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Tris(2-aminoethyl)amine based tripodal urea receptors for oxalate: encapsulation of staggered *vs*. planar conformers†

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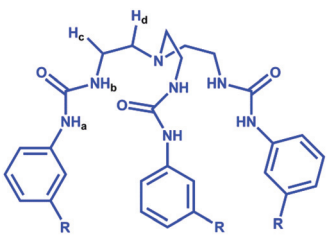
Simple tris(2-aminoethyl)amine (TREN) based tripodal urea receptors are investigated for the encapsulation of divalent oxalate ($C_2O_4^{2-}$) in a semi-aqueous medium. A single crystal X-ray diffraction study shows that the receptor with 3-cyanophenyl functionality captures a staggered conformer whereas the 3-fluorophenyl functionalized receptor encapsulates a less stable planar conformer.

The recognition and transportation of substrates containing carboxylate functionalities are of great importance due to their crucial role in the metabolism of cells.[1] The recognition and sensing of the simplest dicarboxylate anion, $C_2O_4^{2-}$, is very useful in food chemistry and it is also an important nutrient found in many plants.[2] Insoluble calcium oxalate is a prime constituent of renal stones.[3] A high level of $C_2O_4^{2-}$ in urine may be indicative of renal failure, kidney lesions and pancreatic insufficiency.[4] Oxalate exists in two different conformers as illustrated by single crystal X-ray crystallography, one of which is a planar conformer with D_{2h} molecular symmetry, while the other one is a staggered conformer with approximate D_{2d} symmetry.[5] The calculated rotational energy barrier between the D_{2h} and D_{2d} conformers of $C_2O_4^{2-}$ is about 2–6 kcal mol^{-1}.[5,6] The staggered conformer is the stable form of $C_2O_4^{2-}$ in solution. Surprisingly, a reverse pattern is observed in most of the structural evidence.[6] Only a few examples of the staggered $C_2O_4^{2-}$ conformer have been reported in the solid state.[6,7,10a]

Oxalate recognition by a macrobicyclic polyammonium cryptand was first explored by Nelson *et al.* [8] Delgado *et al.* recently reported the recognition of dicarboxylates in the solution state by macrobicyclic polyammonium receptors.[9] Very recently, a bis-amidocarbazolyl urea based receptor has been utilized for the recognition of dicarboxylate anions which also represents the rare example of solid state structural evidence of $C_2O_4^{2-}$ recognition by neutral urea receptors.[10a] The sensing of $C_2O_4^{2-}$ *via* the indicator displacement assay technique using a dicopper complex is also reported, where quite a large binding constant value ($\sim 10^5$) is calculated in aqueous media.[10b,c] TREN based tripodal ureas/thioureas are some of the most popular and widely used classes of anion receptors in recent times.[11–35] These receptors have an interesting property to form a capsular assembly that creates a microenvironment for recognition of various anionic guests.[29,32,34,35] Herein, two closely related tripodal ureas **L1** and **L2** (Chart 1) are explored for $C_2O_4^{2-}$ encapsulation in a semi-aqueous environment. Importantly, we have shown the trapping of a staggered conformer of $C_2O_4^{2-}$ in the dimeric capsular aggregation (9.815 Å) of **L1**, whereas a relatively bigger dimeric capsular assembly (10.823 Å) of **L2** encapsulates the planar form of $C_2O_4^{2-}$ by a single crystal X-ray structural study.

To synthesize the $C_2O_4^{2-}$ complexes we have carried out the reaction between **L1**/**L2** and TBAI (2 equiv.) with excess potassium oxalate in a DMSO–H_2O binary solvent system. Eventually, we were able to isolate $C_2O_4^{2-}$ encapsulated capsular aggregates **C1** and **C2** of **L1** and **L2** in ~75–80% yield after slow evaporation of the 5% H_2O–DMSO solvent mixture. **C1** crystallizes in the triclinic crystal system with a $P\bar{1}$ space group. The asymmetric unit of **C1** has two receptor units **L1**, two TBA



L1; R = CN
L2; R = F

Chart 1 Chemical structures of **L1** and **L2**.

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†Electronic supplementary information (ESI) available: Synthesis and characterization of **L2**, **C1** and **C2**, details of ^{1}H NMR titration including a Job's plot and stack plots of the ^{1}H NMR, details of the X-ray structure determination, X-ray crystal structures, hydrogen bonding parameters and scatter plots of **C1** and **C2**. CCDC 914147 (**C1**) and 914149 (**C2**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob41071d

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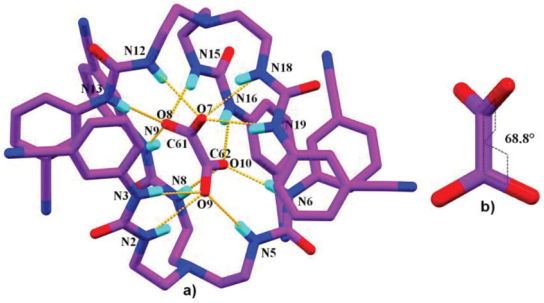

Fig. 1 (a) Ball–stick representation of capsular aggregate **C1** showing encapsulated $C_2O_4^{2-}$ *via* twelve N–H···O interactions in the dimeric capsular assembly of **L1**; (b) view of the O–C–C–O dihedral angle of the encapsulated staggered $C_2O_4^{2-}$ conformer in **C1** (all the non-acidic hydrogen atoms and TBA counter cations are omitted for clarity).

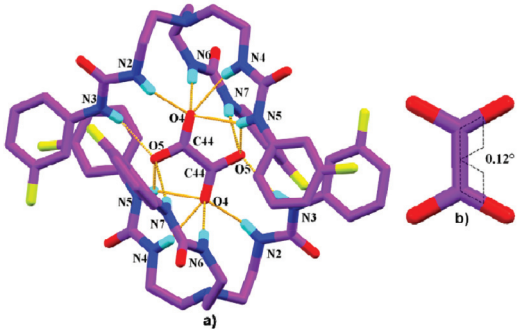

Fig. 2 (a) Ball–stick representation of capsular aggregate **C2** showing encapsulated $C_2O_4^{2-}$ *via* twelve N–H···O interactions in the dimeric capsular assembly of **L2**; (b) view of the O–C–C–O dihedral angle of the encapsulated planar $C_2O_4^{2-}$ conformer in **C2** (all the non-acidic hydrogen atoms and TBA counter cations are omitted for clarity).

counter cations and one $C_2O_4^{2-}$. In **C1** two molecules of **L1** form a cavity that engulfs a staggered form of $C_2O_4^{2-}$ at its centre *via* hydrogen bonding interactions with six urea NH protons. There are a total of twelve hydrogen bonding interactions between twelve NH units of two **L1** and four O atoms of $C_2O_4^{2-}$. All four O atoms of $C_2O_4^{2-}$, namely O7, O8, O9 and O10, accept three N–H···O hydrogen bonds each. From the scatter plot diagram it is clear that all the twelve hydrogen bonding interactions fall in the strong hydrogen bonding region (*i.e.* $d_{H\cdots O} < 2.5$ Å and $d_{N\cdots O} < 3.2$ Å) (Fig. 1, Fig. 8S and Table 2S in the ESI†). Receptors **L1** and **L2** differ only in the attached electron withdrawing functionality at the *meta* position. **C2** obtained from **L2** crystallizes in the monoclinic crystal system with a $P2_1/c$ space group. In the case of **C2**, $C_2O_4^{2-}$ is perfectly encapsulated by two receptor units *via* a dimeric capsular assembly like **C1**. Unlike **C1**, the asymmetric unit of **C2** consists of one **L2**, a half unit of $C_2O_4^{2-}$ and one TBA counter cation. **C2** is centrosymmetric in nature as required by the space group symmetry, having one inversion centre (*i*) passing through the centre of encapsulated $C_2O_4^{2-}$. In **C2** the $C_2O_4^{2-}$ is in the special position. There are eight $C_2O_4^{2-}$ present at the eight corners of the unit cell and two $C_2O_4^{2-}$ situated at the two opposite faces of the unit cell (Fig. 9S in the ESI†). There are twelve hydrogen bonds which are involved in binding the $C_2O_4^{2-}$ deep inside the capsular cavity. The oxygen atoms of $C_2O_4^{2-}$, namely O4 and O5, accept three N–H···O hydrogen bonds each. All the N–H···O hydrogen bonding parameters fall in the strong hydrogen bonding regime (Fig. 2, Fig. 10S and Table 3S, ESI†).

The capsular size of **C1** and **C2** varies substantially. The capsular size of **C1** is determined as 9.815 Å from the apical nitrogen distances, whereas the capsular size is relatively higher for **C2** (10.823 Å). Further insight into the geometry of the trapped $C_2O_4^{2-}$ reveals their conformational differences. The central C–C bond length and dihedral angle differ upon moving from smaller to bigger capsular aggregates. In the case of **C1**, the cavity of the dimeric assembly encapsulates the staggered conformer of $C_2O_4^{2-}$ where the O–C–C–O dihedral angle is 68.8° (Table 1). The central C–C (C61–C62) bond length around the staggered $C_2O_4^{2-}$ in **C1** is 1.501 Å, which is slightly lower than the normal C–C single bond length. In contrast, the trapped $C_2O_4^{2-}$ in **C2** shows almost planar conformation with an O–C–C–O dihedral angle of 0.12° (Table 1). The C–C bond length in $C_2O_4^{2-}$ is found to be 1.576 Å, which indicates the single bond characteristic nature of $C_2O_4^{2-}$ compared to other staggered conformers. Thus, by simply tuning substituents from –CN to –F, discrimination between different conformers (staggered and planar) of $C_2O_4^{2-}$ is achieved in the solid state inside the dimeric capsular assembly of the receptors.

Table 1 C–C bond length and torsion angles of $C_2O_4^{2-}$ in capsular aggregates **C1** and **C2** and in $K_2C_2O_4$

Compounds	C–C bond distance (Å)	Torsion angle (°)	Apical N···N distance (Å)
C1	1.501	68.81	9.815
C2	1.576	0.12	10.823
$K_2C_2O_4$	1.595	0.00	—

The solution state binding properties of **L1** and **L2** with $C_2O_4^{2-}$ are investigated by ^{1}H NMR titration in a D_2O–DMSO-d_6 solvent system at 298 K in the presence of potassium oxalate. In a typical NMR titration experiment, a standard solution of $C_2O_4^{2-}$ is prepared in D_2O–DMSO-d_6 (1.1 : 1, v/v) and titrated into a solution of the respective receptor in a D_2O–DMSO-d_6 (1 : 9, v/v) solvent mixture. To maintain a similar solvent system throughout the titration, we have prepared a stock solution of the receptor in D_2O–DMSO-d_6 (1 : 9, v/v). However, the lower solubility of potassium $C_2O_4^{2-}$ in pure DMSO-d_6 or even in DMSO-d_6–D_2O (1 : 1) prevents us from maintaining an exactly similar solvent system during titration. Further during titration, after addition of 2 equiv. of $C_2O_4^{2-}$, slight precipitation is observed in the NMR tube. In each case, a gradual downfield shift of $NH_{a/b}$ protons and an upfield shift of $CH_{c/d}$ protons are observed upon addition of a guest aliquot. All the titration curves give the best fit for the 1 : 1 binding model for receptors **L1** and **L2** to $C_2O_4^{2-}$ in agreement with the Job's plot indicating an optimum $\Delta\delta$ at around 0.5 = [**L**]/([**L**] + [$C_2O_4^{2-}$]), and the association constant values are calculated using WINEQNMR software.

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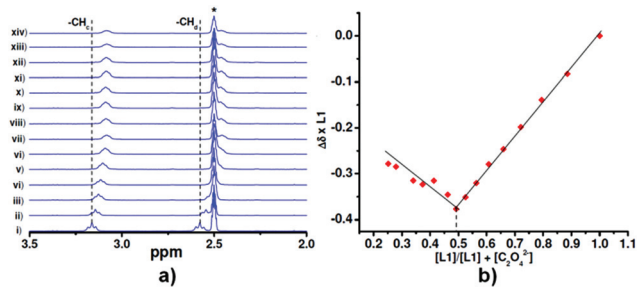

Fig. 3 (a) Partial ^{1}H NMR (300 MHz) spectral changes of **L1** in D_2O–DMSO-d_6 (1 : 9, v/v) with added standard $K_2C_2O_4$ solution in D_2O–DMSO-d_6 (1.1 : 1, v/v) (298 K) ([**L1**]$_0$ = 4.94 mM). Ratio of concentration [$C_2O_4^{2-}$]/[**L1**]: (i) 0, (ii) 0.129, (iii) 0.258, (iv) 0.387, (v) 0.517, (vi) 0.646, (vii) 0.775, (viii) 0.904, (ix) 1.033, (x) 1.162, (xi) 1.421, (xii) 1.938, (xiii) 2.584 and (xiv) 2.971; (b) Job's plot for **L1** with $K_2C_2O_4$ in D_2O–DMSO-d_6 (1.1 : 1, v/v) ([**L1**] is varied from 4.94 to 3.61 mM by the addition of aliquots of 39.91 mM $K_2C_2O_4$) ('*' indicates the DMSO-d_6 solvent peak).

One such representative titration experiment between **L1** and $C_2O_4^{2-}$ is described in Fig. 3. The upfield shift of CH_c and CH_d protons is monitored upon gradual addition of a guest solution. Job's plot analysis shows the presence of minima at [**L1**]/([**L1**] + [$C_2O_4^{2-}$]) ≈ 0.5, which indicates 1 : 1 host–guest association in solution for **L1** (Fig. 3, Fig. 11S–13S in the ESI†). Fig. 14S–16S in the ESI† describes the NMR titration profile along with a Job's plot for the titration of **L2** with $C_2O_4^{2-}$. The association constant (log *K*) and the corresponding free energy change (Δ*G*) values for $C_2O_4^{2-}$ binding with **L1** and **L2** are calculated and tabulated in Table 2. This stoichiometric discrepancy between solid and solution state binding properties is common for this type of tripodal urea/thiourea receptor.[29,35] From NMR titration experiment data the 3-cyanophenyl substituted urea **L1** shows slightly higher binding affinity towards $C_2O_4^{2-}$ (log *K* = 4.82) compared to that of the 3-fluorophenyl substituted urea **L2** (log *K* = 4.29). Further solution state characterization for encapsulated $C_2O_4^{2-}$ is confirmed by ^{13}C NMR analysis. An additional peak at ~172–174 ppm corresponding to the encapsulated $C_2O_4^{2-}$ can be assigned in ^{13}C NMR spectra of isolated $C_2O_4^{2-}$ based capsular aggregates of **C1** and **C2** (Fig. 17S, ESI†). Attempts have been made to see the effect of other mono- and dicarboxylates (acetate, benzoate, terephthalate dianion) on **L1** and **L2** in the solution state. Eventually, except for $C_2O_4^{2-}$ other investigated anions show insignificant changes in the chemical shift of $CH_{c/d}$ protons during comparative ^{1}H NMR experiments under identical experimental conditions (Fig. 18S and 19S in the ESI†). However, selectivity of **L1** for oxalate over other carboxylates (acetate, benzoate, terephthalate dianion) is confirmed by competitive crystallization. When a mixture of the sodium salts of the above-mentioned anions and oxalate is added to a 5% H_2O–DMSO solution of **L1** and allowed to crystallize, crystals of **C1** are isolated, which are confirmed by single crystal X-ray diffraction analysis.

Table 2 Binding constants and free energy change of **L1** and **L2** with $C_2O_4^{2-}$

Host	log K^a	Δ*G* (kcal mol^{-1})
L1	4.82	−6.62
L2	4.29	−5.89

[a] Error range < 15%.

In conclusion, we have investigated the binding studies of the organic dicarboxylate anion $C_2O_4^{2-}$ by two closely related TREN based neutral tripodal urea receptors. Solid state structural evidence reveals the trapping of two possible conformers of $C_2O_4^{2-}$ in the cavity of dimeric capsular assemblies of the receptors. Conformational insight into the encapsulated $C_2O_4^{2-}$ shows rare evidence of staggered conformer encapsulation in the solid state. Appreciable variation of capsular dimension is also observed depending upon the encapsulated guest conformation. The staggered conformer of $C_2O_4^{2-}$ acts as a template for the formation of smaller capsular assemblies, whereas bigger assemblies are driven by planar conformers.

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