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Ion pair complexes and anion binding in the solution of a ditopic receptor†

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The synthesis and crystal structures with alkali halides of a ditopic benzo-15-crown-5 bis-urea receptor **L** have been presented. In addition, the anion binding properties of **L** and its alkali metal complexes in solution are presented. A comprehensive single-crystal X-ray crystallographic study of **L**, all together 13 crystal structures, including the ion pair complexes with NaCl, NaBr, NaI, KF, KCl, KBr, KI, RbF, RbCl, and RbI, give a detailed view of how **L** behaves in the solid-state with different alkali halides depending on the size of the cation and anion. In the solid-state **L** forms a 1 : 1 complex with a sodium cation and the anion is complexed as a contact (NaCl) or a separate ion pair (NaBr, NaI). With larger potassium and rubidium cations **L** assembles into a 2 : 1 complex and forms a separated ion pair complex with the anion. Reflecting the crystal structures the **L** forms a 1 : 1 complex with Na^+ in solution, and a 2 : 1 complex with K^+, which were verified by Job's plot analysis in 4 : 1 $CDCl_3$/dimethyl sulfoxide. The binding strength of the monomeric $[\mathbf{L}{\cdot}Na]^+$ and the dimeric $[2\mathbf{L}{\cdot}K]^+$ toward chloride, bromide and iodide anions was studied by ^1H NMR titrations in 4 : 1 $CDCl_3$/DMSO, and a clear turn-on effect of the cation complexation compared to the neutral receptor **L** alone (K_a with **L** for Cl^-, Br^- and I^- being 832, 174 and 32 M^{-1}, respectively) was observed. The monomeric $[\mathbf{L}{\cdot}Na]^+$ binds chloride 9, bromide 8, and iodide 12 times stronger than **L**, while for the dimeric $[2\mathbf{L}{\cdot}K]^+$ the corresponding increase in binding is 51 (Cl^-), 84 (Br^-), and 22 (I^-) times with the same stoichiometric ratios as observed for the ion pair complexes in the solid-state.

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Introduction

Cation and anion receptor chemistry has been an integral part of supramolecular chemistry since the establishment of the field. Particularly, the development of cation receptors has been a heavily investigated area from the beginning.[1] A slow rate in the development of anion receptor chemistry originates from the more complicated nature of the anions, *i.e.* larger size, more complicated geometry and higher solvation energy. Nevertheless, the interest toward anion receptor chemistry within the scientific community has been booming according to the large number of developed systems for anion recognition within the last decade.[2–4] The combination of cation and anion recognition sites in a single molecule, *i.e.* ion pair receptors, have recently attracted a growing interest due to their more selective and effective binding toward both the cation and anion. Ion pair recognition has to overcome the difficulty of the ion separation, and also avoid the formation of multiple ion pair complexes in the system.[5–7] In addition the electrostatic and allosteric contributions in the ion pair binding by synthetic receptors are not thoroughly understood, although detailed studies around this topic have been recently presented.[8,9] The recent reviews of ion pair receptors reveal innovative molecular designs, and how the aforementioned difficulties have been addressed in specific ion pair recognition.[10–13] Crown ethers have been studied as building blocks in ditopic receptors for example by Reinhoudt,[14] Beer,[15] Smith,[16,17] and Sessler,[18] and their coworkers. The efficient practical applications in salt extraction[19,20] and solubilization,[21] membrane transport,[22] catalysis,[23] and sensors[24] represent the interesting possibilities of utilizing ion pair receptors in various tasks.

We have recently presented structural and alkali metal halide recognition studies with ditopic benzo-18-crown-6 bis-urea,[25] which manifested efficient binding of halide anions in solution, when complexed with alkali metal cations. We have also looked into the solid-state ion pair complexation by benzo-15-crown-5 and benzo-18-crown-6 uranyl salophen receptors[26] with various alkali halides. These receptors are constructed from simple and well-known structural units, but the combination of the binding units into a single molecule for ion pair recognition is surprisingly less studied. In particular, the solid-state structures of this type of crown ether

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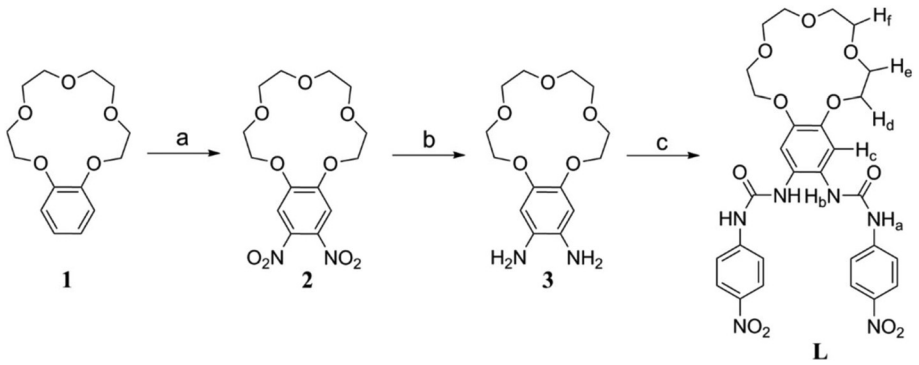

Scheme 1 The synthesis of receptor **L**. (a) HNO_3/H_2SO_4, $CHCl_3$, 77%. (b) $NH_2NH_2{\cdot}H_2O$, 10% Pd/C, EtOH, 98%. (c) 4-nitrophenyl isocyanate, CH_2Cl_2/DMF, 75%. The protons H_a, H_b, H_c, H_d, and H_f were followed in Job's plot analysis and ^1H NMR titrations and are presented in the structure of **L**.

based receptors are scarce. The CSD search[27] combining benzo-15-crown-5 (B15C5) or benzo-18-crown-6 (B18C6) with amide moieties reveals only 21 structures having these binding sites covalently connected. Out of these structures only 13 contain ion pairs in the crystal lattice, of which eight are separate and five are contact ion pairs. In addition, CSD search[28] of urea-functionalized molecules complexed with alkali halides gives only five solid-state structures, although the urea-group is heavily incorporated into other anion receptors. From this point of view, there is a true potential to utilize these simple building blocks to develop new receptor systems for ion pairs. Due to this, and encouraged by our recent results,[25] our focus has been directed to study a benzo-15-crown-5 bis-urea receptor **L** (Scheme 1) to act as a ditopic receptor in the solid-state and solution. We have conducted an extensive single-crystal X-ray crystallographic study of the alkali metal halide complexes of **L** to gain more insight about the interactions governing the ion pair binding of **L** in the solid-state. As the crystal structures might give a biased view on the binding stoichiometry in solution, we have also conducted a series of solution studies by determining the stoichiometry and binding affinities of **L** and its alkali metal complexes toward anions *via* Job's plot analysis and ^1H NMR titrations in moderately competitive 4 : 1 $CDCl_3$/DMSO-d_6 solution.

Experimental

Materials and methods

All the reagents and solvents were purchased from Aldrich, Fluka and Altia and used as received. All the yields refer to spectroscopically homogeneous materials. ^1H NMR spectra were recorded with Bruker Avance 300 and Bruker Avance 500 instruments at 303 K. ^{13}C spectra were recorded with Bruker Avance 500 instrument at 303 K. All the spectra were calibrated using the solvent signals of $CHCl_3$ (^1H = 7.26 ppm, ^{13}C = 77.16 ppm) or DMSO (^1H = 2.50 ppm, ^{13}C = 39.52 ppm) as internal standards. All high-resolution (HR) mass measurements were performed with Micromass LCT ESI-TOF-MS instrument by using a lock-mass method.

Syntheses (Scheme 1)

Dinitrobenzo-15-crown-5 (**2**) and diaminobenzo-15-crown-5 (**3**) were synthesized according to the literature procedure with small modifications.[25] Details are presented in the ESI.†

Synthesis of L. Diaminobenzo-15-crown-5 (**3**) (0.163 g, 0.546 mmol) was dissolved in degassed dichloromethane (20 ml) and DMF (3 ml) under argon. 4-Nitrophenyl isocyanate (0.128 g, 0.780 mmol) was dissolved in degassed dichloromethane (10 ml) and added slowly to **3** through a septum. After the addition, 20 ml of degassed dichloromethane was added to the solution. The reaction mixture was stirred for 18 h under argon. The precipitated solid was filtered and washed with dichloromethane, methanol and diethyl ether. The second batch of the product was obtained from the filtrate by concentrating the solution and precipitating the product with a slow addition of diethyl ether into the solution. The solid was washed as previously; yield 75%. ^1H NMR (500 MHz, DMSO, 303 K): δ = 3.62 (8H, s, CH_2), 3.78 (4H, dd CH_2), 4.04 (4H, dd, CH_2), 7.23 (2H, s, ArH), 7.70 (4H, d, ArH), 8.12 (2H, s, NH), 8.18 (4H, d, ArH), 9.74 (2H, s, NH) ppm. ^{13}C NMR (126 MHz, DMSO, 303 K): δ = 68.79, 68.91, 69.81, 70.33, 110.94, 117.38, 124.31, 125.07, 140.91, 145.57, 146.50, 152.76 ppm. HRMS (+ESI): calcd for $C_{28}H_{30}N_6O_{11}Na$, $[M + Na]^+$: m/z 649.1865; found: m/z 649.1852 (Δ = 1.3 mDa).

Crystallography

Single-crystal X-ray data were collected with Agilent SuperNova, equipped with a multilayer optics monochromated dual source (Cu and Mo) and a Atlas detector, using Cu-Kα (λ = 1.54184 Å) radiation at 123 K or 134 K. Data acquisitions, reductions, and analytical face-index based absorption corrections were made using the program CrysAlisPRO.[29] Single-crystal X-ray data for **2** and **L·DMF** were collected with a Bruker Kappa Apex II diffractometer, using graphite-monochromatized Mo-Kα (λ = 0.71073 Å) radiation at 173 K and 120 K, respectively. Collect software[30] was used for the data measurement and

DENZO-SMN[31] was used for the data processing. Multi-scan absorption correction was done with SADABS2008.[32] The structures were solved with ShelXS,[33] Superflip[34] or Sir2002[35] programs and refined on F^2 by full matrix least-squares techniques with ShelXL[33] program in Olex2[36] (v.1.2) program package. The non-H atoms were refined anisotropically and all hydrogen positions were calculated using a riding atom model with ShelXL[33] default parameters. Solvent masking[37] in Olex2 program package was used for structures **L·NaCl**, **2L·KF**, **2L·KI**, **2L·RbF**, and **2L·RbCl**.

Job's plot analysis

Job's plot measurements were performed in a 4 : 1 $CDCl_3$/DMSO solvent mixture. 2.5 mM stock solutions of **L** and the guest were prepared, and for ion pair investigations 2.5 mM stock solution of **L** with 1 equivalent of $MBPh_4$ (M = Na or K) was prepared. Samples with mole fractions X = 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 according to the guest were prepared in NMR tubes with a total volume of 500 μl. The ^{1}H NMR spectra were recorded with a Bruker Avance 500 spectrometer at 303 K. The spectra were calibrated using the $CHCl_3$ signal (δ = 7.26 ppm) as an internal standard. The Job's plots were obtained by plotting $(\Delta\delta^*[H])/([H] + [G])$ against the mole fraction of the guest (H = **L**, G = guest). The chemical shifts of the receptor's urea protons H_a, H_b, aromatic proton H_c and aliphatic protons H_d and H_f were followed (see Scheme 1 and Fig. S20† for proton assignments).

^{1}H NMR titrations

All titrations were performed in a 4 : 1 $CDCl_3$/DMSO solvent mixture. For anion titrations 0.05 M stock solution of **L** was prepared in DMSO, and the sample was diluted with DMSO and $CDCl_3$ to give a final sample concentration of 2.5 mM in 500 μl. For anion titrations 0.125 M stock solution of corresponding TBA-salt in 4 : 1 $CDCl_3$/DMSO was prepared. For ion pair titrations with the $[\mathbf{L}\cdot Na]^+$ complex, 0.05 M stock solutions were prepared for **L** and $NaBPh_4$. Equimolar amounts of the stock solutions were measured in a NMR tube, and the sample was diluted to give 2.5 mM 1 : 1 $[\mathbf{L}\cdot Na]^+$ complex concentration in 500 μl. For ion pair titrations with the $[2\mathbf{L}\cdot K]^+$ complex, 0.05 M stock solutions of **L** and $KBPh_4$ were prepared. Suitable amounts of **L** and $KBPh_4$ were measured in a 2 : 1 ratio to give 5 mM **L** concentration resulting in approximately 2.5 mM $[2\mathbf{L}\cdot K]^+$ complex concentration in 500 μl. For ion pair titrations 0.125 M stock solution of the corresponding TBA-salt in 4 : 1 $CDCl_3$/DMSO was prepared. ^{1}H NMR spectra of the titrations were measured with a Bruker Avance 500 spectrometer at 303 K and all titrations were performed with 18 measurements with the following amounts of the guest added: 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 2.0, 2.5, 3.0, 4.0, 6.0, 10.0 equiv. The spectra were calibrated using the $CHCl_3$ signal (δ = 7.26 ppm) as an internal standard. Titration data was fitted into a desired binding model with HypNMR2008.[38] The chemical shifts of urea protons H_a and H_b, and aromatic proton H_c were followed during the titration experiments (see Scheme 1 and Fig. S20† for proton assignments).

Results and discussion

Synthesis and characterization

The receptor **L** was prepared by a similar three-step synthesis as described previously.[25] The starting material was a commercially available benzo-15-crown-5 compound **1** (Scheme 1). The starting material was nitrated by a two-phase reaction in chloroform and a nitric acid/sulfuric acid mixture. The dinitro product **2** was obtained in 77% yield. Compound **2** was then reduced with hydrazine monohydrate and 10% palladium on activated charcoal under anaerobic conditions under an argon atmosphere to give diamine product **3**. The yield was nearly quantitative, and the diamine was used without further purification due to the instability of the product. Condensation reaction between **3** and 4-nitrophenyl isocyanate under argon atmosphere afforded the desired product **L**, which precipitated out from the reaction mixture as a yellow solid with total yield of 75%. Products **2** and **L** were analyzed by ^{1}H and ^{13}C NMR, HR-ESI-MS, and single-crystal X-ray analysis (see ESI† and Fig. 1). The diamine **3** was characterized by ^{1}H NMR.

Crystal structures of L and its alkali halide complexes

In the course of this work, three solvate structures of **L** were obtained. Slow evaporation of acetone solution of **L** with NaF added in aqueous solution gave crystals with a dimeric assembly of **L** (Fig. 1a and S7;† structure is discussed later in the text). Crystallization of **L** from dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) solutions by evaporation afforded the respective solvate structures, which both show hydrogen bonding between the solvate molecule and one urea group in **L** (Fig. 1b and S8,† Fig. 1c and S9†).

The solid-state ion pair recognition of **L** was comprehensively studied with single-crystal X-ray crystallography. The ten obtained crystal structures of **L** complexed with NaCl, NaBr, NaI, KF, KCl, KBr, KI, RbF, RbCl, and RbI revealed interesting solid-state behavior of the receptor. Each obtained ion pair complex with a sodium cation shows a 1 : 1 complex formation between **L** and Na^+, with either contact or separate ion pair formation with the anion depending on the size (and polarizability) of the anion. When **L** is complexed with larger potassium or rubidium cations, it forms a dimeric assembly,[39,40] binding the anion separately from the cation, regardless of the nature of the anion. The formation of dimeric assembly is not surprising when considering the previously published solid-state structures with benzo-15-crown-5 (B15C5) based molecules, which all show the dimer formation with potassium (39 structures) or rubidium (3 structures).[41] Also sodium is capable of forming a dimeric assembly with B15C5, with 11 structures (out of 34, 32%) showing this kind of behavior. However, cation induced dimerization was not observed in any of the Na^+ complexes of **L**.

Single-crystals of **L·NaCl** were obtained by slow diffusion of diethyl ether into solution of **L** in acetone/DMSO with excess of NaCl added in water. The complex crystallized in the monoclinic space group $P2_1/n$. The dimeric structure of **L** with complexed NaCl is presented in Fig. 2. The dimerization results

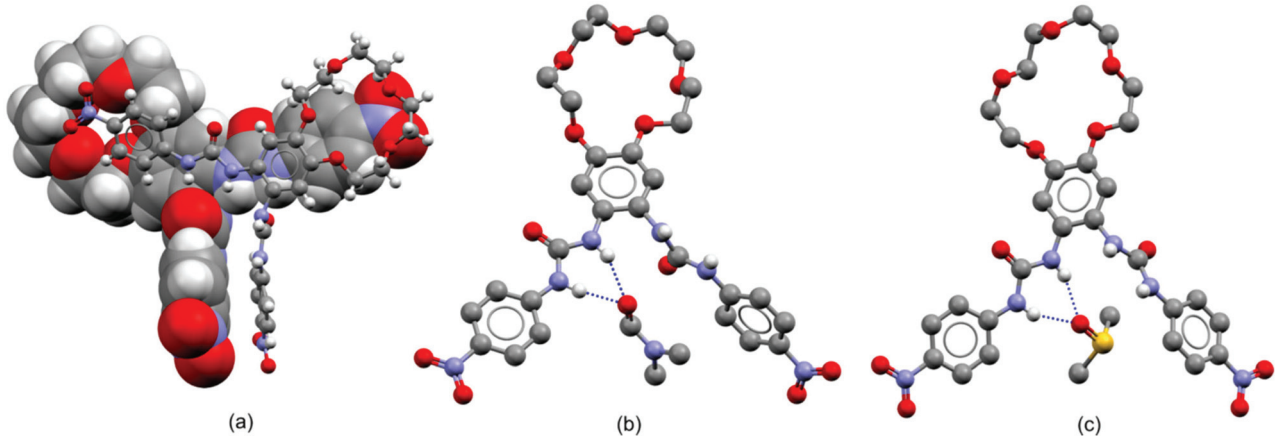

Fig. 1 Single-crystal X-ray structures of (a) **L** [unit cell parameters: monoclinic, a = 15.41305(15) Å, b = 23.7285(2) Å, c = 18.50903(16) Å, β = 95.2966(9)°], (b) **L·DMF** [unit cell parameters: triclinic, a = 10.71590(10) Å, b = 11.3107(2) Å, c = 15.4992(3) Å, α = 101.4580(10)°, β = 95.3000(10)°, γ = 100.4910(10)°], and (c) **L·DMSO** [unit cell parameters: triclinic, a = 8.8481(3) Å, b = 10.1334(4) Å, c = 18.5466(6) Å, α = 86.562(3)°, β = 89.252(3)°, γ = 80.827(3)°]. Water molecules hydrogen bonded to the crown ether ring are omitted from the picture of **L**. The nonbonding hydrogen atoms from structures **L·DMF** and **L·DMSO**, and other solvate molecules are omitted from the picture.

from hydrogen bonding between the urea groups in the adjacent receptor molecules (details are presented in the ESI, Fig. S10†). The chloride anion forms a contact ion pair with the crown ether-complexed sodium cation. The chloride is further hydrogen bonded by the urea group of the adjacent dimer (N3A···Cl1 distance 3.178 Å, N4A···Cl1 distance 3.130 Å, N1B···Cl2 distance 3.258 Å, and N2B···Cl2 distance 3.079 Å, Fig. 2).

Interestingly, this structure is nearly identical to the dimeric **L** structure (Fig. 1a and S7†), in which water molecule occupies the same position as the chloride anion in **L·NaCl** complex (Fig. S7b†). The water molecule forms hydrogen bonds with the crown ether oxygens and urea nitrogens, resulting in the same kind of positioning of the receptor molecules (Fig. S10c†), and nearly identical packing between the two structures. The dimerization of the two **L** molecules is reminiscent of the general solid-state binding motif with benzo-18-crown-6 bis-urea receptor presented previously.[25] In that binding motif the dimerization resulted from hydrogen bonding between the receptor and the anion, and ion–dipole interactions between the complexed cation and the nitro group oxygen. In the **L·NaCl** complex the dimerization results solely from the hydrogen bonding between the urea groups, and there is no coordinative bond between the nitro group oxygen and the sodium cation. The strong point charges of the small and weakly polarized ions result in a strong ion pair, and the weak interactions present in the solid-state might not be powerful enough to separate the ions, thus resulting in a contact ion pair complex. **L·NaCl** was the only solid-state complex of **L** where this type of contact ion pair was observed.

The **L·NaBr** complex was crystallized with slow diffusion of diethyl ether into acetonitrile solution of **L** with NaBr added in excess in water. The complex crystallized in the triclinic space group $P\bar{1}$. In this structure **L** forms a separated ion pair complex with NaBr (Fig. 3 and S11†). Sodium is coordinated to the crown ether, and carbonyl oxygen O2′ of the adjacent molecule and acetonitrile solvate molecules fill the coordination sphere of the cation (Fig. 3b).[42,43] Positioning of the receptors forms a urea proton-coated binding pocket hosting two bromide anions, capped by the acetonitrile molecule coordinated to the sodium cation in the adjacent complex (not shown). Bromide is interacting with the two receptor molecules through four hydrogen bonds, three of them being formed to urea groups in **L** [N1···Br1 distance 3.594 Å, N2···Br1 distance 3.350 Å, and N4···Br1 distance 3.499 Å], and one to the urea group in the adjacent **L′** molecule (N3′···Br1 distance 3.397 Å).

The complex **L·NaI** was crystallized by slow diffusion of diethyl ether into an acetone solution of **L** with NaI added in excess in water. The complex crystallized in the monoclinic space group $I2/a$, consisting of **L** and a separated ion pair complex with NaI. **L** forms a 1 : 1 complex with the sodium (Fig. 4), and the iodide is hydrogen bonded with three urea protons [N1···I1 distance 3.934(3) Å, N3···I1 distance 3.515(3) Å, and N4···I1 distance 3.646(3) Å]. Interestingly, one urea nitrogen is hydrogen bonded to the nitro group of an adjacent receptor molecule [N2···O5′ distance 3.088(3) Å, N2···O6′ distance 3.240(3) Å] leading to a different packing of the **L** molecules in the crystal lattice compared to the **L·NaBr** structure. There is a coordinative bond between sodium and the carbonyl oxygen (Fig. S12b†), resulting in the formation of a 1D coordination polymer along the crystallographic b-axis. The coordination sphere of sodium is filled by the seventh coordinative bond to the nitro group oxygen in the adjacent receptor (not shown).

All the crystal structures of **L** obtained with potassium and rubidium consist of a dimeric assembly of the receptors. Dimerization leads automatically to a separated ion pair complex, and the anion is located in a urea-hydrogen functionalized binding pocket. Fig. 5a shows the crystal structure

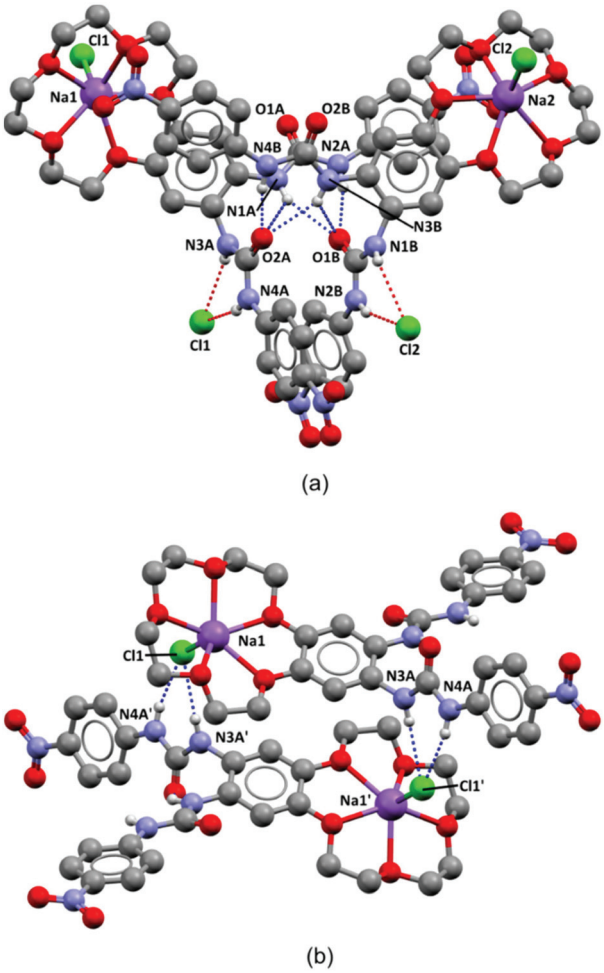

Fig. 2 Crystal structure **L·NaCl**. (a) Hydrogen bonding between the urea functionalities results in dimerization of two **L** molecules. Chloride forms a contact ion pair with the sodium complexed in the crown ether ring. (b) Chloride anion is further hydrogen bonded with the adjacent dimer. Only one molecule of the dimer is shown [unit cell parameters: monoclinic, a = 15.83850(18) Å, b = 23.7838(3) Å, c = 18.5462(2) Å, β = 90.8013(11)°].

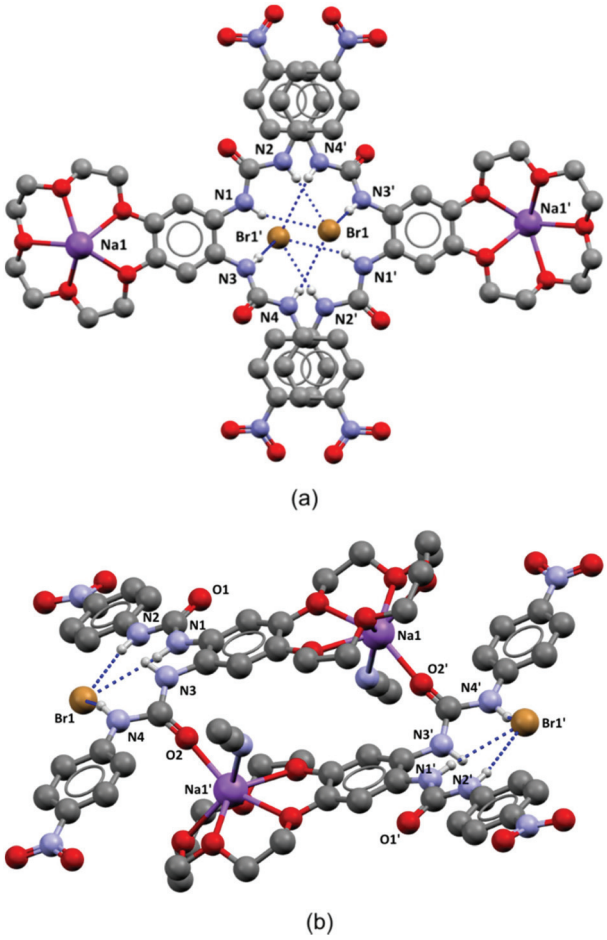

Fig. 3 Crystal structure of **L·NaBr**. (a) **L** forms a separated ion pair complex with NaBr in the solid-state. Bromide anions are located in a urea proton-coated binding pocket. (b) The coordination sphere of sodium is filled by a coordinative bond to carbonyl oxygen O2′ of the adjacent receptor and an acetonitrile solvate molecule [unit cell parameters: triclinic, a = 9.4682(3) Å, b = 12.1247(3) Å, c = 16.1742(5) Å, α = 72.838(3)°, β = 87.307(2)°, γ = 87.437(2)°].

2L·KCl, which was obtained by the slow evaporation of the acetone solution of **L** with excess KCl added in water. The complex crystallized in the triclinic space group $P\bar{1}$. The dimer is formed through cation coordination by ten crown ether oxygens, and intermolecular hydrogen bonds between O2B and urea nitrogens N3A and N4A [N3A···O2B distance 2.892 Å, N4A···O2B distance 2.942 Å]. The dimerization leads to a favorable orientation of the urea nitrogens N1A, N2A, N1B, and N2B toward the center of the cavity formed by the receptor arms. The chloride anion is hydrogen bonded with these urea nitrogens [N1A···Cl1 distance 3.389 Å, N2A···Cl1 distance 3.171 Å, N1B···Cl1 distance 3.264 Å, and N2B···Cl1 distance 3.194 Å], the distances being close to the average N···Cl distance in complexes with chloride hydrogen bonded to the urea group (3.203 Å).[44] The dimers are further packed by hydrogen bonds between the urea groups in adjacent dimers [N3B···O1B′ distance 2.891 Å, N4B···O1B′ distance 2.750 Å]. Details of the packing are presented in the ESI (Fig. S14b†).

In the other fluoride and chloride complexes of **L** with potassium and rubidium, there are solvent molecules also interacting with the anion. In **2L·KF** (Fig. 6 and S13†), **2L·RbF** (Fig. S17†), and **2L·RbCl** (Fig. S18†) structures, there are either water or methanol molecules hydrogen bonded with the anion, resulting in complex solvent-mediated hydrogen bonding networks. Interestingly, this is not observed in any of the structures obtained with bromide or iodide. The dimeric assemblies of **L** with KBr (Fig. S15†), KI (Fig. S16†), and RbI (Fig. S19†) are structurally very similar (Fig. 5b), differing only slightly in the receptor arm orientations and unit cell dimensions. Surprisingly, crystals of **L** with RbBr were not obtained in spite of numerous attempts. Taking into consideration the similarities in the structures with bromide and iodide salts of potassium and rubidium, probably this complex would not differ much from the already obtained structures.

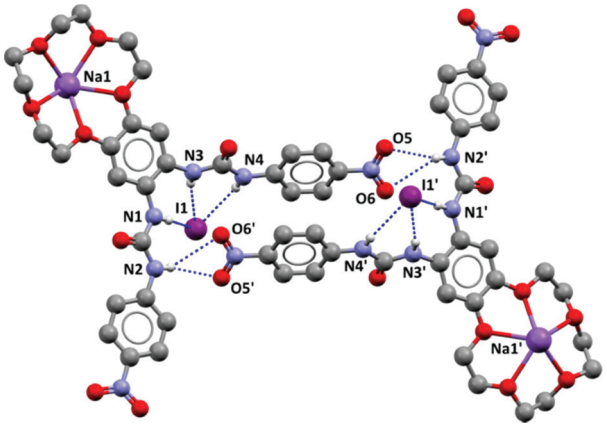

Fig. 4 Crystal structure of **L·NaI**. Structure consists of a separated ion pair complex, with sodium complexed in the crown ether and iodide anion hydrogen bonded with three urea hydrogen bonds. Fourth urea proton forms hydrogen bonds to the adjacent receptor's nitro group [unit cell parameters: monoclinic, a = 22.1422(5) Å, b = 7.22931(19) Å, c = 42.6101(13) Å, β = 100.291(3)°].

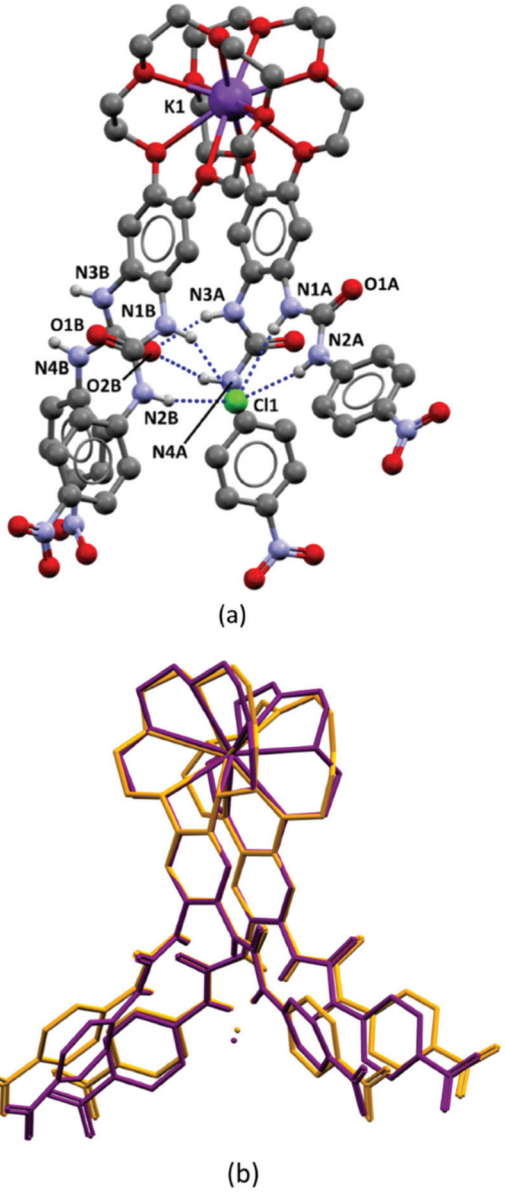

Fig. 5 (a) Crystal structure of **2L·KCl**. Complexation of K^+ in 15C5 moiety leads to dimerization of two receptor molecules. Dimerization is further enhanced by intermolecular hydrogen bonds between carbonyl oxygen O2B and urea nitrogens N3A and N4A [unit cell parameters: triclinic, a = 10.5214(2) Å, b = 15.4120(4) Å, c = 21.1832(5) Å, α = 105.004(2)°, β = 97.408(2)°, γ = 109.292(2)°]. (b) Overlay of structures **2L·KBr** (yellow) and **2L·KI** (purple) showing very similar conformation of the receptor molecules in the dimeric assemblies.

Although all the solid-state structures of **L** with potassium and rubidium have basic similarities in the dimer formation and ion pair complexation, all the structures are not identical to one another. The most strikingly different structure was obtained with **L** and KF. The X-ray quality crystals of **2L·KF** were grown by slow diffusion of diethyl ether into methanol/DMF solution of **L** with excess KF added in water. The complex crystallized in the orthorhombic space group *Fdd*2, having an extremely large unit cell (63 500 Å^3) and large voids (8.6% of the unit cell)[45] in the crystal lattice (Fig. S13b†). The structure can be formulated as a tetramer, *viz.* dimer of two **2L·KF** complexes (Fig. 6). The fluoride anion is bound inside the binding pocket by a water-mediated hydrogen bonding network (Fig. 6c). The hydrogen bond lengths of the urea-groups vary between 2.633 Å–2.957(6) Å for F1, and 2.707 Å–2.871 Å for F2. Both fluoride anions are further hydrogen bonded with water molecules [O12···F1 distance 2.557(8) Å, O16···F2 distance 2.658(6) Å]. The dimers are hydrogen bonded *via* urea-groups resulting in dimer of dimers [N1D···O2B distance 3.017(6) Å, N2D···O2B distance 2.866(6) Å, N1B···O2D distance 3.039(6) Å, and N2B···O2D distance 2.798(6) Å]. These interactions are reminiscent of the urea group interactions responsible for dimer formation in structures **L** and **L·NaCl.** The structure consists of a large number of solvent molecules, but because of the large unit cell and porous structure, all the solvent molecules within the structure could not be successfully modelled.

Anion binding studies in solution

The stoichiometry of the complexation in solution with **L** and a set of alkali metal cations, anions and ion pairs were studied with Job's plot analysis. In addition, the behavior of **L** and its alkali metal complexes as anion receptors was studied *via* ^{1}H NMR titrations. These studies were performed in 4 : 1 $CDCl_3$/DMSO-d_6, using alkali metal tetraphenylborates ($MBPh_4$, M = Na and K) as the cation source and the tetrabutylammonium halides (TBAX, X = Cl, Br, and I) as the anion source. The BPh_4^- and TBA^+ ions do not interact with the very similar benzo-18-crown-6 bis-urea receptor and are thus not affecting the binding event.[25] In addition to solubilizing **L** in weakly polar $CDCl_3$, DMSO was used to create more competitive media for the binding, which is known to be strong in less competitive solvent systems.[25] The host and guest concentrations and the binding induced chemical shifts were used in

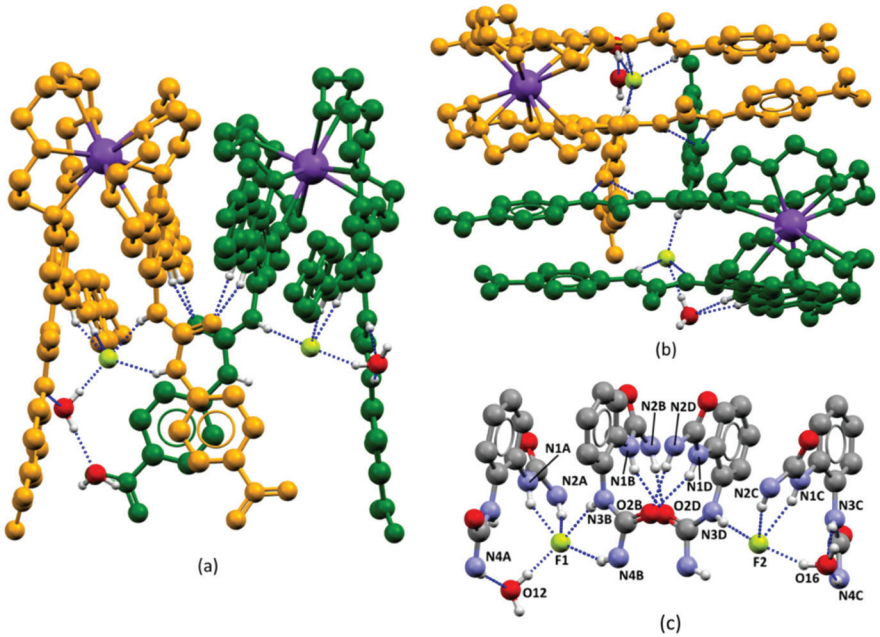

Fig. 6 Crystal structure of **2L·KF**. (a) Side view of the structure. It consists of dimer of dimers formed through hydrogen bonding between urea groups in the neighboring dimers. (b) Top view of the structure. The interactions of "inner" molecules resemble to those seen in structures **L** and **L·NaCl**. (c) The fluoride anion is located inside the binding pocket hydrogen bonded with the urea protons and water molecules [unit cell parameters: orthorhombic, a = 52.080(2) Å, b = 43.9225(8) Å, c = 27.7395(6) Å].

the HypNMR2008 program,[38] utilizing global analysis[46] with the help of H_a, H_b, and H_c proton (see Scheme 1) signals to calculate the binding constants (K_a).

In order to estimate the halide binding affinity of the cationic complexes of **L**, some simplifications were made in the binding constant calculations. The guests are used as their BPh4$^-$ and TBA$^+$ salts which are considered as "innocent" counter ions. The effect of these counter-ions is considered to be so small that it can be safely neglected from the binding constant calculation. The above is supported by the fact that the ion pairing of $NaBPh_4$ and $TBABPh_4$ has been quantified in a 4 : 1 $CDCl_3/CD_3CN$ solvent system, where the ion pair formation between Na^+ and BPh_4^- was found to be extremely weak,[8] and weak for $TBABPh_4$.[8,47] Considering the similarity of the solvent system in this study (4 : 1 $CDCl_3$/DMSO), Na^+ can be considered to be a non-contact ion pair and free from the BPh_4^- counter-anion, and thus its interaction with the B15C5 moiety is not perturbed by ion pairing. Complexation of the cation into the crown ether moiety is known to be strong,[39] and can be considered to induce a turn-on effect, resulting in stronger anion binding compared to the neutral receptor.[21,25,48,49]

The anion binding stoichiometry of the neutral receptor **L** alone was studied with Job's plot analysis (Fig. S22†), and then the anion binding affinity was measured *via* ^{1}H NMR titrations in 4 : 1 $CDCl_3$/DMSO. The binding constant calculation using 1 : 1 binding stoichiometry (verified by the Job's plot analysis) resulted in K_a = 828 for chloride, 175 for bromide, and 32 M^{-1} for iodide. These values are in very close agreement with those obtained previously for a benzo-18-crown-6 based bis-urea receptor, and a reference bis-urea receptor without the crown ether unit.[25] Details of the binding constant calculations and the binding isotherms are given in the ESI (Fig. S24–S26†).

The Job's plot analysis confirms the expected 1 : 1 complex of **L** and Na^+ (Fig. S21a†) and $[\mathbf{L}{\cdot}Na]^+ + Cl^-$ (Fig. 7a) in 4 : 1 $CDCl_3$/DMSO. The halide binding affinity of the cationic complex $[\mathbf{L}{\cdot}Na]^+$ was measured *via* ^{1}H NMR titrations in the same 4 : 1 $CDCl_3$/DMSO solvent system. The chemical shift differences observed upon stepwise addition of chloride in titrations of $\mathbf{L} + Cl^-$ and $[\mathbf{L}{\cdot}Na]^+ + Cl^-$ are presented in Fig. 7b.

The turn-on effect of the sodium cation on the chloride binding is clearly seen from the chemical shift differences between **L** and $[\mathbf{L}{\cdot}Na]^+$ (Fig. 7b). The more drastic chemical shift changes of $[\mathbf{L}{\cdot}Na]^+$ with small chloride concentrations indicate stronger chloride binding. The binding constant for the $[\mathbf{L}{\cdot}Na]^+ + Cl^-$ complexation calculated with the 1 : 1 binding stoichiometry was K_a = 7609 M^{-1}, being *ca.* nine times larger than with **L** alone (Fig. S27†). Titration of $[\mathbf{L}{\cdot}Na]^+$ with bromide and iodide gave binding constants of 1411 and 374 M^{-1}, respectively (Fig. S28 and S29†), being eight and 12 times larger than with **L** alone. These eight to twelve times larger binding constants clearly manifest the turn-on effect induced by the sodium complexation in the crown ether part.

Based on the X-ray structures discussed above, the larger potassium cation is expected to form a dimer and thus show different binding properties in solution. To verify the stoichiometry of the $\mathbf{L} + K^+$ in solution, a Job's plot analysis with **L** and $KBPh_4$ was done (Fig. S21b†) showing clearly a 2 : 1 complex, *viz.* $[2\mathbf{L}{\cdot}K]^+$. The stoichiometry of the anion complexation of $[2\mathbf{L}{\cdot}K]^+$ was then done *via* Job's plot analysis. As is

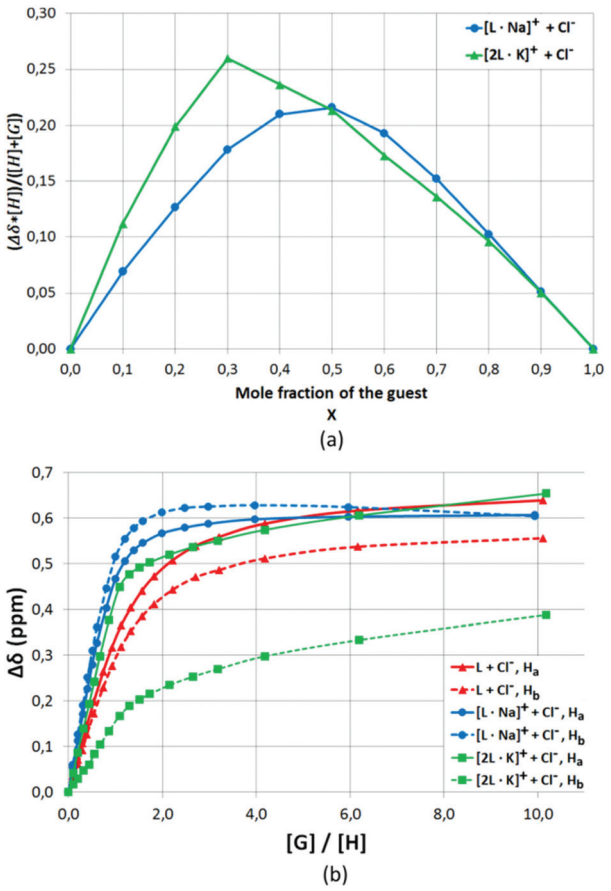

Fig. 7 Job's plot analysis of (a) $[L{\cdot}Na]^+$ + Cl^- and $[2L{\cdot}K]^+$ + Cl^- complexations. (b) The chemical shift differences of urea-protons H_a (solid line) and H_b (dashed line) in L (red), $[L{\cdot}Na]^+$ (blue), and $[2L{\cdot}K]^+$ (green) upon stepwise addition of Cl^-.

clearly evident from the Job's plot presented in Fig. 7a, the same 2 : 1 stoichiometry of **L** persists also in the anion complexation when **L** is complexed with potassium.

The halide binding behavior of the dimeric complex $[2\mathbf{L}{\cdot}K]^+$ in solution was done *via* ^1H NMR titrations in the same 4 : 1 $CDCl_3$/DMSO solvent system. As is evident from the chemical shift differences presented in Fig. 7b, the dimerization *via* the potassium cation complexation has clearly a different effect on the binding mode of **L** toward chloride. This is seen from the different effect on chemical shifts of H_a and H_b in $[2\mathbf{L}{\cdot}K]^+$ complex compared to $[\mathbf{L}{\cdot}Na]^+$ upon chloride binding.

The crystal structure indicates that the stoichiometry for $[2\mathbf{L}{\cdot}K]^+$ + Cl^- complexation is 1 : 1 (Fig. 5a), but the chemical shift changes observed in the titration between $[2\mathbf{L}{\cdot}K]^+$ and chloride are best modeled with a mixed 1 : 1 + 1 : 2 binding stoichiometry (where 1 : 1 is considered as $[2\mathbf{L}{\cdot}K]^+$ + Cl^-, and 1 : 2 as $[2\mathbf{L}{\cdot}K]^+$ + $2Cl^-$ with both species in equilibrium). However, the 1 : 1 complex has >99% abundancy with the secondary 1 : 2 complex being present <1% with up to *ca.* 1 equiv. of chloride (Fig. S30d†). The binding constant calculation using the above model for $[2\mathbf{L}{\cdot}K]^+$ + Cl^- complexation gives binding constant K_{a1} = 42 247 M^{-1} for the 1 : 1 complex while it is only 96 M^{-1} for the 1 : 2 complex (Fig. S30†). The large binding constant for chloride is logical considering the pre-organization of the dimeric assembly to host a suitably sized anion inside the binding pocket, and larger number of interacting groups in the dimer for anion binding. The second binding event with excess chloride is explainable by hydrogen bonding interactions of the chloride with the urea-groups outside of the binding pocket.

The corresponding titration of $[2\mathbf{L}{\cdot}K]^+$ with bromide resulted in similar chemical shift changes as with chloride. The binding behavior was modeled in similar manner giving binding constants K_{a1} = 14 713 M^{-1} for the 1 : 1 complex and 51 M^{-1} for the 1 : 2 complex (Fig. S31†). The smaller binding constants obtained for bromide are in agreement with weaker hydrogen bond acceptor nature of the bromide. The chemical shift changes obtained from titrations between iodide and $[2\mathbf{L}{\cdot}K]^+$ were clearly smaller and due to the weakest hydrogen bond acceptor character of iodide the 1 : 2 complex was absent. The simple 1 : 1 binding model produced binding constant K_a = 717 M^{-1} (Fig. S32†).

In summary, the results obtained from ^1H NMR titrations do clearly show the turn-on effect of the cation complexation in the anion recognition behavior of **L**. Receptor **L** forms a 1 : 1 complex with sodium in solution, and this positively charged complex has larger binding affinity toward halide anions compared to **L** alone. When complexed with K^+ in solution, dimerization of **L** receptors *via* crown ether complexation is observed. For binding constant calculations, the active receptor is considered as the $[2\mathbf{L}{\cdot}K]^+$ complex, which shows very interesting solution-state behavior toward chloride (and bromide) with a very strong 1 : 1 complex formation with the anion. With these anions also a secondary complex formation (1 : 2) has to be taken into account for successful modelling of the observed chemical shifts. However, binding constants for 1 : 2 complexations are negligible when compared with the 1 : 1 binding, and thus the 1 : 1 complex between $[2\mathbf{L}{\cdot}K]^+$ and the anion is the main component (>99%) with chloride concentrations up to one equivalent. The obtained anion binding constants with the fitting errors are presented in Table 1.

Table 1 Binding constants (K_a) obtained from for L, $[L{\cdot}Na]^+$, and $[2L{\cdot}K]^+$ ^1H NMR titrations in 4 : 1 $CDCl_3$/DMSO-d_6 at 303 K

		L	$[\mathbf{L}{\cdot}Na]^+$	$[2\mathbf{L}{\cdot}K]^+$
Cl^-	K_a [a]	828 ± 22	7609 ± 576	—
	K_{a1} [b]	—	—	42 247 ± 20 877
	K_{a2} [b]	—	—	96 ± 29
Br^-	K_a [a]	175 ± 3	1411 ± 69	—
	K_{a1} [a]	—	—	14 713 ± 2657
	K_{a2} [b]	—	—	51 ± 21
I^-	K_a [a]	32 ± 3	374 ± 16	717 ± 58

[a] 1 : 1 (K_a) binding model used. [b] 1 : 1 (K_{a1}) + 1 : 2 (K_{a2}) binding model used (see the text and ESI for details).

Conclusions

In this work we have comprehensively studied the behavior of a ditopic benzo-15-crown-5 bis-urea receptor **L** as an ion pair receptor in the solid-state and the anion binding properties of the receptor's sodium and potassium complexes in solution. The synthesized benzo-15-crown-5 receptor with bis-urea functionality (**L**) has binding sites for both the cation and anion, respectively. A total of 13 crystal structures, from which 10 are complexes with alkali halides, show how **L** acts as a ditopic ion pair receptor in the solid-state. With smaller (and with better size-fit) sodium cation, **L** forms a 1 : 1 complex, and binds the anion as a contact (Cl^-) or separate (Br^- and I^-) ion pair, depending on the size and the polarizability of the anion. When complexed with larger potassium or rubidium cations, **L** forms a dimeric structure with intermolecular hydrogen bonding enhancing the dimerization. This dimeric complex binds all halide anions (F^-, Cl^-, Br^-, and I^-) as a separated ion pair in the solid-state, and the anion is always bound *via* hydrogen bonds formed to the urea groups. Although similar in the dimerization behavior, the structures obtained with potassium and rubidium halides also show differences to one another. For example, complex **2L·KF** is actually a tetramer, formed by dimer of dimers with the fluoride anion being bound through a complex solvent-mediated hydrogen bonding network, found also in a few other obtained structures. In solution the Job's plot analyses of **L** with Na^+ and K^+ confirmed the formation of 1 : 1 and 2 : 1 complexes, respectively. The ^{1}H NMR titrations performed with monomeric $[\mathbf{L}\cdot Na]^+$ and the dimeric $[2\mathbf{L}\cdot K]^+$ with chloride, bromide, and iodide show that the anion binding affinity of $[\mathbf{L}\cdot Na]^+$ and $[2\mathbf{L}\cdot K]^+$ is clearly higher than with receptor **L** alone showing clear positive cooperativity and turn-on effect in anion binding upon cation complexation. Stronger anion binding of $[\mathbf{L}\cdot Na]^+$ compared to **L** alone is explainable by electrostatic interactions between the cationic receptor complex and the anion. The even stronger binding of all the studied halides with the $[2\mathbf{L}\cdot K]^+$ complex is explainable by the formation of an excellent anion binding site upon dimerization, having a larger number of urea groups to form more hydrogen bonding interactions between the receptors and the anion, as seen in the solid-state complexes of **L** with potassium and rubidium halides. Thus, the differences in solution behavior between $[\mathbf{L}\cdot Na]^+$ and $[2\mathbf{L}\cdot K]^+$ is explainable by the structures formed upon cation complexation as also seen in the solid-state.

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