Self-complementary hydrogen bonding heterocycles designed for the enforced self-assembly into supramolecular macrocycles

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A series of 2-oxopyrimido[4,5-*d*]pyrimidin-5(6*H*)-ones are synthesised that contain a hydrogen bond code that mediates their self-organisation into a hexameric supramolecular macrocyclic structure.

Hydrogen bonding (HB) has been extensively used to direct the self-assembly of suitably encoded component molecules into a variety of supramolecular architectures, presenting linear, cyclic or three-dimensional arrangements.[1–3] Cyclic structures are of particular interest and a number of supramolecular macrocycles have been obtained (see for instance refs 2–6), starting with the tetrameric entity formed by four guanine nucleotides.[5,6] However, in all these cases the formation of the cyclic array rested on additional factors, such as metal ion binding or steric effects, the HB pattern itself being not sufficient to univocally determine the outcome of the assembly. Such is the case for the species obtained from the interaction of triaminopyrimidine (TAP)[7] or triaminotriazine (TAT)[2] derivatives with substituted barbituric acid (BA) components, which may generate either linear (ribbon, tape, crinkled tape)[2,7] or cyclic (rosette)[2] arrays.

We present here the design, synthesis and some properties of two-faced, Janus-type molecules[8] **1** and **2**, presenting two HB patterns designed so as to enforce the self-assembly uniquely into a supramolecular cyclic entity.

It was noted earlier[8] that a macrocyclic species would result from the assembly of two different, symmetrical molecules presenting each two identical triple HB subunits of DDA and AAD type respectively (A, D: hydrogen bond acceptor, donor site). When these two different HB arrays are in the same structure, a self-complementary molecule results that, if full use is made of all its HB capabilities, will necessarily generate a macrocyclic supramolecular architecture on the basis of the HB information alone. Such a species is HB-programmed to self-assemble into a cyclic array. This is the case for molecules **1** and **2** which are expected to form a macrocyclic hexameric supermolecule of type **M** (Fig. 1), *via* linear hydrogen bonds between the components.

Two routes were pursued to these targets. The first, (Scheme 1) is applicable to 2-oxopyrimido[4,5-*d*]pyrimidin-5(6*H*)-ones which are substituted with both alkyl and aryl groups, whereas the alternative (Scheme 2) applies only to aryl-substituted systems.

Addition of four equivalents of octylamine to 2,4,6-trichloropyrimidin-5-carbaldehyde **3**[9] followed by treatment with sodium benzyloxide gave aldehyde **4** (Scheme 1). The two amino groups were differentiated by protection of N-2 with *tert*-butyloxycarbonyl (Boc) giving **5** and the aldehyde converted to the nitrile. Treatment of the N-4 amine with chlorocarbonyl isocyanate[10] gave the expected urea which was cyclised with trimethylsilyl triflate (Me_3SiOTf) to **6** *via* the more nucleophilic silyl ketenimine. Deprotection was then carried out with refluxing trifluoroacetic acid to generate the desired product, **1**.§,¶

A similar procedure was also carried out starting with the addition of 4-*tert*-butylaniline to **3**, followed by sodium benzyloxide to give **7**. The pyrimidopyrimidine **9**, obtained *via* **8**, was deprotected with 2 mol dm^{-3} hydrochloric acid in refluxing THF to give the desired product **2** as a white solid.¶

The shorter route (Scheme 2) relies on the bifunctional nature of chlorocarbonyl isocyanate which is used to cyclise intermediate pyrimidine **10** to give bicyclic **11**. Treatment of this material with phosphorous oxychloride gave, not the chloride as expected but apparently, a phosphorous intermediate which, upon exposure to ammonia yielded a phosphoramidite. Deprotection of the benzyl group with trifluroacetic acid also removed this phosphoramidite affording product **2**, identical to material prepared by the previous route.

The self-assembly of molecules **1** and **2** was studied by various physico-chemical means. The ^1H NMR spectrum indicates that strong intermolecular hydrogen bonding is taking place in solutions of **1** as shown by downfield shifts of exchangeable protons. In particular, the N-2 proton moves from δ 5.48 to 8.90 (in $CDCl_3$).

The material is sparingly soluble in chloroform at room temperature, although it dissolves completely in [$^2H_8$]toluene at 70 °C and a variable temperature experiment up to *ca.* 100 °C allowed more complete assignment of the ^1H NMR signals. The intramolecularly H-bonded N-4 H was assigned to the singlet at δ_H 9.19 since the chemical shift remains unchanged. The other signals do not change by more than δ 0.20, indicative of strong association. Quantitative estimation of the association constant in apolar solvent was impractical due to low solubility. Analogue **2** displayed particularly low solubility in apolar solvents, but despite improved crystallinity compared with **1**, crystals suitable for X-ray structure determination could not yet be obtained.

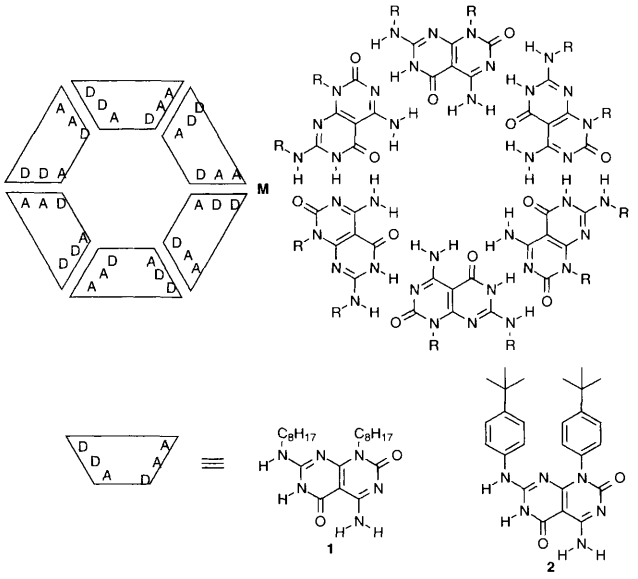

Fig. 1 Proposed self-assembly of the self-complementary heterocycles **1** and **2** into a supramolecular macrocycle **M**; schematic and structural representation (A/D: hydrogen acceptor–donor site)

Estimation of the mass of the species formed in chloroform was made from vapour pressure osmometry (VPO) measurements as 2600 ± 10%. Since the estimated molecular mass of a hexameric structure is 2511, from this data one cannot be certain that the complex does not contain 5 or 7 units, but linear HB between the components is expected to generate the closed cyclic hexamer. Qualitative measurements using gel permeation chromatography (GPC) indicate formation of a stable supramolecular species with M_W greater than the M_W 2200 polystyrene standard used. No species higher than dimer in the electrospray mass spectrum although this probably indicates lack of a suitably charged species. Approaches using electrospray 'active' derivatives (for instance *via* 'ion-labelling')[11] are the subject of further investigation. The directed generation of a supramolecular hexameric macrocycle **M** on the basis of DDA/AAD HB encoded components has been achieved independently and confirmed by crystal structure determination.[12]

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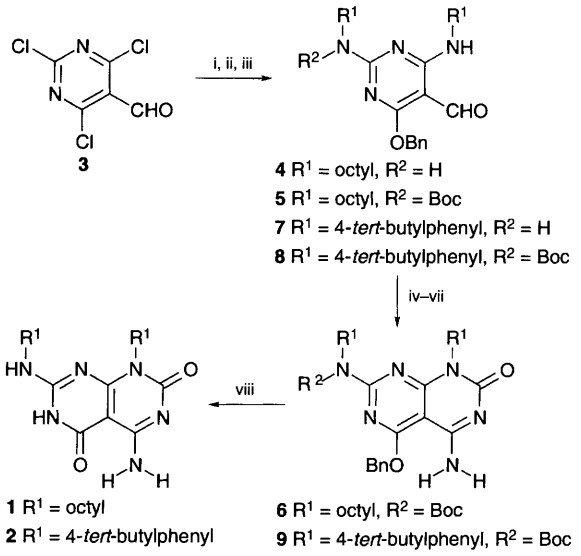
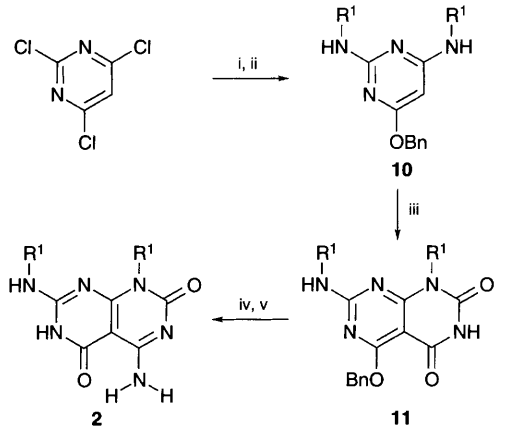


Scheme 1 *Reagents and conditions*: R¹ = octyl. i, octylamine (4 equiv.), Et_3N, THF, 74%; ii, BnONa, THF, reflux; iii, Boc anhydride, Et_3N, DMAP, THF, 55% over 3 steps; iv, $NH_2OH{\cdot}HCl$, methanol, $KHCO_3$ 65 °C, 71%; v, TFAA, Et_3N, THF, 0 °C to reflux, 64%; vi, ClCONCO, CH_2Cl_2 0 °C to room temp., 45–60%; vii, Me_3SiOTf, CH_2Cl_2, −78 °C, 73%; viii, CF_3COOH, reflux, then aqueous work-up, *ca.* 95%. R¹ = 4-*tert*-butylphenyl. i, 4-*tert*-butylaniline, Et_3N, THF, 56%; ii, BnONa, THF, reflux, 56–66%; iii, Boc anhydride, Et_3N, DMAP, THF, 96%; iv, NH_2OSO_3H, THF–water, 40 °C 95%; v, TFAA, Et_3N, THF, reflux, 61%; vi, ClCONCO, CH_2Cl_2 0 °C to room temp., 78%; vii, Me_3SiOTf, CH_2Cl_2, −78 °C, 59–83%; viii, 2 mol dm^{-3} HCl, THF, reflux, 73%.



Scheme 2 *Reagents and conditions*: R¹ = 4-*tert*-butylphenyl. i, *N*-lithio-4-*tert*-butylaniline, 6 equiv., −78 °C to room temp., 83%; ii, BnONa, BnOH, 160 °C, 6 h, 68%; iii, *sec*-BuLi (1.3 equiv.) −78 to 0 °C then ClCONCO (−78 °C to room temp. overnight); iv, $POCl_3$, Et_3N, 110 °C 20 min., then NH_3/MeOH, 57%; v, CF_3COOH, reflux, 88%

Footnotes

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§ All new compounds exhibited ^1H and ^{13}C NMR, mass spectra and microanalytical or accurate mass data consistent with the structures indicated.

¶ *Selected spectroscopic data* for **1**: ν_{max} (KBr)/cm^{-1} 3368, 3250, 3184, 2924, 2853, 1704, 1636, 1534, 1374, 1293, 1266, 1207, 1128, 918, 839, 805, 742, 723 and 597; δ_H ($CDCl_3$, 200 MHz) 12.70–12.10 (1 H, br s, N-1 H), 9.25 (1 H, s, NH_2), 9.10 (1 H, s, NH_2), 8.90 (1 H, t, C-2 NH), 4.10 (2 H, t, α-CH_2 C-2), 3.48 (2 H, q, α-CH_2 C-4), 1.65–1.50 (4 H, m, β-CH_2 × 2), 1.45–1.15 (20 H, m, CH_2 × 10) and 0.88 (6 H, t , CH_3); δ_C ($CDCl_3$, 50 MHz) 161.4, 159.6, 156.4, 155.2, 148.0, 81.5, 41.0, 40.3, 31.1, 28.6, 27.1, 26.3, 22.0 and 13.4; *m/z* (FAB) 419 (MH^+) [Found (MH^+): 419.3126. $C_{22}H_{38}N_6O_2$ (MH^+) requires 419.3134]. For **2**: ν_{max} (KBr)/cm^{-1} 3400, 3284, 3195, 3100, 2962, 1720, 1695, 1620, 1512, 1410, 1363, 1299, 1267, 1203, 1148, 1114, 1084, 1017, 989, 934, 861, 833, 805, 752, 716, 678 and 633; δ_H ([$^2H_6$]Me_2SO, 200 MHz) 10.05 (1 H, s, NH), 8.97 (1 H, s, NH), 8.42 (1 H, s, NH), 7.58 (2 H, d, *J* 7.5 Hz, Ar), 7.28 (2 H, d, *J* 7.5 Hz, Ar), 1.40 (9 H, s, Bu^t) and 1.18 (9 H, s, Bu^t); *m/z* (FAB) 459 (MH^+) [Found: (MH^+), 459.2497. $C_{26}H_{30}N_6O_2$ requires (MH^+), 459.2508].

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