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COMMUNICATIONS

Published on Web 04/29/2006

Quadruply Hydrogen Bonded Cytosine Modules for Supramolecular Applications

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The design of novel supramolecular materials requires the synthesis of core modules capable of forming strong hydrogen bonds.[1−3] Despite the considerable progress achieved in recent years, the synthesis of supramolecular polymers based on the self-assembly of DDAA modules has been mainly restricted to the ureidopyrimidinones (UPy) reported by Meijer et al.[3a] In view of the range of properties required from supramolecular materials, there is clearly a need for alternative strong quadruple hydrogen bonded modules, which can be used in polymer or copolymer synthesis via the self- or hetero-association of complementary units. In addition, the UPy modules can exist in three different tautomeric forms depending on the environment, which can increase the complexity of the species present.[3a,4] Therefore, modules that do not undergo such tautomeric changes are preferable for use in controlled material design. One approach to reduce the number of tautomers is by the replacement of NH moieties with CH groups, or NH with NR to give UPy-like modules. However, this can result in conformational flexibility in the ureido fragment between folded and unfolded forms.[5] Herein, we describe a new quadruple hydrogen bonding module **1**, based on a ureido-substituted cytosine moiety.

Cytosine is well-known for its hydrogen bonding capabilities in DNA and RNA, and numerous cytosine derivatives have been reported for use in biological applications[6] and in self-assembling triple hydrogen bonded systems.[2d] Compound **1** does not undergo tautomeric exchange and is capable of a self-assembly via DDAA/AADD interactions or hetero-assembly with another matching unit, such as UPy. Conformationally, both folded (**1′**)[6c] and unfolded (**1**) forms may exist (Figure 1), with the desired unfolded form stabilized by strong quadruple hydrogen bonding on dimerization, and possibly a weak intramolecular C5−H···O interaction.

Compound **1** was readily synthesized in three steps: *N*-4-acetylcytosine was reacted with bromohexane. Subsequent *N*-acetyl deprotection using ammonia in methanol and reaction with hexyl isocyanate gave **1** in 37% overall yield. Single-crystal XRD of **1** (from chloroform) revealed the presence of quadruple hydrogen bonding (Figure 2) with the outer hydrogen bonds N−H···O (d = 1.89(2) Å, D = 2.724(2) Å, θ = 172(2)°) shorter than the inner N−H···N (d = 2.29(2) Å, D = 3.135(2) Å, θ = 178(2)°) bonds. The side chain carbonyl and the C5−H of the ring were nearly planar with the measured geometry of the intramolecular interaction between C5−H···O═C8 (d = 2.12(2) Å, D = 2.773(2) Å, θ = 125(2)°) in agreement with that for a weak hydrogen bond.[7] In addition, a short intermolecular distance between C6−H···O═C8 (d = 2.22(2) Å, D = 3.164(2) Å, θ = 161(2)°) was observed which appears to order the dimers into 1-D infinite chains. The 3.2 Å interlayer separation of these chains (slightly less than the expected 3.4 Å of just the van der Waals radii) suggested that polymers based on **1** may also be stabilized via stacking-type interactions.[8]

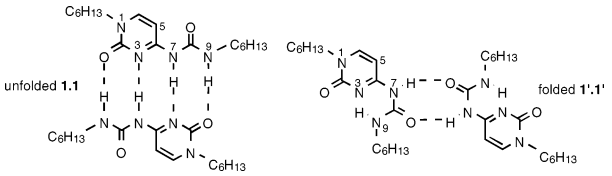

Figure 1. Hydrogen bonded dimers of functionalized cytosine.

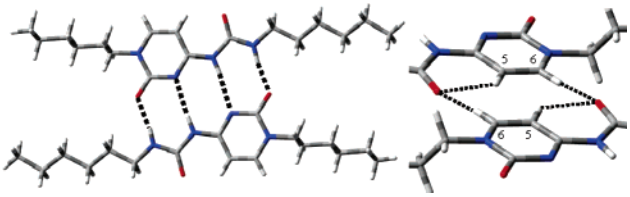

Figure 2. Left: quadruple hydrogen bonding (dotted lines) in the X-ray structure of **1**. Right: inter- and intramolecular C−H···O═C close contacts (dotted lines).

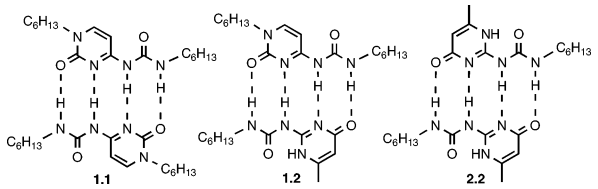

Figure 3. Homo- and hetero-association of **1** and **2**.

Similarities between ^{13}C and ^{15}N NMR chemical shifts in $CDCl_3$ and the solid state indicated that the DDAA dimer was preserved in $CDCl_3$. In particular, at C2, a chemical shift of 157.2 ppm in $CDCl_3$ and 157.4 ppm in the solid state was observed, in agreement with a hydrogen-bonded CO shift. By comparison, the folded monomer **1′** in DMSO-d_6 with a free CO group showed a chemical shift at C2 of 153.4 ppm. The ^{1}H NMR spectrum in $CDCl_3$ showed protons 7-H and 9-H at 10.9 and 9.0 ppm, respectively, indicating their involvement in hydrogen bonding. In addition, a positive NOE was observed between 7-H and 9-H, which is expected for the linear arrangement of these protons in the unfolded dimer **1.1** (Figure 1). Strong dimerization of **1** in $CDCl_3$ was also apparent from a comparison of its diffusion coefficient with that of the UPy analogue **2** (Figure 3): 6.0×10^{-10} m^2 s^{-1} for **1.1** and 6.2×10^{-10} m^2 s^{-1} for **2.2**. However, a small amount (5%, Figure 4a) of the folded dimer **1′.1′** was found in $CDCl_3$ (δ_{5-H} = 6.10 ppm; for comparison, δ_{5-H} = 6.15 ppm in DMSO-d_6), in exchange with **1.1** (δ_{5-H} = 7.54 ppm). From variable temperature ^{1}H NMR measurements in $CDCl_3$, the free energies of activation were calculated to be 67 and 60 kJ mol^{-1} for $\Delta G^{\ddagger}_{\mathbf{1.1}\rightarrow\mathbf{1'.1'}}$ and $\Delta G^{\ddagger}_{\mathbf{1'.1'}\rightarrow\mathbf{1.1}}$, respectively, at the coalescence temperature of 320 K.

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10.1021/ja0587289 CCC: $33.50

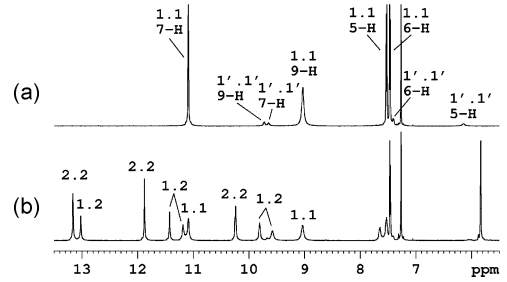


Figure 4. ^{1}H NMR spectra in $CDCl_3$ at 256 K of (a) **1** and (b) a 1:1 mixture of **1** and **2**. Low-temperature measurements were used for better resolution of the NH peaks.

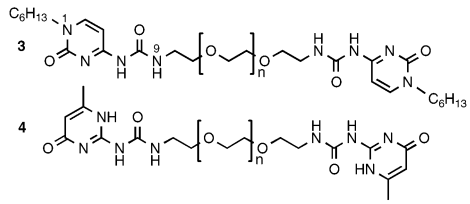
Only the unfolded dimer **1.1** was found in C_6D_6, $C_6D_5CD_3$, and in the solid state. The concentration dependence of **1** in ^{1}H NMR spectra was measured in C_6D_6. No chemical shift changes occurred or new peaks appeared on dilution to 5 μM. Assuming that at this concentration there is less than 10% dissociation not detected by ^{1}H NMR (as in ref 3a), a lower limit of 9×10^6 M^{-1} was found for the dimerization constant (K_{dim}) of **1** in C_6D_6.[9]

Capacity of the new module **1** to disrupt the strong UPy dimerization was then explored in order to reveal its potential for the construction of hetero-assembled supramolecular copolymers. In particular, the hetero-association of **1** and UPy **2** (Figure 3) via quadruple hydrogen bonding was examined.

A solution of a 1:1 mixture of compound **1** and **2** in $CDCl_3$ was studied. The ^{1}H NMR spectrum at 256 K (Figure 4b) showed all the expected NH peaks in the high frequency region. The ratio of **1.1**:**1.2**:**2.2** was approximately 5:6:5, indicating that the new cytosine-based DDAA module competes well with UPy.

To further evaluate the ability of the new module to polymerize via intermolecular quadruple hydrogen bonds, the bifunctional derivative **3** was synthesized together with a structurally related UPy derivative **4** for comparison purposes. From reports on UPy derivatives, **4** should form mainly cyclic dimers at millimolar concentrations, with an equilibrium between cyclic dimers and higher molecular weight species on increasing the concentration.[10] Amine-terminated poly(ethylene glycol) ($\sim$3400 g mol^{-1}) was reacted with the corresponding imidazole-activated units to generate **3** and **4**. Both materials were solids with melting points of 46 °C (**3**) and 43 °C (**4**) and T_g values of -57 °C (**3**) and -58 °C (**4**). The ^{1}H NMR analysis of **3** revealed the presence of two hydrogen bonded protons at 10.7 and 9.2 ppm in $CDCl_3$, suggesting that the linear DDAA array was preserved.

Diffusion coefficient (D) measurements in 6.5 mM solutions of **3** and **4** in $CDCl_3$ were undertaken in order to compare the degree of self-association of both **3** and **4**. The measured values were 7.6 $\times 10^{-11}$ m^2 s^{-1} for **3** and 10.3 $\times 10^{-11}$ m^2 s^{-1} for **4**. Both the ^{1}H NMR spectra and the diffusion rates were therefore consistent with the presence of small oligomers of **3** and **4** in dilute chloroform solutions. Further polymerization occurred on increasing the concentration, and this was confirmed by a considerable slowing of diffusion in 37 mM solutions: 1.9×10^{-11} m^2 s^{-1} for **3** and 3.0×10^{-11} m^2 s^{-1} for **4**. The slow diffusion of **3** suggests a high degree of polymerization in the cytosine derivative. These results confirm that the new cytosine module can be used successfully for the generation of novel supramolecular materials. Investigations are currently underway aimed at the preparation of new polymers and cyclic oligomers using bifunctional cytosines linked at either N9 (as in **3**) or N1.



In summary, unlike other systems that do not possess a strong intramolecular hydrogen bond,[5] the cytosine module described above is capable of forming strong quadruple hydrogen bonding and has potential for the construction of supramolecular arrays. Other DNA bases may also be useful in supramolecular material design; indeed guanidine-based modules have recently been reported.[11] Potentially, hydrogen bonding of cytosine and guanidine modules can be explored to generate novel supramolecular architectures.

Acknowledgment. We thank AWE for a studentship (V.G.H.L.) and EPSRC for provision of X-ray facilities.

Supporting Information Available: Experimental data for **1**, **3**, and **4** and description of NMR and XRD analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA0587289