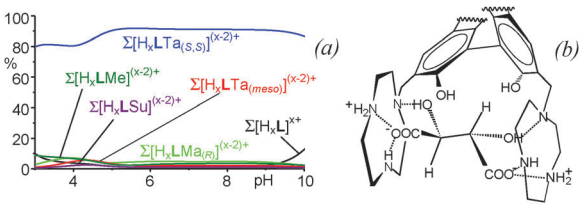

Fig. 4 (a) Plot of the overall percentages of **L** complexed species with (*S*,*S*)-tartaric ($H_2Ta_{(S,S)}$), (*R*)-malic ($H_2Ma_{(R)}$), maleic (H_2Me) and succinic (H_2Su) acids as a function of pH in a competitive system containing **L**, (*S*,*S*)/(*R*,*R*)-tartaric, (*S*)/(*R*)-malic, (*S*)/(*R*)-lactic, succinic, maleic and fumaric acids in equimolecular ratio ([**L**] = 1×10^{-3} M); (b) proposed interaction mode between (*S*,*S*)-tartrate and $(H_2\mathbf{L})^{2+}$.

the two macrocyclic moieties and simultaneous interaction of each carboxylate group with a single protonated [9]aneN$_3$ unit can be easily envisaged.

Besides $H_2\mathbf{L}A$, however, other complexes are also formed in solution, in particular in the acidic pH region, due to overlapping complexation equilibria involving the mono-protonated HA^{-} anion and/or differently protonated forms of **L**. In these cases, the selectivity properties of a receptor can be better analyzed by considering a competitive system containing receptors and anions in equimolar concentrations and calculating the overall percentages of the different complexed anions on changing the pH.[11] In the case of **L**, a similar plot (Fig. 4a) shows that the formation of adducts with (*S*,*S*)-tartaric acid prevails in the pH range considered, while the other acids are complexed in very low percentages (at most 7%) or totally not complexed, as in the case of (*R*,*R*)/*meso*-tartaric, (*S*)-malic and fumaric acid. This suggests that the configuration of the stereo-centres and the number of –OH functions play a relevant role in the recognition process, probably because of their interaction *via* H-bonding with the amine groups of [9]aneN$_3$.

The formation constants of the adducts were also determined by ^{1}H NMR titrations at pH 7 (TRIS buffer). The receptor displays a set of 4 aliphatic signals, attributable to the CH_2 groups 1–4 (see Fig. 1a for labelling), which undergo marked downfield shifts, up to 0.49 ppm, upon anion binding. Minor shifts are observed for the aromatic signals. The determined constants (Table S3, ESI†) well compare with those obtained from potentiometric titrations for the formation of the adduct $H_2\mathbf{L}A$, the species largely prevalent at pH 7. Once again, no interaction is found with (*S*)/(*R*)-lactate anions. Interestingly, the largest shifts measured at complete complex formation are normally observed for the signals of the CH_2 groups 1 and 2 (0.49 and 0.41 ppm, respectively, in the case of (*S*,*S*)-tartrate), adjacent to the secondary amine groups, in keeping with their strong interaction with the charged carboxylate groups of substrates. The shift observed for the CH_2 groups 3 and 4, adjacent to the tertiary amine groups, is lower. Of note, (*S*,*S*)-tartrate complexation causes shifts of these resonances (*ca.* 0.25 ppm for both 3 and 4) larger than those produced by the other dicarboxylate anions (at most 0.14 ppm, down to 0.07–0.03 ppm for succinate, maleate and fumarate), indicating a larger involvement of the tertiary amines in (*S*,*S*)-tartrate binding (Table S4).†

In the light of these results, selective binding of (*S*,*S*)-tartrate over (*R*,*R*)/*meso*-tartrate can tentatively be explained considering that in $(H_2\mathbf{L})^{2+}$ the acidic protons are likely to be located on a secondary amine group, more basic than tertiary one,[1] of each [9]aneN$_3$ unit. In small macrocyclic polyamines, the acidic protons

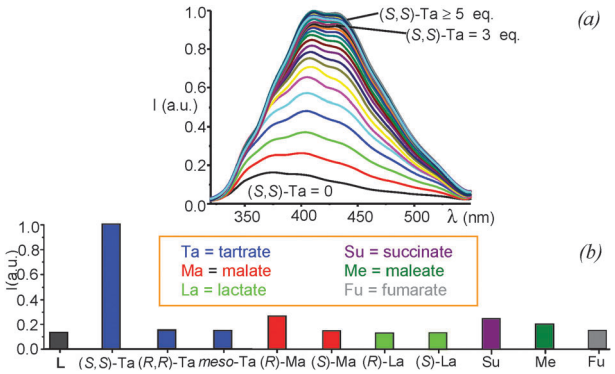

Fig. 5 (a) Fluorescence spectra of **L** in the presence of increasing amounts of (*S*,*S*)-tartrate (0.2 eq. each addition) at pH 7 (λ_{exc} = 279 nm); (b) emission intensity at 410 nm after addition of 10 eq. of each substrate.

can also be shared between the two adjacent secondary amines *via* H-bonding.[1] Therefore, both carboxylate groups in the anionic guests, by assuming a *gauche* disposition, could simultaneously interact, *via* charge–charge and H-bonding interactions, each with both protonated secondary amine groups of a single [9]aneN$_3$ unit (Fig. 4b). The two [9]aneN$_3$ units in $(H_2\mathbf{L})^{2+}$ are in fact *ca.* 70° rotated relative to each other. Preferential binding of maleate with respect to fumarate supports this interaction mode. In the case of (*S*,*S*)-tartrate binding, such interaction of the two carboxylates would also enable the simultaneous interaction of both –OH functions, each with the tertiary amine group of a single [9]aneN$_3$ unit. The different configuration of the chiral centers prevents this interaction in the case of (*R*,*R*)-tartrate, while only a single OH group could be involved in H-bonding in the case of *meso*-tartrate, which in fact forms a somewhat more stable $H_2\mathbf{L}A$ complex than (*R*,*R*)-tartrate (see above).

Spectrofluorimetric measurements point out that **L** also acts as an effective and selective fluorescent chemosensor for (*S*,*S*)-tartrate in water. In fact, addition of increasing amounts of this anion to a solution of **L** at pH 7 (TRIS buffer) leads to a progressive red-shift of the typical band of BINOL at 370 nm, accompanied by marked increase in the emission intensity at 420 nm (Fig. 5a), accounting for deprotonation of the –OH groups in the BINOL unit (see above). This increase is observed up to the addition of *ca.* 5 eq. of (*S*,*S*)-tartrate (under these conditions the emission at 420 nm is more than eightfold enhanced). The formation of a new red-shifted band at 410 nm is also observed in the presence of the other substrates. However, besides the smaller red-shift, the emission increase at 410 nm is observed only in the presence of larger excesses of the anions (see Fig. S10–S16)† and, overall, far lower than that found for (*S*,*S*)-tartrate, as summarized in Fig. 5b.

The fluorescence emission is not affected by the addition of the (*S*)/(*R*)-lactic acids. Of note, the UV-vis and CD spectra of **L** at pH 7, featuring the typical band of the protonated BINOL moiety, are almost not affected by the presence of all anions, including (*S*,*S*)-tartrate, suggesting that deprotonation of the naphthol units at pH 7 upon substrate binding occurs in the excited state, probably *via* a proton transfer process from the –OH groups of BINOL to the carboxylate groups. This process may be favoured by a strong host–guest interaction, accounting for the high sensing ability of **L** for (*S*,*S*)-tartrate.

L is the first polyammonium-based fluorescent chemosensor featuring both enantiomeric recognition of tartaric acid in pure water and great binding selectivity for (*S*,*S*)-tartrate, not only over (*R*,*R*)/*meso*-tartrate, but also over (*S*)/(*R*)-malate, succinate, maleate, fumarate and (*S*)/(*R*)-lactate, accompanied by a marked fluorescence sensing selectivity for this anion.

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