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Synthesis of novel rigid triazine-based calix[6]arenes

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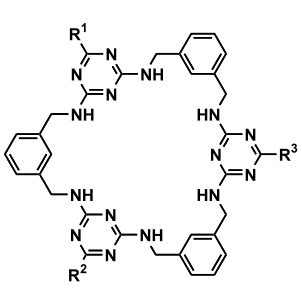
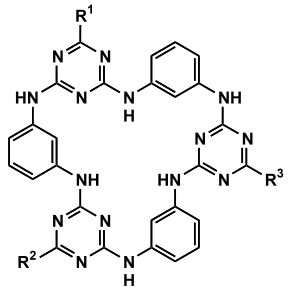
Abstract—In this report, the stepwise synthesis of a novel rigid and functionalised macrocycle **2** based on triazine and phenylenediamine linkers, is presented. Poor recognition of the macrocycle **2** for its substrates is observed, which shows experimentally that for the meltriazine based-calix[6]arene system, the binding ability of the melamine moiety gets more benefit from the ring flexibility derived from a xylenediamine linker **1** than from a phenylenediamine linker **2**. © 2003 Elsevier Science Ltd. All rights reserved.

Cavitand bowls are fascinating supramolecular building blocks.[1] Methylene bridged resorcinarene derivatives form the basis for several classes of host compounds of significant contemporary interest, including carcerands, hemicarcerands and calixarenes. The calix[4]arenes in the cone conformation present an internal cavity which can potentially host neutral guest molecules of complementary size.[2] The importance of rigidity and, consequently, of preorganisation of the cone conformer of calix[4]arenes in determining their recognition ability, recently has been combined.[3] Since recent findings show the possibility of rigidifying calix[4]arene-based hosts by using different strategies, other approaches to the recognition of biological molecules by the melamine moiety have been investigated. The melamine moiety has been shown to perform well as a recognition element providing both hydrogen bond donor and acceptor sites for the recognition of biological molecules, such as uracil,[4] thymine[4] and carbohydrates.[5] More recently, it has been shown that novel triaminotriazine scaffold-based receptors inhibit substrate binding in the presence of Cu(I).[6] In this case, the receptors bearing two bipyridine arms coordinate with the Cu(I) to form a metal–ligand coordination compound which forces two of the exocyclic C–N bonds of the triazine to rotate thereby distorting the hydrogen-bonding surface, and resulting reduction of the affinity of the melamine receptor for uracil. Recently, some macrocyclic molecules based on building blocks comprising a triazine ring and a diamine linker were synthesised in our group.[7] These studies have shown that the triazine–xylenediamine macrocycle **1** (Scheme 1) exhibited promising binding properties towards cyanuric acid and glycosides.

The association behaviour is determined predominantly by the presence of multiple hydrogen bond donor and acceptor sites. Although there are many examples of artificial systems that display positive effects, where the induced conformational change increases the binding efficacy of the receptor, there are few reports of simple negative receptors. Obviously, it is very helpful to view the recognition ability in both ways, in order to understand the intermolecular interactions and allow design of molecular receptors useful for the preparation of a new generation of sensing devices where efficiency and selectivity are governed by molecular recognition processes. We report here a stepwise synthetic route to build up a novel rigid and functionalised macrocycle **2** based on triazine and phenylenediamine linkers, whose structure is shown in Scheme 1. Investigation of the binding ability shows limited recognition of molecules,



1: $R^1=R^2=R^3=\sim NH(CH_2)_4CH_3$



2: $R^1=R^2=R^3=\sim NH(CH_2)_4CH_3$

Scheme 1.

Keywords: triazine; macrocycle; inhibitor; hydrogen-bonding.

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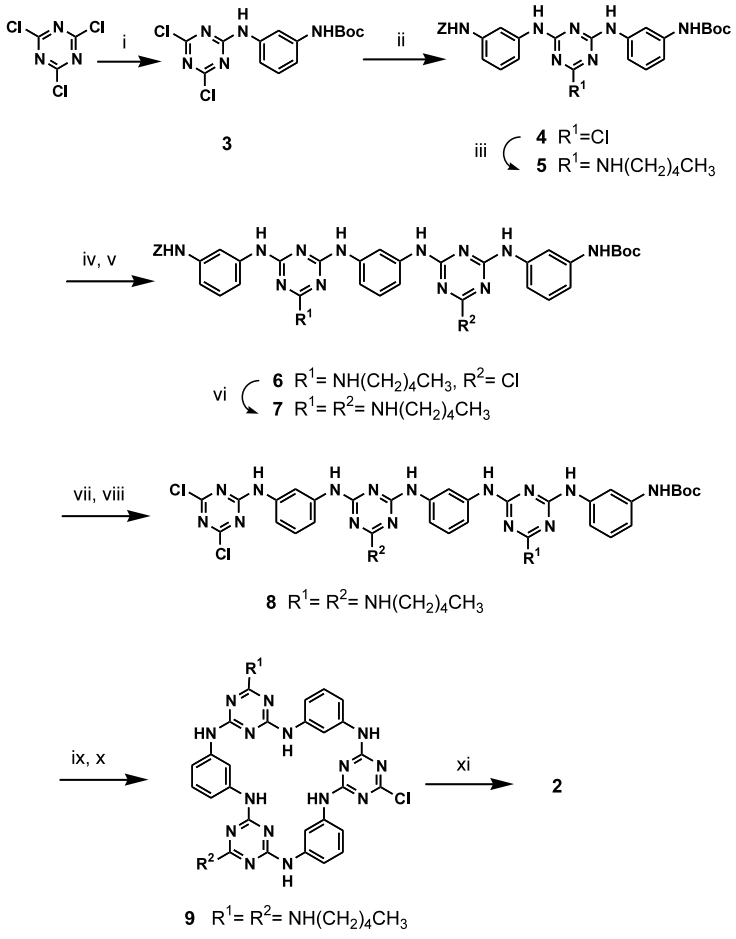

Scheme 2. *Reaction conditions and yields*:[8] (i) (3-amino-phenyl) carbamic acid *tert*-butyl ester, $NaHCO_3$, in acetone–H_2O, at 0°C, 85%; (ii) (3-amino-phenyl) acetic acid benzyl ester, $NaHCO_3$, in acetone–H_2O, at 50°C, 91%; (iii) $CH_3(CH_2)_4NH_2$, THF, at 60°C, 95%; (iv) TFA, CH_2Cl_2; (v) **3**, $NaHCO_3$, in acetone–H_2O, at 50°C, 84%; (vi) $CH_3(CH_2)_4NH_2$, THF, at 60°C, 91%; (vii) H_2/Pd/C, MeOH; (viii) cyanuric chloride, $NaHCO_3$, in acetone–THF–H_2O, at 0°C, 77%; (ix) 2 M HCl in dioxane; (x) DIPEA, DMF, 62%; (xi) $CH_3(CH_2)_4NH_2$, DMF, at 60°C, 73%.

such as cyanuric acid, Me-α-*O*-D-glucopyranoside, biotin and thymine, and suggests that for the meltriazine based-calix[6]arene system, the binding ability of the melamine moiety gets more benefit from the ring flexibility derived from a xylenediamine linker **1** than from a phenylenediamine linker **2**, where the methylene bridge makes the melamine moiety form a well-ordered hydrogen bonding surface which offers good recognition to the substrates.

The receptor **2** was prepared from cyanuric chloride and mono-protected 1,3-phenylenediamine, as outlined in Scheme 2. At each step of the synthesis, the chain can either be elongated or cyclised to a macrocycle of interest. The use of two different orthogonal protective groups on either side of the oligomers allows control of the length of the triazine–phenylenediamine chain. With the aim of creating a rigid macrocycle bearing melamine moieties, phenylenediamine was chosen as a linker, instead of the xylenediamine exploited in macrocycle **1**.[7] The cyclic chloride **9** was synthesised from the triazine–pheneylenediamine oligomers **8** by subsequent treatment with acid and base, and was substituted with

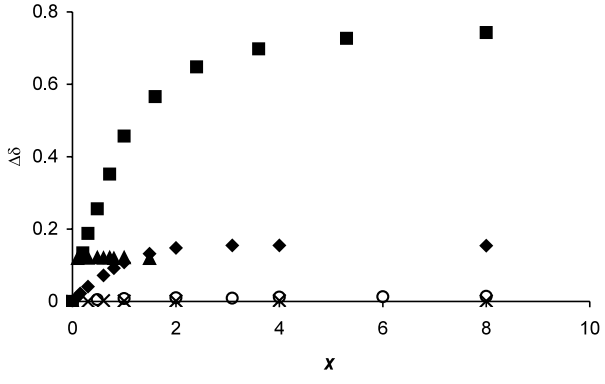

Figure 1. The plot of change of chemical shift ($\Delta\delta$) versus equivalents of titrant (***x***). Titration of triazine–xylenediamine macrocycle **1** with *n*-octyl-α-D-glucopyranoside (■), *n*-octyl-β-D-glucopyranoside (◆) and cyanuric acid (▲) in $CDCl_3$.[7b] Titration of triazine–phenylenediamine macrocycle **2** with Me-α-D-glucopyranoside (×) and cyanuric acid (○) in d_6-DMSO.

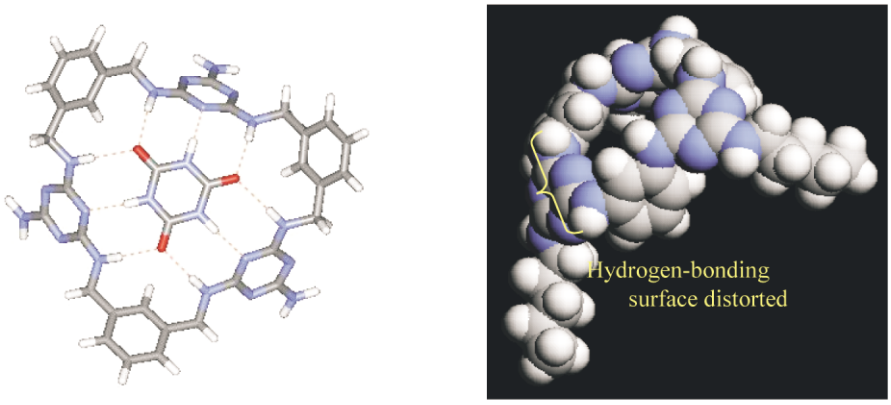

Figure 2. (a) Modelling structure for the binding of macromolecule **1** ($R^1=R^2=R^3=NH_2$) with cyanuric acid; (b) the lowest energy structure for macrocycle **2** bearing a rigid cavity.

an excess of a third amine to give the macrocycle **2**. No significant dimer as identified by mass spectrometry was found under the conditions employed. All new species were characterised by ^1H and ^{13}C NMR spectroscopy and mass spectrometry.[8]

The binding efficacy of the receptor **2** to a substrate was compared with macrocycle **1**, and evaluated by analysing the change that occurred in the ^1H NMR spectra upon titrating solutions of cyanuric acid, Me-α-*O*-D-glucopyranoside, biotin and thymine with macrocycle **2** in d_6-DMSO. ^1H NMR data of both macrocycles **2** and **1** with their substrates are shown in Figure 1, although no significant downfield shift for the macrocycle **2** was observed for any substrates. In our previous results,[7b] the macrocycle **1** exhibited promising binding properties towards cyanuric acid, *n*-octyl-α-D-glucopyranoside and *n*-octyl-β-D-glucopyranoside. Computer modelling showed that the successful binding with cyanuric acid benefits from the relative flexibility of macrocycle **1**, where the methylene bridge is an automatic adjuster, and changes its conformation to create well-ordered hydrogen-bonding surfaces for the melamine moiety, depending on the different substrates. This self-adjusting is limited, nevertheless. Unlike macrocycle **1**, there is no methylene bridge adjuster in macrocycle **2** derived from the xylenediamine linker, resulting in distortion of the hydrogen-bonding surfaces in the rigid macrocycle. The modelled structure is shown in Figure 2(b), which suggests why the rigid macrocycle **2** presents a poor binding ability.

Acknowledgements

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8. Oligomers **8**: Pd/C (10%, 350 mg) was added to a solution of **7** (0.27 mmol) in MeOH (14 mL). After stirring the solution under a hydrogen atmosphere for 3 h, the catalyst was filtered off and the filtrate was evaporated. The residue was dissolved in acetone–THF (1:1, 2 mL) and the resulting solution was added to a fresh suspension of cyanuric chloride (0.26 mmol) in acetone–H_2O (1:2, 6 mL) followed by the addition of $NaHCO_3$ (0.27 mmol). After stirring for 2 h at 0°C, water was added, the aqueous suspension was extracted with DCM and the combined organic layers were dried with $MgSO_4$ and evaporated. Flash column chromatography (eluent: 10% MeOH in DCM) yielded 77% of product **8**. **^1H NMR** ($CDCl_3$; 400 MHz): 0.82 (m, 6H), 1.23 (m, 8H), 1.47 (m, 13H), 3.15 (m, 4H), 5.52 (b, 2H), 6.28 (m, 2H), 6.88 (m, 10H), 7.66 (m, 6H); **^{13}C NMR** ($CDCl_3$; 100.5 MHz): 171.06, 170.44, 166.88, 165.39, 164.99, 153.67, 141.78, 141.45, 141.07, 137.79, 129.60, 129.38, 129.12, 118.00, 115.13, 113.21, 111.17, 79.92, 41.54, 29.96, 29.95, 28.62, 23.17, 14.37 **MS-ESI**: *m*/*z* 896.5 [M^+].
Macrocycle **9**: A solution of **8** (57 μmol) in 2 M HCl in dioxane (5 mL) was stirred for 3 h. The volatiles were removed and the residue was coevaporated with THF twice. The intermediate was dried overnight, then dis-

solved in DMF (25 mL) and a solution of DIPEA (1.2 mmol) in DMF (5 mL) was added dropwise at 45°C, to the resulting solution and stirring continued for 5 h at 45°C. The mixture was further purified by flash column chromatography (eluent: 1% MeOH in DCM) to afford 62% of macrocycle **9**. **^{1}H NMR** (d_6-DMSO+D_2O; 500 MHz): 0.81 (m, 3H), 0.87 (m, 3H), 1.30 (m, 8H), 1.52 (m, 4H), 3.29 (m, 4H), 6.79–7.16 (m, 12H); **^{13}C NMR** (d_6-DMSO; 100.5 MHz): 168.42, 165.62, 163.72, 162.46, 150.47, 141.00, 128.37, 113.22, 40.69, 29.08, 29.03, 28.93, 28.89, 22.17, 22.14, 14.21, 14.17; **HRMS-ESI**: m/z calcd 760.3576, found: 760.3560 [MH^+].

Macrocycle **2**: A solution of **9** (20 μmol) and pentylamine (0.20 mmol) in DMF (3 mL) was heated at 60°C overnight. The solvent was removed in vacuo and the residue was purified by column chromatography (eluent: 10% MeOH in DCM) followed by gel permeation chromatography (eluent: DCM/MeOH, 2:1) to yield 73% of product **2**. **^{1}H NMR** (d_6-DMSO+D_2O; 500 MHz): 0.84 (m, 9H), 1.30 (m, 12H), 1.52 (m, 6H), 3.29 (m, 6H), 6.79–7.16 (m, 12H); **^{13}C NMR** (d_6-DMSO; 100.5 MHz): 162.31, 160.87, 151.48, 139.20, 128.04, 124.91, 40.65, 29.07, 28.90, 28.77, 28.69, 28.55, 22.03, 21.99, 21.04, 14.09, 14.02, 13.91; **HRMS-ESI**: m/z calcd 811.4857, found: 811.4858 [MH^+].