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COMMUNICATION

A bis-bisurea receptor with the *R*,*R*-cyclohexane-1,2-diamino spacer for phosphate and sulfate ions†

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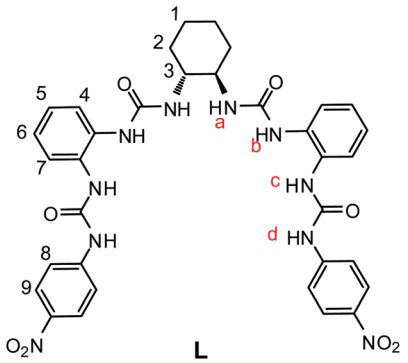
A bis-bisurea receptor (L) based on the *R*,*R*-cyclohexane-1,2-diamino scaffold forms an uncommon 2 : 2 complex (1) with the monohydrogen phosphate ion (HPO_4^{2-}) and a 1 : 1 complex (2) with the sulfate ion (SO_4^{2-}). Solution binding properties of the two anions were studied by ^1H NMR, UV-vis, and circular dichroism (CD) methods.

The binding of phosphate and sulfate ions has attracted special attention due to their ubiquitous presence in biological systems and environments. Examples in biology include the sulfate binding protein (SBP)[1] and phosphate binding protein (PBP),[2] which employ seven and twelve hydrogen bonds, respectively, to recognize or transport the anion. In addition, phosphate and sulfate anions are known as inorganic pollutants, which can cause the eutrophication of waterways or problems in nuclear waste treatment.[3] Due to the large solvation energies of phosphate and sulfate ions, their separation is highly challenging. Therefore, many efforts have been devoted to the design of artificial receptors for these two anions.[4–12]

We have recently developed a series of *ortho*-phenylene-bridged oligourea ligands, whose anion coordination behavior with the tetrahedral phosphate and sulfate anions greatly resembles the oligo-pyridine ligands with transition metals.[13] Through the self-assembly of a bis-bisurea receptor and a phosphate anion, the first triple anion helicate [A_2L_3] was obtained,[13a] in which the two coordinated PO_4^{3-} ions adopt the same configuration (Δ–Δ or Λ–Λ) in one helix but the compound is racemic, consisting of both *P* and *M* enantiomers. This lack of stereo-preference is common in the assembly by achiral ligands.[14] To modulate the relative population of the helical structures and obtain optically pure isomers, an effective strategy is to introduce chiral segments into the ligand.[15] The chiral 1,2-diaminocyclohexane subunit is a widely used source of chirality because of its geometrical pre-organization nature.[16] For example, Fabbrizzi *et al.*[17] and Albrecht *et al.*[18] incorporated optically pure 1,2-diaminocyclohexane into the linking unit of bis-imino bis-quinoline or dicatechol diimine ligands, respectively, and isolated homochiral metal helicates.

In the present work, the *R*,*R*-cyclohexane-1,2-diamine linker was included in the bis-bisurea moiety (receptor **L**, Scheme 1) in order to realize chiral resolution of triple anion helicates. Unexpectedly, the assembly of **L** with phosphate ions did not afford the desired 3 : 2 (host to guest) homochiral triple-stranded helicate, but resulted in a 2 : 2 anion complex with the uncommon monohydrogen phosphate ion (HPO_4^{2-}), $[Bu_4N]_4[(HPO_4)_2\mathbf{L}_2]$ (**1**). In addition, a 1 : 1 complex of ligand **L** and the sulfate anion, $(Bu_4N)_2[SO_4\mathbf{L}]$ (**2**), has also been obtained.

The ligand **L** was synthesized by the reaction of *p*-nitrophenylisocyanate and 1,1-bis-(2-aminophenyl-urea)-(1*R*,2*R*)-cyclohexane (see ESI† for the synthesis). Slow diffusion of diethyl ether into a THF solution of **L** and excess $(Bu_4N)H_2PO_4$ and $(Bu_4N)OH$ afforded yellow crystals of the monohydrogen phosphate complex $(Bu_4N)_4[(HPO_4)_2\mathbf{L}_2]$ (**1**). Interestingly, though different equivalents of $(Bu_4N)OH$ were added, only the complex of the monoprotonated phosphate ion was isolated, while the desired complex of the fully deprotonated phosphate (PO_4^{3-}) or other species with the dihydrogen phosphate ($H_2PO_4^-$) was not observed. Moreover, attempts to prepare the PO_4^{3-} complex by using Na_3PO_4, K_3PO_4 and $[K([18]crown-6)]_3PO_4$ have also been unsuccessful. For the sulfate anion,



Scheme 1 Structure of the receptor **L**.

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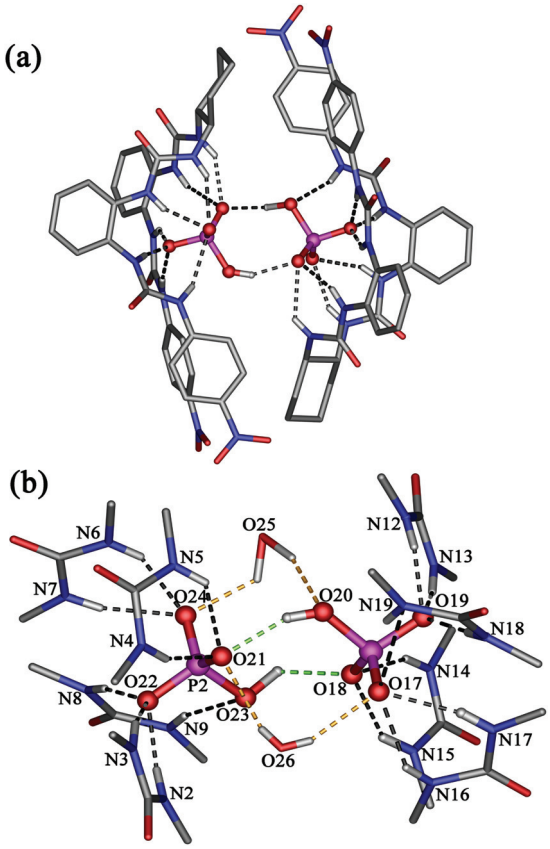

Fig. 1 (a) Crystal structure of $[(HPO_4)_2\mathbf{L}_2]^{4-}$ (**1**; non-acidic hydrogen atoms, Bu_4N^+ countercations and solvent molecules are omitted for clarity). (b) Detailed view of the binding sites for the HPO_4^{2-} dimer, showing the 12 hydrogen bonds around each anion.

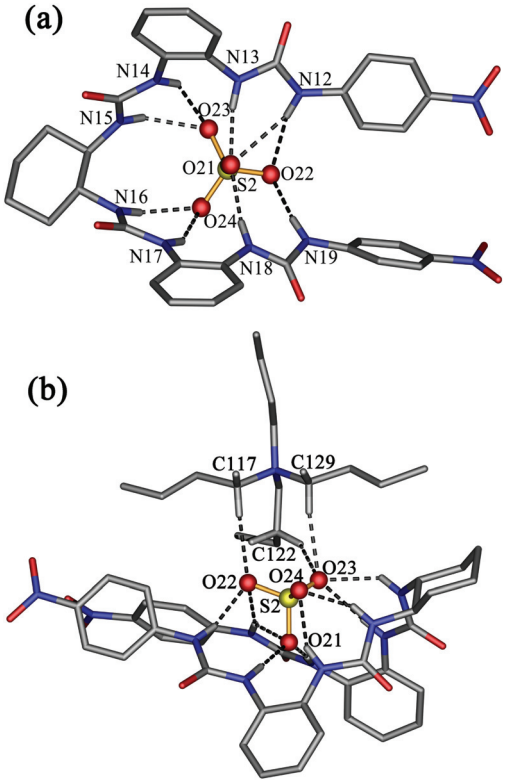

Fig. 2 (a) Crystal structure of the complex $[(SO_4)\mathbf{L}]^{2-}$ (**2**). (b) Hydrogen bonds around the SO_4^{2-} ion.

yellow crystals of the complex $(Bu_4N)_2[SO_4\mathbf{L}]$ (**2**) were obtained from the ligand **L** and excess $(Bu_4N)_2SO_4$ in a DMSO/H_2O solution.

The crystal structure of complex **1** shows a 2 : 2 binding ratio of **L** and the HPO_4^{2-} anion. The receptor adopts a "saddle" conformation and two receptor molecules are arranged in an antiparallel face-to-face manner, creating a cavity in which two HPO_4^{2-} ions are located. Each anion is bound strongly by one **L** molecule *via* eight N–H···O hydrogen bonds (N···O distances range from 2.685 to 3.083 Å, average 2.880 Å; and N–H···O angles from 132° to 174°, average 154°) with all of the four urea moieties (Fig. 1 and Table S2†). The two encapsulated HPO_4^{2-} ions dimerize through two P═O···HO–P hydrogen bonds (O–H···O: 2.640(5) Å, 155°, and 2.604(6) Å, 113°), and two water molecules serve as bridges between the two anions, providing four slightly weaker O–H···O bonds for the anion dimer (2.712(6)–2.946(6) Å, 126–164°) (Fig. 1b). Thus, each HPO_4^{2-} ion indeed forms a total of twelve hydrogen bonds (eight N–H···O, two P═O···HO–P, and two O–H_w···O bonds). This coordination number (12) is consistent with the phosphate binding protein, which also binds the monoprotonated form (HPO_4^{2-}) of phosphate by seven N–H···O, four O–H···O, and one PO–H···O hydrogen bonds.[2] For artificial receptors, however, most studies have been focused on the dihydrogen form of phosphate ($H_2PO_4^-$),[19–21] whereas binding of the monohydrogen phosphate ion is quite rare. An unusual phosphate dimer, $[H_3PO_4{\cdot}PO_4]^{3-}$, was obtained by Jurczak *et al.*[22] Very recently, Gale *et al.*[10a] reported a similar HPO_4^{2-} dimer binding by an acyclic amido-indole decorated diindolylurea receptor, which has eight NH hydrogen bond donors as in the ligand **L**.

In the 1 : 1 sulfate complex $(Bu_4N)_2[SO_4\mathbf{L}]$ (**2**), the receptor **L** also displays a saddle shape with a "pocket" for the anion. There are two independent molecules in the complex, whose structural parameters are very close. All of the eight NH groups point to the pocket and donate nine hydrogen bonds to the sulfate ion (N···O distances range from 2.745 to 3.260 Å, average 2.972 Å; N–H···O angles from 120° to 178°, average 154°) (Fig. 2a). While the binding mode is similar to the amido-indole decorated diindolylurea receptor,[9a] the latter shows a more "flat", quasi-square conformation rather than the curved **L** molecule in complex **2**. Moreover, there is a Bu_4N^+ ion above the SO_4^{2-} anion, which forms additional C–H···O hydrogen bonds with the anion (Fig. 2b and Table S3†). The sulfate binding mode in **2** also distinguishes from that in all the *o*-phenylene-bridged tetrakis(urea) ligands, which encapsulates the sulfate ion in a helical cavity by eight hydrogen bonds.[13c]

The solution binding behavior of **L** with phosphate and sulfate anions was investigated by ^1H NMR experiments. For the $H_2PO_4^-$ anion, all of the urea NH groups showed gradual downfield shifts when adding 0 to 5.0 equiv. of $H_2PO_4^-$ (as Bu_4N^+ salt) (Fig. 3). Job's plot pointed to a 1 : 2 binding mode, and the association constants for $H_2PO_4^-$ were calculated to be $K_1 = 1.10 \times 10^4\ M^{-1}$ and $K_2 = 6.39 \times 10^1\ M^{-1}$ by fitting the

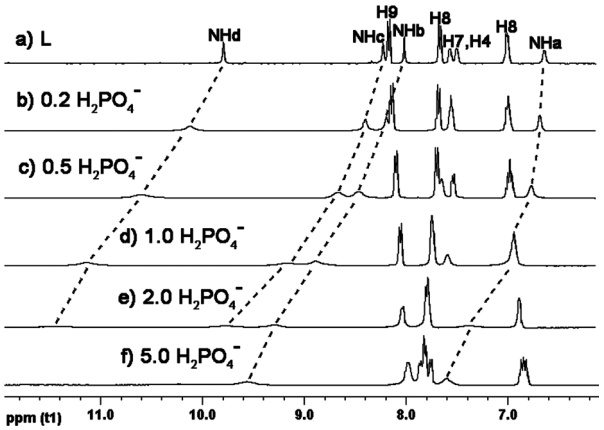

Fig. 3 ^{1}H NMR titration of **L** (5.0×10^{-3} M) with $(Bu_4N)H_2PO_4$ in DMSO-d_6.

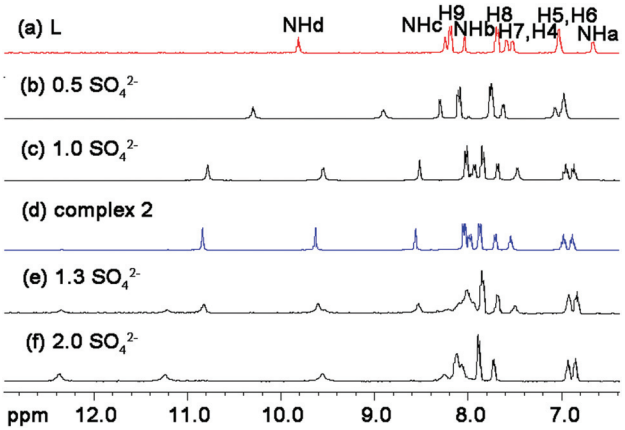

Fig. 4 ^{1}H NMR titration of **L** (5.0×10^{-3} M) with $(Bu_4N)_2SO_4$ in DMSO-d_6.

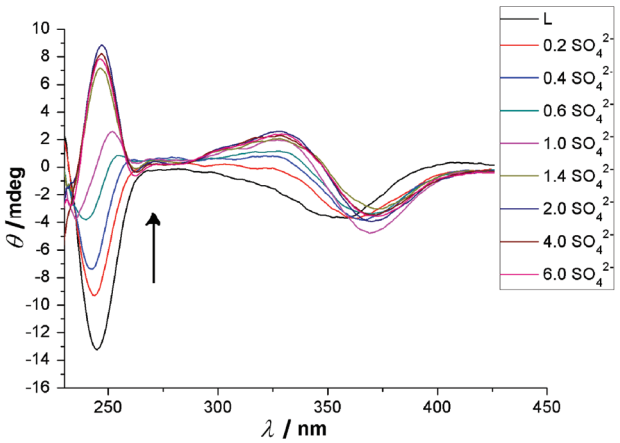

Fig. 5 CD spectra of **L** (1.5×10^{-4} M) upon addition of $(Bu_4N)_2SO_4$ in CH_3CN–0.5% DMSO.

titration data with the EQNMR program (Fig. S1 and S2†).[23] In the case of sulfate ions (Fig. 4, Fig. S1†), all urea NH signals of **L** also shifted gradually downfield upon titration of $(Bu_4N)_2SO_4$, and the spectrum of **L** with 1 equiv. of SO_4^{2-} resembles closely that of complex **2**. When more than 1 equiv. of sulfate ions were added, a slow exchange process was observed, with the appearance of a new set of NH signals in further downfields besides those of complex **2** (Fig. 4e). This may be due to the conversion of the 1 : 1 complex to the 1 : 2 (host–guest) binding mode, in which the ligand molecule may assume an "S" shape and binds one anion on each side, as observed for the sulfate complex of the ethylene-bridged bis-bisurea ligand.[13a] The spectrum reached saturation with 2 equiv. of the anion, and Job's plot also gave a 1 : 2 binding stoichiometry (Fig. S1†). The downfield shifts ($\Delta\delta$ = 1.53–3.00 ppm) induced by 2.0 equiv. of SO_4^{2-} were larger than those observed with the $H_2PO_4^-$ ion, indicating stronger binding with SO_4^{2-}.

In the UV-vis titration experiments (Fig. S3 and S4†), the $H_2PO_4^-$ and SO_4^{2-} ions induced obvious bathochromic shifts with clear isosbestic points, implying the formation of one single complex. All absorption spectra reached saturation after addition of 2.0 equiv. of anions, suggesting 1 : 2 (host–guest) binding mode. The association constants between **L** and SO_4^{2-} determined by Dynafit[24] were 2.81×10^4 M^{-1} (K_1) and 3.47×10^5 M^{-1} (K_2).

The chirality properties of **L** upon addition of the above anions were investigated by circular dichroism in CH_3CN–0.5% DMSO (1.5×10^{-4} M) (Fig. 5, Fig. S5†). The free ligand exhibited strong negative CD signals at around 245 and 364 nm corresponding to the phenyl and nitrophenyl segments, respectively. Interestingly, upon addition of $H_2PO_4^-$ and SO_4^{2-} ions, the Cotton effect at 245 nm reduced gradually in intensity and finally became positive, which is attributed to the conformational change of the receptor **L** (see below the DFT studies) upon binding the anions. A similar "chirality reduction–inversion" phenomenon has also been reported in the literature.[25] Meanwhile, the signal at 364 nm began to show an exciton couplet with the first negative and second positive Cotton effects corresponding to the chromophores ($\lambda_{abs} \approx 355$ nm) during the addition of 1.0 equiv. of the anions.[26] The intensity of this exciton couplet decreased when adding 1.0 to 2.0 equiv. of anions, which may be due to the increasing interchromophore distance[27] caused by the change of the ligand **L** from a "saddle" shape to a stretched "S" shape to accommodate two anions as in the previously reported sulfate complex of a related bis-bisurea ligand.[13a]

As mentioned above, the initial goal of this work was to obtain enantiomerically pure triple anion helicates. However, the ligand adopts the bent conformations and acts as a "tetradentate" tetrakis(urea) in both the phosphate (HPO_4^{2-}) and sulfate complexes rather than the desired bis-chelating bis-bisurea form. Thus the rigidity and conformational preference of the ligand **L** was studied by DFT calculations using the B3LYP/6-311++G(d,p) method. Different from complexes **1** and **2**, the optimized structure of the free ligand in the gas phase displays a twisted conformation in which three urea groups converge to a cleft but the fourth urea arm points away, with intra-molecular N–H···O hydrogen bonds between the urea groups (Fig. S6†). The cyclohexane-1,2-diamino spacer does not show the "*anti*" orientation expected for the helical structures. The calculated N–C–C–N torsion angle of the cyclohexylene diamine moiety in the free ligand is −65.8°, while it is −54.3° in complex **1** and −49.5° in

2. These values are far from those (157.2–179.6°) found in the ethylene-bridged bis-bisurea receptor in the triple anion helicate.[13a]

In conclusion, we report a chiral bis-bisurea receptor based on the *R*,*R*-cyclohexane-1,2-diamine scaffold. Crystallization of **L** with the anions resulted in the formation of a rare monohydrogen phosphate complex **1** and the sulfate complex **2**. In contrast to the 1 : 1 binding in the solid state, the ligand displays the 1 : 2 (host to guest) binding ratio with phosphate and sulfate anions in solution. Theoretical results demonstrated that the cyclohexane-1,2-diamine spacer might be too rigid to form anion helicates. Thus more flexible chiral ligands may be necessary for the construction of optically pure anion helicates.

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