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Janus Molecules: Synthesis of Double-Headed Heterocycles Containing Two Identical Hydrogen Bonding Arrays

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Abstract: The synthesis of three heterocycles 1-3 presenting identical faces containing a hydrogen bonding code for self-assembly is described. Pyrimidoquinazolinetetrone **1** and diaminopyrimidoquinazolinedione **2** were approached using a double Chapman rearrangement followed by closure to the double uracil-type structure **1**. Diaminopyridoisoquinolinedione **3** was obtained in three steps from pyromellitic anhydride.

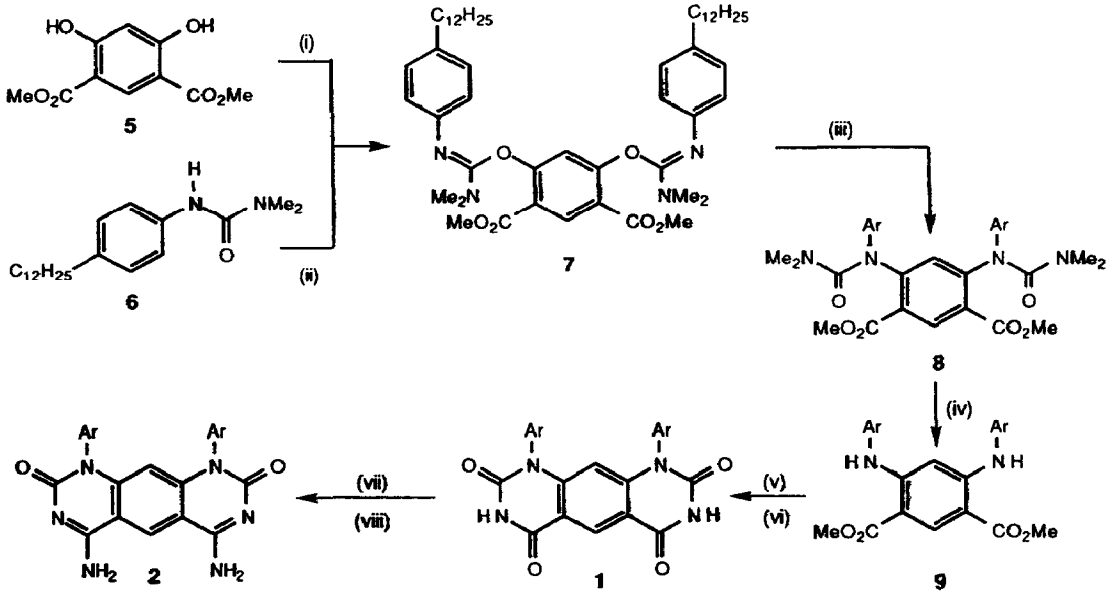
The self-assembly of supramolecular structures[1,2] *via* molecular recognition between complementary hydrogen bonding components has developed into a central theme for constructing well-defined arrangements of molecules in both the solid state[3] and solution.[4] The accessibility of a number of two-dimensional (*e.g.* ribbons,[5a,b] tapes[5c] and a rosette[6]) motifs has been demonstrated using the hydrogen bond as mediator for the association of the component molecules. Clearly the choices of molecular shape and size and especially the arrangement of hydrogen bonding sites are paramount to the correct tesselation of a supramolecular array. The buildup of two-dimensional and three-dimensional shapes requires the presence of two or three hydrogen bonding subunits whose disposition determines the final supramolecular architecture. To this end we have designed a series of planar heterocyclic components containing two arrays of hydrogen bonding subunits that may form different assemblies depending on the encoded hydrogen bonding instruction. We present here the synthesis of three such molecules **1-3**, containing the same two sequences of H-bonding sites on each side and which for this reason may be termed *Janus* molecules.[7] These compounds may be termed homotopic according to the designation of polytopic receptors.[8] They are also enantiotopic when considering chirality in two dimensions.[9]

Diaminopyrimidoquinazolinedione **2** and its complement diaminopyridoisoquinolinedione **3** contain a matching pair of faces bearing acceptor-donor-donor hydrogen bonding recognition units that are reminiscent of the cytosine-guanine pair in which the disposition of hydrogen bond donors and acceptors avoids repulsive secondary electrostatic interactions[10] and encodes a program for self-assembly.[11]

***Synthesis of pyrimidoisoquinazolinetetrone* 1 *and diaminopyrimidoisoquinazolinedione* 2**

The chosen route is analogous to known chemistry[12] and allowed construction of the symmetric tricyclic system around a central aromatic ring *via* intermediate bisuracil **1**. This was particularly attractive since **1** is also of interest as a potential component of self-assembling systems.

Dimethyl 4,6-dihydroxy-1,3-benzenedicarboxylate, **5**, was synthesised from resorcinol by double carboxylation[13] and esterification.[14] *N*-(4-Dodecylphenyl)-*N'*,*N'*-dimethylurea **6** was prepared in straightforward fashion from 4-dodecylaniline and converted quantitatively into the chloroamidine with phosphorous pentachloride in toluene. Coupling of the disodium salt of **5** with two equivalents of freshly prepared chloroamidine proceeded in high yield to give unstable intermediate **7**. This material rearranged slowly even at room temperature, and upon heating under argon at 100-140°C the desired Chapman rearrangement took place to furnish bis(*N*,*N*-dimethylurea) **8**. Acidic hydrolysis of **8** to diamine **9**[15] was somewhat problematic but optimal conditions were found which avoided intramolecular Friedel-Crafts acylation.

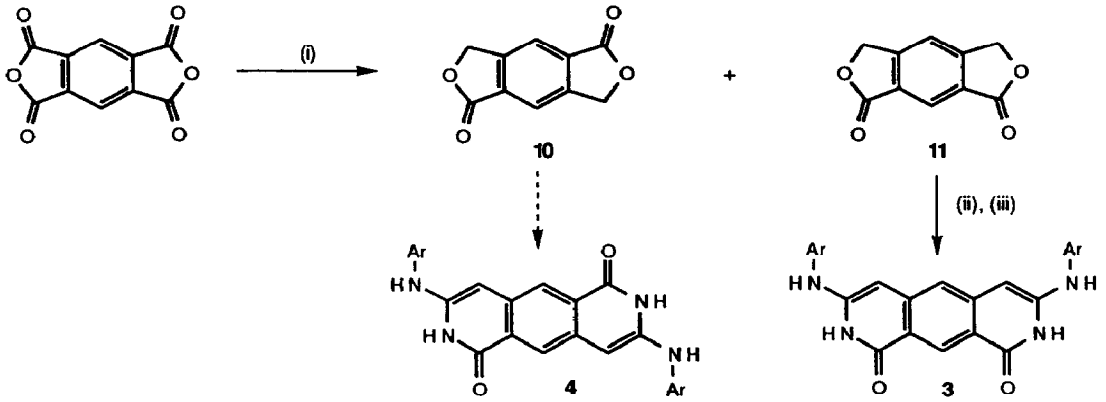


(i) 2.1 eq NaH, THF then add 2.2 eq chloroamidine (93%); (ii) PCl_5, PhMe; (iii) 100-140°C (70-74%); (iv) 1:1 AcOH:MeOH, c. H_2SO_4 (86%); (v) ClCONCO, CH_2Cl_2, 0°C to r.t., H_2O (87%); (vi) AcOH, THF, reflux (73%); (vii) $POCl_3$, Et_2NPh, 100°C, 1h; (viii) NH_3, MeOH, r.t. to 60°C (52% over two steps).

Scheme 1

Acylation of diamine **9** was achieved using chlorocarbonyl isocyanate[16] which was found to give a cleaner reaction than the more reactive chlorosulfonyl isocyanate. The product diurea was admixed with *ca.* 50% of the material which was cyclized on one side. After purification by flash chromatography on silica gel the mixture was heated with acetic acid in THF to give clean cyclization to pyrimidoisoquinazolinetetrone **1**.[17] Conversion of this key intermediate to the desired diaminopyrimidoisoquinazolindione **2**[18] was effected by reflux in phosphorous oxychloride with *N*,*N*-diethylaniline as base and treatment of the dichloride with a saturated solution of ammonia in methanol.[19]

***Synthesis of diaminopyridoisoquinolinedione* 3** This compound was prepared from the *m*-pyromellitide **11** by analogy with the synthesis of 3-amino-1(2*H*)-isoquinolines from phthalide[20] (Scheme 2). Although the pyromellitides **10** and **11** are known compounds,[21] we found them easier to obtain by direct reduction of pyromellitic anhydride in DMF,[22] followed by either flash chromatography (SiO_2, acetone: chloroform 1:9) or fractional crystallization (DMF-H_2O). The lactone function could then be opened with cyanide ion in DMSO.[20a, 23] Diaminopyridoisoquinolinedione **3**[24] was obtained by heating the product diacid with the appropriate 4-substituted aniline. One may envisage conversion of the *p*-pyromellitide **10** to **4** using a similar sequence.



(i) $NaBH_4$, DMF, (1:1, 70%); (ii) KCN, DMSO, 18-crown-6, 120°C (68-83%); (iii) 4-toluidine, PhCl:DMSO, 9:1, 130°C (44-52%, Ar = 4-methylphenyl).

Scheme 2

The synthesis of the Janus-type heterocycles **1-3** exhibiting two encoded hydrogen bonding faces (reminiscent of those found in nucleic acids) opens the way to the study of their binding and self-assembly features. Heteroassembly of **2** with **3** should give a cyclic supramolecular structure (Figure, left) whereas **1** would form linear (Figure, right) or wavy ribbons by interactions with 2,4,6-triaminopyrimidine or triazine (see ref. 5a). These aspects are the subject of continuing investigation and will be presented elsewhere.

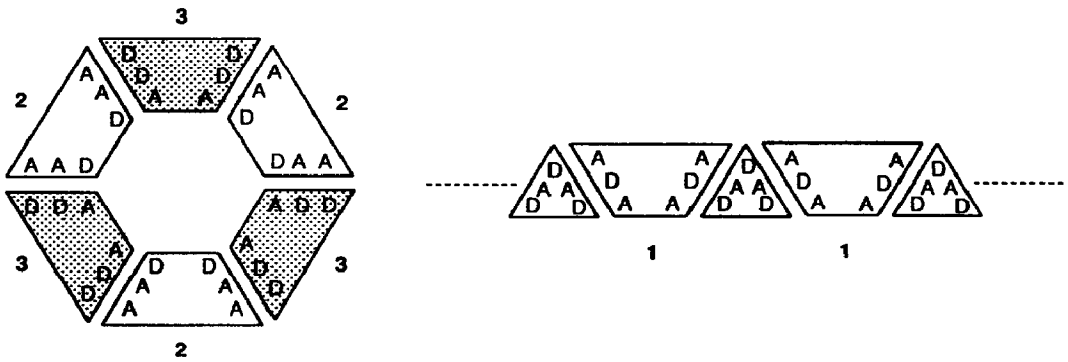


Figure - D and A represent hydrogen bond donating and accepting sites.

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15. Data for **9**: needles (hexane) m.p. 109-110.5°C, υ_{max} (thin film) *inter alia* 3300, 1665, 1610 cm^{-1}; δ_H ($CDCl_3$, 200MHz) 9.72 (2H, s, 2 NH), 8.68 (1H, s, H-6), 7.06 (8H, s, Ar), 6.69 (1H, s, H-3), 3.88 (6H, s, 2 CH_3O), 2.55 (4H, t, 7 Hz, 2 CH_2), 1.65-1.50 (4H, m, 2 CH_2), 1.40-1.15 (36H, m, 18 CH_2), 0.90 (6H, t, 6.7 Hz, 2 CH_3); *m/z* (FAB) 712.5 (MH^+); (Found: C, 77.48; H, 9.61. $C_{46}H_{68}N_2O_4$ requires: C, 77.24; H, 9.55%).
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17. Data for **1**: leaflets (DMF) m.p. >380°C (browns *ca.* 320°C) υ_{max} (KBr) *inter alia* 3425, 1741, 1716 cm^{-1}; δ_H ($CDCl_3$-DMSO-d_6 9:1, 200MHz) 11.30 (2H, br. s, 2 NH), 8.82 (1H, s, H-5), 7.09 (4H, d, 8 Hz, Ar), 6.86 (4H, d, 8 Hz, Ar), 5.42 (1H, s, H-10), 2.60 (4H, t, 7 Hz, 2 CH_2), 1.60-1.40 (4H, m, 2 CH_2), 1.35-1.10 (36H, m, 18 CH_2), 0.78 (6H, t, 6.8 Hz, CH_3) (Found: C, 74.96; H, 8.51; N, 7.57. $C_{46}H_{62}N_4O_4$ requires: C, 75.17; H, 8.50; N, 7.62%).
18. Data for **2**: m.p. >380°C (browns *ca.* 310°C) υ_{max} (KBr) *inter alia* 3363, 1686, 1600 cm^{-1}; δ_H ($CDCl_3$-DMSO-d_6 *ca.* 9:1, 200MHz) 8.86 (1H, s, H-5), 7.40-7.30 (4H, s, 2 NH_2), 7.05 (4H, d, 8 Hz Ar), 6.82 (4H, d, 8 Hz, Ar), 5.35 (1H, s, H-10), 2.45 (4H, m, 2 CH_2), 1.60-1.40 (4H, m, 2 CH_2), 1.25-1.10 (36H, m, 18 CH_2), 0.80 (6H, t, 7 Hz, 2 CH_3); *m/z* (FAB) 733.5 (MH^+). Found: (MH^+), 733.5169. $C_{46}H_{65}N_6O_2$ requires (MH^+), 733.5138.
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24. Data for **3**: m.p. >360°C (browns *ca.* 340°C) υ_{max} (Fluorolube) *inter alia* 3300, 1680 cm^{-1}; δ_H (DMSO-d_6, 250MHz) 10.43 (2H, s, HNCO), 8.68 (1H, s, H-10), 7.87 (2H, s, ArNH), 7.12 (8H, m, Ar), 7.02 (1H, s, H-5), 5.76 (2H, s, H-4, H-6), 2.28 (6H, s, 2 CH_3); *m/z* (FAB) 422.2 (M^+).

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