Highly stable cyclic dimers based on non-covalent interactions†

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Highly stable cyclic dimers have been assembled through a combination of non-covalent interactions, including multiple hydrogen bonding, parallel stacking and hydrophobic shielding.

Non-covalent interactions direct the formation of a range of assemblies in synthetic and biological systems, and can significantly influence their properties. Detailed studies of these interactions *via* theoretical and experimental modelling on a smaller scale have proved successful for leading to a better understanding of them, which in turn has led to a variety of useful applications.[1] The structural stability that can be achieved using a number of non-covalent interactions or their combination is of particular importance, as it enables greater control over molecular shape and properties. Here we report our preliminary findings into the formation of highly stable cyclic dimers, which are assembled *via* non-covalent interactions such as multiple hydrogen bonding, stacking type interactions and hydrophobic shielding.

The ureidopyrimidinone (UPy) functionality was selected for our studies as a source of multiple hydrogen bonding. Bifunctional UPys have been widely used for the synthesis of linear supramolecular polymers,[2] and the presence of cyclic dimers in equilibrium with linear polymers has been established in dilute solutions.[3,4] In terms of fundamental studies, cyclic dimers have attracted considerable interest due to their unusual three-dimensional structure.[3,4] However, their explicit formation as highly stable species is not straightforward, and this in turn has limited investigations into their properties and potential applications. The use of rigid or bulky linkers has been shown to lead to cyclic dimers stabilised by twelve hydrogen bonds,[4] and various ways of optimizing the yield of specific cyclic dimers have also been discussed.[3] Unlike previous reports, we chose to study bifunctional UPys with relatively long and flexible linkers. In the first instance, no additional stabilisation of the cyclic forms might be expected, based on previous reports.[3,4] However, as shown below, an unprecedented high stability of the cyclic dimers was achieved by the introduction of specific non-covalent interactions, comprising of hydrogen bonding between the side chain and the UPy, as well as hydrophobic shielding of the core hydrogen bonding arrangement.

The assembly of new compounds based on structure **1** (Fig. 1), incorporating a flexible alkyl linker and a small chiral branched unit for a possible directional change of the linker conformation, was investigated. Initial experiments were carried out by incorporating diethyl tartrate (L or D), linked through a carbamate to a flexible spacer $(CH_2)_6$ to give **2**. The UPy derivative **2a** was prepared by the reaction of the corresponding mono-UPy isocyanate[2d] with L-diethyl tartrate, using dibutyltin dilaurate as a catalyst, in chloroform, with evaporation of the reaction solvent over 2 hours.‡ Compound **2a** was isolated in 30% yield and studied by ^{1}H, ^{13}C and ^{15}N NMR techniques. Analysis of the NMR data indicated that the tautomeric behaviour of **2a** in solution was consistent with other UPys, with the 4[1*H*]-pyrimidinone (4-keto) tautomer present in $CDCl_3$ and the 6[1*H*]-pyrimidinone (6-keto) tautomer in DMSO-d_6.[5] However, unusually high ^{1}H NMR chemical shifts were measured for some of the protons (typical reported values in linear polymers[2d] are included in brackets): $\delta_{1\text{-H}}$ 13.41 (13.1), $\delta_{5\text{-H}}$ 6.41 (5.8) and $\delta_{16\text{-H}}$ 7.68 (4.9 and 4.6). In particular, the high frequency shift for 16-H was indicative of hydrogen bonding, and non-equivalence of the spacer methylene protons, including 10-H*H* and 15-H*H* (Fig. 2), suggested a cyclic arrangement of the flexible spacer with a fixed conformation. The chemical shifts in the solid state ^{13}C and ^{15}N CP-MAS NMR spectra were similar to those in $CDCl_3$, indicating little or no change in the hydrogen bonding arrangement or side chain conformation upon dissolution. To further investigate the spatial arrangement of protons, NOEs and ROEs were measured. Small negative NOEs were observed in $CDCl_3$ (Fig. 2), favouring a dimeric aggregate (M_w = 1586); positive NOEs being expected for smaller monomeric species.[6] Upon selective excitation of proton 5-H, the strongest NOE and ROE were found for proton 16-H, suggesting the spatial proximity of protons 16-H and 5-H. In addition, a small NOE for 16-H and 9-H indicated that 16-H is in proximity to the quadruply hydrogen bonded array. The relative ratios of the NOEs, together with the published geometry of a UPy derivative in the 4-keto form,[4e] were used to estimate the internuclear distances between corresponding protons in $CDCl_3$, which were then used as constraints in force field geometry optimisations.[7] The energy minimisation led to a dimeric structure in $CDCl_3$ (Fig. 3). This was very similar to the structure subsequently determined by single crystal XRD (Fig. 3), which showed the core hydrogen bonding arrangement to be well defined.§

The results showed that the cyclic dimer was maintained through a total of sixteen hydrogen bonds, eight from the two DDAA (D = donor, A = acceptor) arrays, four from the intramolecular hydrogen bonds within each DDAA unit and four from the new intramolecular hydrogen bond N_{16}–H···O=C_4. The single crystal X-ray structure indicated that the two UPy fragments of the same molecule were in an *anti*-conformation, with a twist angle of *ca.* 70°. The alkyl chain spacer formed a loop to the outside of the UPy planes, explaining the non-equivalence of the

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† Electronic Supplementary Information (ESI) available: Synthesis and characterisation of compounds **2a**, **2b**, **3a** and **4a**. Descriptions of NMR and XRD analyses. See DOI: 10.1039/b600459h

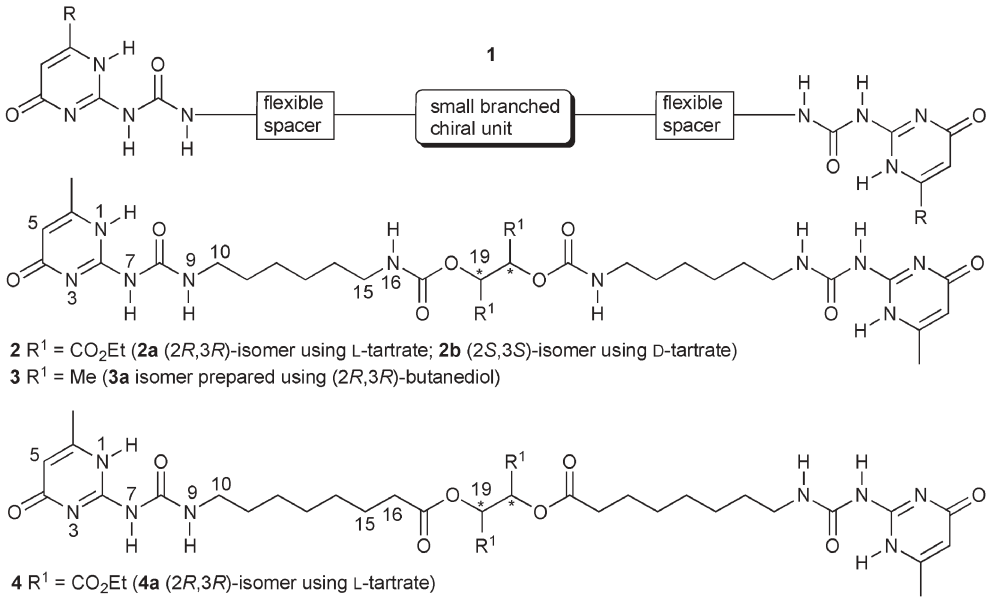

Fig. 1 Bifunctional ureidopyrimidinones **1–4**.

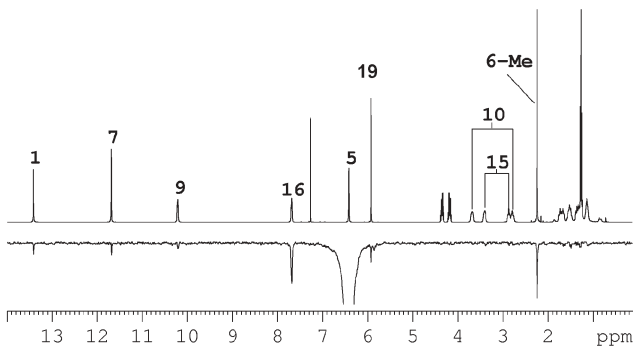

Fig. 2 ^{1}H NMR (top) and NOE (bottom, proton 5-H is selectively excited) spectra of **2a** in $CDCl_3$.

CH_2 protons observed in the ^{1}H NMR spectrum. Confirmation that the looped geometry was also predominant in $CDCl_3$ solution was obtained from the large $^3J_{HH}$ couplings of 11.5 and 11 Hz measured for proton pairs (10-H, 11-H) and (14-H, 15-H), respectively. Finally, unlike previously reported cyclic dimers with short linker units showing a highly non-planar geometry,[4e,4f] **2a** showed an almost planar orientation ($\leqslant 3^\circ$) of the pair of UPy units forming quadruple hydrogen bonding. In addition, the X-ray structure showed that the two DDAA planes in each cyclic dimer were parallel, with *ca.* 3.3 Å between them. Such an arrangement of the four UPy units is expected to further increase the stability of the cyclic dimer *via* stacking type interactions.[8]

To assess the stability of the cyclic dimer towards either dissociation or polymerisation, concentration dependence studies were undertaken in $CDCl_3$ at 298 K. Diffusion NMR experiments were performed on **2a** at 10 mM and 135 mM. The solvent corrected values of the diffusion coefficients (D) at these concentrations were 4.5×10^{-10} and 4.4×10^{-10} m^2 s^{-1}, respectively. No changes in the ^{1}H NMR chemical shifts were observed upon increasing the concentration from 1.4 μM to 500 mM and no additional peaks due to possible polymeric species were detected, suggesting that the cyclic structure was highly stable

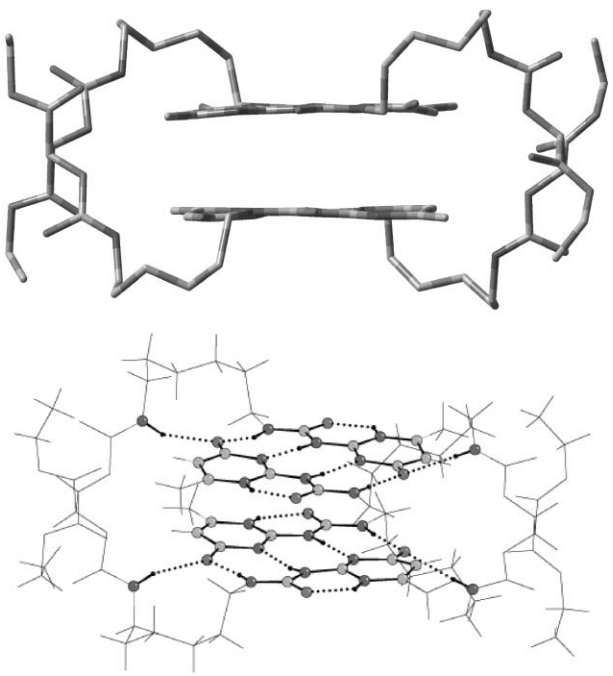

Fig. 3 The solution ($CDCl_3$) and solid state structure of **2a**. The bottom view highlights the hydrogen bonding arrangements (dotted lines).

in solution with a critical concentration (if any) above 500 mM. From the lowest concentration used, the dimerisation constant (K_{dim}) was estimated to be greater than 1.3×10^8 M^{-1} (assuming that there is 5% of monomer in the 1.4 μM solution that is not detected by ^{1}H NMR chemical shift measurements).

The dependence of the cyclisation process on the enantiomeric nature of the tartrate unit was examined, and **2b** was prepared using D-diethyl tartrate. As expected, NMR spectra were identical for both **2a** and **2b**, whereas the synthesis of a racemic mixture displayed a new set of peaks by ^{1}H NMR due to the presence of a heterodimeric assembly **2a**–**2b**, together with **2a**–**2a** and **2b**–**2b** in a

ratio of 1 : 1 : 1. This indicated that, unlike a previous report,[4e] the dimeric cyclisation was not enantioselective in the case of **2**.

An analogue of **2**, compound **3a** (Fig. 1), was also prepared to establish whether alternative small chiral diols can be incorporated and similar cyclic species formed. Compound **3a** was synthesised using (2*R*,3*R*)-butanediol in 20% yield. Based on NMR measurements in $CDCl_3$, a cyclic dimer was formed, similar to compound **2**.¶

To assess the importance of carbamate N–H hydrogen bonding in stabilising the cyclic species, compound **4a** (Fig. 1), the 16-CH_2 analogue of **2a** incorporting L-diethyl tartrate, was also prepared. Diffusion coefficient measurements were performed on **4a** in $CDCl_3$ at 298 K. A gradual and significant increase in the diffusion rate was found upon dilution; at 10 and 135 mM the solvent corrected values of the diffusion coefficients were 4.8×10^{-10} and 1.8×10^{-10} m^2 s^{-1}, respectively. Since compounds **2** and **4** have similar molecular weights, a comparison of their diffusion rates was then possible. The similarity in the diffusion rates of **2a** (see above) and **4a** at 10 mM suggested that, at low concentrations, mainly cyclic dimers of **4a** were present, stabilised by twelve hydrogen bonds. Unlike **2a**, however, a significant decrease in the diffusion rate was observed for **4a** at higher concentrations (27–135 mM), suggesting the presence of high molecular weight species (denoted as $(\mathbf{4a})_{n\geqslant 3}$). The observed decrease of *D* upon increasing the concentration can be explained either by the shift of the $(\mathbf{4a})_2 \rightleftharpoons (\mathbf{4a})_{n\geqslant 3}$ equilibrium towards $(\mathbf{4a})_{n\geqslant 3}$ or by an increase in *n* upon increasing the concentration. To conclude, the results of the diffusion measurements showed that the formation of high molecular weight species with $n \geqslant 3$ is favoured when the carbamate bond of **2** is replaced by the ester linkage of **4**. However, due to the flexibility of the alkyl chain, there is the possibility of forming a twelve hydrogen bonded cyclic dimer of **4**, which is predominant at low concentrations in $CDCl_3$. Such behaviour of **4** is common and has been described for other bifunctional UPys.[4d]

The examples presented here demonstrate how the cyclic dimer $\rightleftharpoons$ polymer equilibria can be controlled by only minor adjustments to the structure. From the comparative studies, it is apparent that the presence of additional intramolecular hydrogen bonds between the UPy unit and the carbamate NH in the side chain of **2** is critical for the formation of highly stable cyclic dimers, even in the presence of flexible linkers. As a consequence of this extra hydrogen bonding, the hexamethylene chains in **2** form hydrophobic shields (Fig. 3),‖ which in turn prevent any further polymerisation through columnar stacking of the cyclic dimers.[4d] In summary, the intra- and intermolecular hydrogen bonds, the nearly parallel stacking of the UPy planes and the presence of the hydrophobic loops act as the three main factors stabilising the cyclic dimer.

The formation of highly stable cyclic dimers is not restricted only to UPys. Similar structures could also be generated using, for example, modified DNA bases such as quadruply hydrogen bonded cytosine units.[9] Further experimental and computational studies are currently under way to explore these possibilities and to establish the structure-stabilising role of the combination of non-covalent interactions involved. It is noteworthy that the combined effect of pairs of non-covalent interactions has already been shown to be highly efficient for UPy tautomers,[8c] DNA replication[10a] and for self-assembly in micelles.[10b]

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Notes and references

‡ Amylene-stabilised $CHCl_3$ was used since EtOH-stabilised $CHCl_3$ led to a side reaction between EtOH and the monoisocyanate.

§ Crystal data for **2a**: $C_{34}H_{52}N_{10}O_{12}$, M = 792.86, orthorhombic, $Pca2_1$, a = 20.776(5), b = 21.001(7), c = 19.800(4) Å, V = 8639(4) Å^3, Z = 8, T = 120(2) K, μ = 0.093 mm^{-1}, 54394 reflections measured, 10142 independent reflections (R_{int} = 0.0791). Final R indices ($F^2 > 2\sigma(F^2)$): $R1$ = 0.2162, w$R2$ = 0.5037; R indices (all data): $R1$ = 0.2469, w$R2$ = 0.5187. The relatively high value of $R1$ is associated with increasing disorder towards the peripheral ester groups. CCDC 295047. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b600459h

¶ Selected ^{1}H and ^{13}C NMR shifts in favour of a cyclic dimer ($CDCl_3$): $\delta_{1\text{-H}}$ 13.51, $\delta_{5\text{-H}}$ 6.08, $\delta_{10\text{-H}H}$ 2.96 and 3.63, $\delta_{16\text{-H}}$ 7.13, $\delta_{C\text{-}4}$ 173.7.

‖ The conformational preference about the C_{15}–N_{16} bond, with the C_{14}–C_{15} bond direction approximately perpendicular to the carbamate plane (Fig. 3), may be another factor stabilising the cyclic dimer, though it is expected to be less significant than the formation of the additional hydrogen bond.

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