Novel molecular clip: synthesis, structure and encapsulation of small solvent molecule in the crystal state

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A novel glycoluril molecular clip has been designed, synthesised and characterised. The X-ray crystallographic analysis revealed that the molecular clip had a large enough cavity to show the capability of encapsulate DMSO molecule. The supramolecular structure formed via N–H…O and π–π interactions, the molecules were linked into a two-dimensional structure.

Keywords: crystal engineering, molecular clip, glycoluril

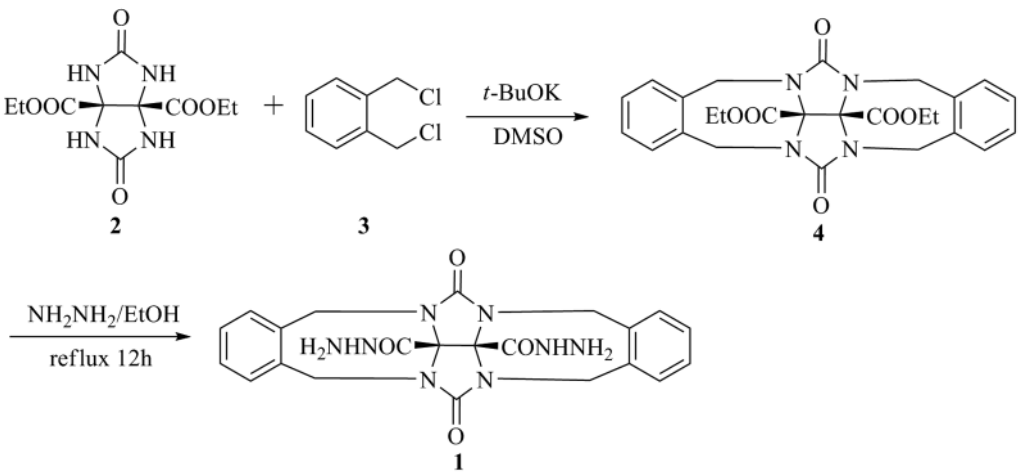
Glycoluril and its derivatives are now widely used as building blocks for studies of self-assembly in homogeneous solution and in solid state.[1,2] Supramolecular chemistry based on glycoluril can be traced to the work of Mock and co-workers in the 1980s on cucurbit[6]uril (CB[6]).[3] However, it was the pioneering work of Rebek and Nolte, that made glycoluril commonplace. Rebek's group, focused on the H-bond driven self-assembly of glycoluril derivatives into "sports-balls" in organic solvents and used them to encapsulate guest molecules and to promote reactions.[2,4,5] Nolte's work has more direct relevance to our studies. This work has pioneered the use of diphenylglycoluril derived molecular clips in supramolecular chemistry.[1,6] Nolte demonstrated that these diphenylglycoluril molecular clips have various functions including acting as receptors for resorcinols,[7] ammonium ions,[8] amino acids,[9] and viologens,[10] as components of supramolecular vesicles,[11] and as enzyme mimics.[12,13] In recent years, Nolte's group has also studied the self-association of diphenylglycoluril derived molecular clips in water and organic solvents,[1,12–18] which can be used to build up lamellar thin films.[19]

As part of our interest in the crystal engineering using the glycoluril skeleton as a building block,[20,21] we designed a number of fascinating molecular clips.[23,24,31,32] Furthermore, we obtained structural details for a wide variety of compounds by X-ray crystallography. We considered that glycoluril derivatives might be good building blocks for studies of crystal engineering because of their potential to engage in H-bonding and π–π interactions. To investigate more complicated self-assembling structures in the crystal engineering, we decided to endow these molecular clips with more H-bond donating or accepting functional groups. Here, we report the X-ray crystal structure of a molecular clip **1** which bears two $CONHNH_2$ groups on its convex face and two *o*-xylylene walls.

We obtained a crystal of **1** that was suitable for X-ray crystal structure determination by slow evaporation of a DMSO solution. Figure 2 shows the molecular structure of **1** in the crystal. The geometrical features of this new molecular clip are similar to those reported previously.[18,28,29,31] For example, the =O…O= distance is 5.44 Å.

All Csp^2–N and Csp^3–N distance range between 1.361(6)–1.379(6) and 1.446(6)–1.474(5). Obviously, the N–C (carbonyl) bond distances are much shorter than the other N–C bond in the four fused rings, indicating some electron delocalisation within these rings. The angle between the mean planes defined by the five-membered ring is 111.7°. The molecular clip adopts the more commonly observed anti-conformation where the *o*-xylylene walls are pointed away from the CO_2NHNH_2 groups on their convex face.[22,25] This is responsible for the formation of a hydrophobic cleft, at least in the solid state.[18,26,27] Again, the *cis*-fused five-membered rings bearing the $CONHNH_2$ group enforce its cup-shaped geometry.

The distance between the centres of the phenyl rings of 6.42 Å is suitable for encapsulating a DMSO molecule. The solvating DMSO molecule fills the cleft of **1** by interacting with the xylyene wall by C–H…π hydrogen bonds. In the process of recognition, the aromatic subunits provide the binding sites, while the unique structure of the molecular clip **1** provides the large cavity and fixed cup conformations in which the guest molecule resides.



Scheme 1 Synthesise routine of molecular clip **1**.

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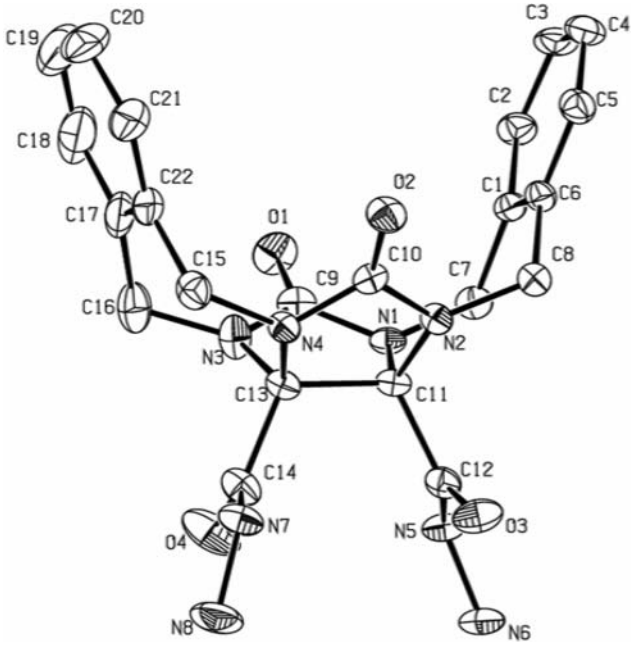

Fig. 1 The molecular structures of compounds **1**, showing the atom-numbering schemes. The displacement ellipsoids are drawn at the 30% probability level. Hydrogen atoms and solvent molecule are deleted for convenience.

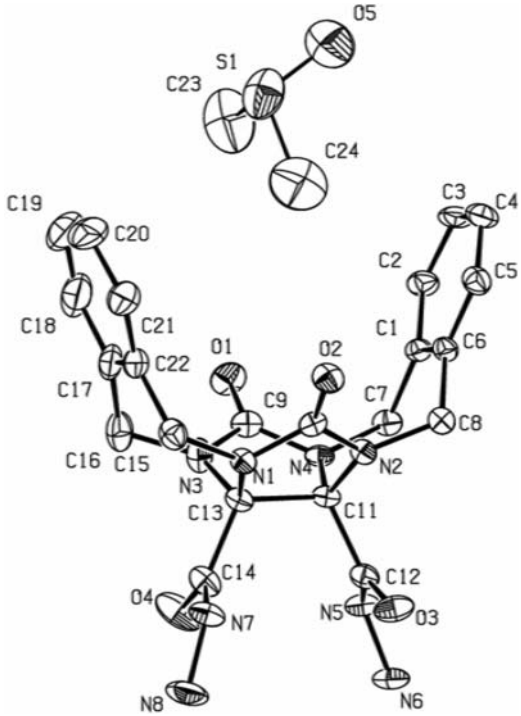

Fig. 2 X-ray crystal structure of **1**·DMSO complex.

Interestingly, in the supramolecular structure which is formed via N–H…O and π–π interactions, the molecules are linked into two-dimensional structure (Table 1).[28,29] In the first substructure, as shown in Fig. 3, two parallel chains are interlinked by an approximately centrosymmetric $R_2^2(10)$[30] hydrogen-bonding (N6…O3 = 3.095 Å) motif and an $R_2^2(6)$[30] hydrogen-bonding (N5…N6 = 3.110 Å) motif to form a one-dimensional network parallel to the (100) direction. Furthermore, the crystal structure reveals that a N7–H7C…O1 (N7…O1 = 2.805 Å) hydrogen bond and N6–H6B…N8 (N6…N8 = 3.282 Å) hydrogen bond are responsible for the stability of the supramolecular network.

Table 1 Hydrogen bonds for **1** [Å and °]

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
N(7)–H(7C)...O(1)[a]	0.87	2.01	2.805(5)	153.7
N(6)–H(6A)...O(3)[b]	0.87	2.32	3.095(5)	149.4
N(6)–H(6B)...N(8)[b]	0.87	2.51	3.282(7)	149.4
N(5)–H(5A)...N(6)[c]	0.88	2.35	3.110(5)	144.1

Symmetry codes: [a] $x+1,y,z$; [b] $-x+2,-y+2,-z+1$; [c] $-x+1,-y+2,-z+1$.

In the second substructure shown in Fig. 4, the xylylene walls of **1** pack against the identical walls of their neighbours, which result in the tape-like structure being formed in the

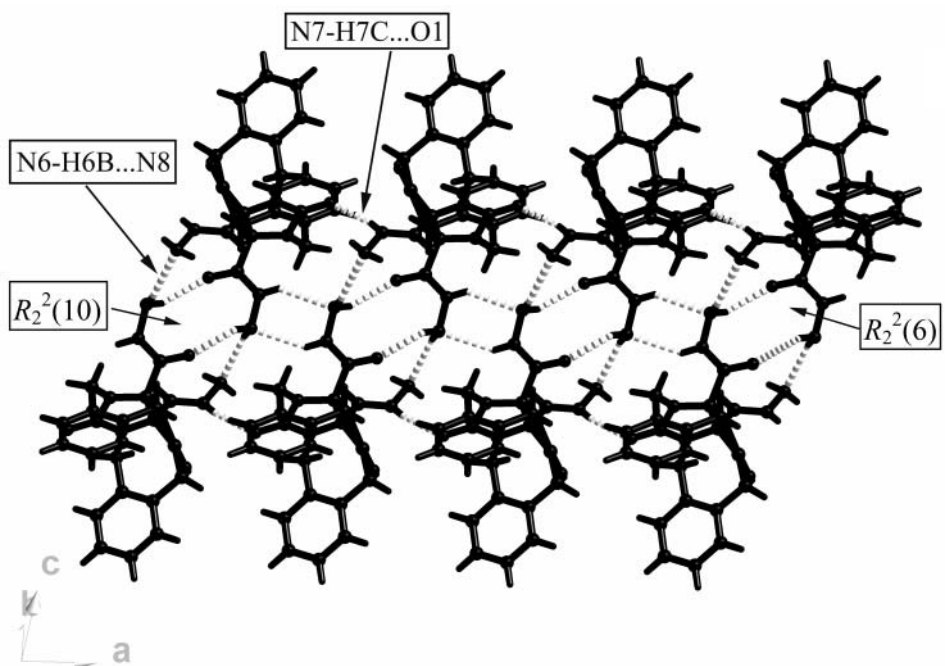

Fig. 3 The packing of **1**, showing the formation of a one-dimensional chain along the [100] direction involving C–H…O interactions and N–H…O interactions. The interactions are drawn as arrow.

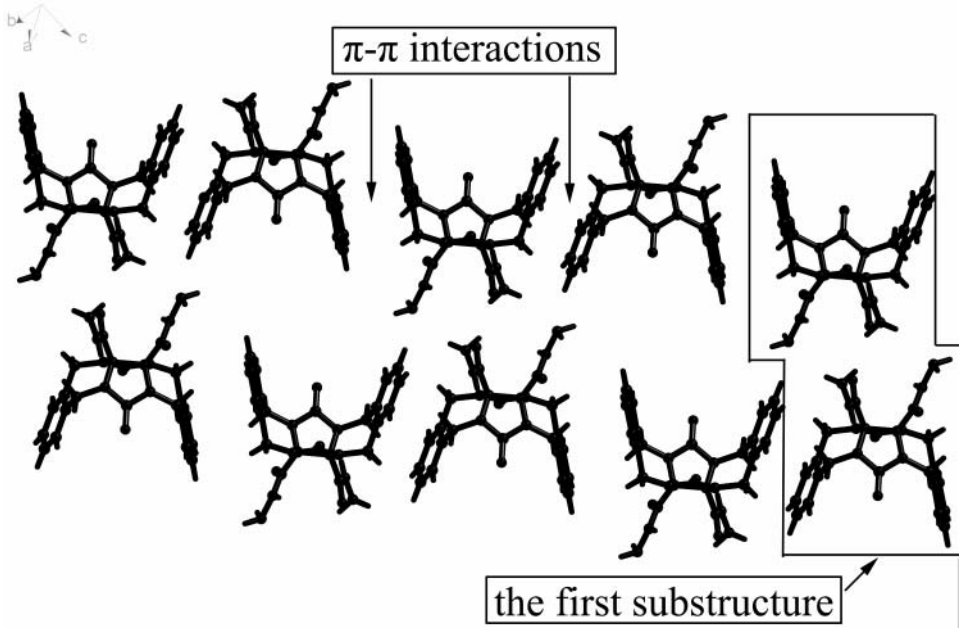

Fig. 4 Part of the crystal structure of **1**, showing the formation of the two-dimensional network linked by π–π interactions along the [111] direction. π–π interactions are shown as arrows.

crystal. Although this appears at first glance to be due to direct π–π interactions, an examination of the distance between the mean planes of the adjacent aromatic rings (π–π mean plane separation: 3.58 and 3.78 Å, respectively) suggests this motif may also result from dispersive interactions between the CH_2 groups and the adjacent Ph ring. The strong π–π interactions between the mean planes of the adjacent aromatic rings lead to a two-dimensional chain running to the [111] direction.

In summary, we have synthesised a novel molecular clip with more hydrogen bond sites and more complicated packing in the crystal. Moreover, the X-ray crystallographic analyses further revealed that the molecular clip has a large enough cavity to encapsulate a DMSO molecule. This new type of molecular clip based on glycoluril which we have presented here promises well in hosting other molecules. Further work will focus on preparation of its analogues with different functional groups to allow for recognition of larger guests and in exploring their potential applications in supramolecular assemblies via the intrinsic hydrogen bonding interactions.

Experimental

Glycoluril **2** was prepared according to the literature procedures.[33] Bis-(halomethyl) **3** and other reagents were obtained from commercial suppliers and were used without further purification. Melting points were determined using XT-4 apparatus and are not corrected. TLC analysis was performed using pre-coated glass plates. Column chromatography was performed using silica gel (200–300 mesh). IR spectra were recorded on a PE-983 spectrophotometer as KBr pellets and were reported in cm^{-1}. ^1H NMR spectra were recorded on a Varian Mercury 400 spectrometer operating at 400 MHz. Chemical shifts are reported in ppm, relative to the internal standard of tetramethylsilane (TMS). Electron impact (EI) mass spectra were acquired using a Finnegan Trace MS spectrometer.

Preparation of **1**; *general procedure*

Chart 1 shows the structure of glycoluril **2** and 1,2-bis(chloromethyl) benzene **3** used as starting material. Compound **2** (1.43 g, 5.00 mmol) was dissolved in anhydrous DMSO (30 mL) under N_2 and *t*-BuOK (2.24 g, 20.0 mmol) was added in one portion. After stirring for 15 min, **3** (1.59 g, 11.0 mmol) was added in one portion and stirring was continued for 6 h.

The reaction mixture was poured into 0.1 N HCl (500 mL) and extracted with EtOAc (3 × 400 mL). The extracts were washed with brine (2 × 300 mL) and dried over anhydrous MgSO4. After filtration and rotary evaporation the residue was purified by flash chromatography (SiO2, CHCl3/MeOH, 100:1) to give **4** (0.860 g, 1.75 mmol, 35%) (m.p. 271–272 °C. lit.[34]) successfully. After compound **4** (0.2 mmol, 100 mg) was refluxed 12 hours with hydrazine (80%, 2 mmol, 30 mL) in ethanol, we evaporated the solution on the rotary evaporator. The crude oil product was obtained in good yield (81%, 74 mg). In order to purify the crude product, about 2 mL ethanol was added and the solution was vibrated by ultrasonic oscillator. At this stage a white solid appeared. Finally, the solvent and the desired white solid compound **1** were separated by centrifugation.

Clip ***1***: M.p. >300 °C. IR (KBr, cm^{-1}): 3322m, 1741s, 1705s, 1629m, 1510m, 1459s, 1423s, 1359w, 1309m, 1282m, 1183w, 1155m, 1101w, 939m. ^1H NMR (400MHz, DMSO-d_6): δ 9.66 (s, 2H, NH), 7.19–7.10 (m, 8H, Ph), 4.52 (d, 4H, J = 15.6Hz), 4.25 (d, 4H, J = 15.6Hz), 3.37 (br, 4H, NH_2 included the peak of water). ^{13}C NMR (100MHz, DMSO-d_6): δ 162.6, 155.8, 137.3, 129.2, 127.5, 80.6, 44.9. HRMS (ESI): m/z $[M + Na]^+$ Calcd for $C_{22}H_{22}N_8O_4Na$: 485.1656. Found: 485.1646. Crystal data for **1**: $C_{22}H_{22}N_8O_4{\cdot}C_2H_6OS$, M_r = 540.60. Triclinic, space group *P-1*, a = 7.5238(14), b = 10.2342(19), c = 17.321(3) Å, Z = 2, V = 1274.9(4) $Å^3$, D_c = 1.408 g cm^{-3}, μ = 0.180 mm^{-1}, θ_{max} = 25.00°, $F(000)$ = 568, reflections collected/unique, 4419/2866 (R_{int} = 0.0887), final R indices [$I > 2\sigma(I)$] R_1 = 0.0887, wR_2 = 0.1910, R indices (all data) R_1 = 0.1319, wR_2 = 0.2140, GOF = 1.072 for all data. CCDC 759434 for **1** contains the supplementary crystallographic data for this paper, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request /cif.

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