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Hydrogen-Bonded Cyclic Tetramers Based on Ureidopyrimidinones Attached to a 3,6-Carbazolyl Spacer

Yong Yang, Min Xue, Laura J. Marshall, and Javier de Mendoza*

Institute of Chemical Research of Catalonia (ICIQ), 43007-Tarragona, Spain

jmendoza@iciq.es

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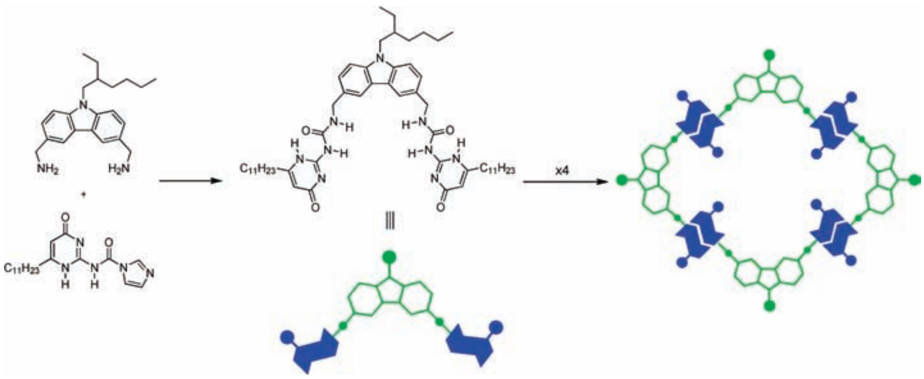
ABSTRACT



Direct attachment of two 2-ureido-4-[1*H*]-pyrimidinone (UPy) subunits to a 3,6-carbazolyl core gives rise to a highly viscous, supramolecular polymer. However, insertion of a methylene spacer between the UPy's and the carbazole leads to a well-defined, cyclic tetramer, in a belt-shaped arrangement, as evidenced by MALDI-TOF, DOSY, and NOESY spectra.

Self-assembly based on hydrogen bonding has been widely employed to build up large rosette-like, often flat supramolecular structures.[1,2] In addition to cyanuric acid–melamine combinations,[3] hydrogen bonded scaffolds inspired by G-C pairs,[4] G-quartet mimics,[5] or on pyridines,[6] hydrazides,[7] and carboxylic acids,[8] among others,[9] have been reported. In this context, the 2-ureido-4-[1*H*]-pyrimidinone (UPy) scaffold has been efficiently employed to design and build up self-assembled supramolecular architectures,[10] due to the remarkable strength of the dimers arising from its quadruple hydrogen bonding edge [K_a (chloroform) $> 10^7$ M^{-1}].[11] Well-defined rosettes

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result when two UPy subunits are attached to a suitable rigid spacer. Thus, cyclic pentamers with 20 hydrogen bonds are favored with 1,3-disubstituted adamantyl (109° angle), whereas hexamers containing 24 hydrogen bonds arise from *m*-phenylene (120°).[10b] Similarly, cyclic tetramers are formed when a metalloporphyrin containing UPy's at two vicinal *meso*-positions (90°) is employed.[10d]

We reasoned that a 3,6-disubstituted carbazolyl spacer with an angle of ~90° would also favor tetrameric cyclic arrangements, stabilized by 16 hydrogen bonds, and we were curious to discover whether flat rosette-like or tubular belt-like aggregates would predominate. To test this idea, we first synthesized compounds **1** and **2** (Figure 1) from the corresponding readily available nitro-derivatives, resulting in the direct attachment of the UPy moiety to the carbazole ring.

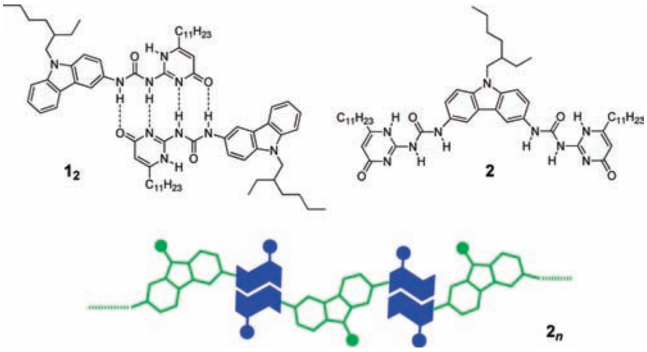

Figure 1. Mono- and disubstituted carbazoles with UPy subunits **1** ($\mathbf{1_2}$ dimer shown) and **2** (monomer), and schematic representation of linear oligomers $\mathbf{2_n}$.

Although the well-defined, typical signature for a UPy dimer $\mathbf{1_2}$ was observed in the ^{1}H NMR spectrum of compounds **1** in $CDCl_3$ (sharp peaks at 13.20, 12.36, and 12.25 ppm) in the downfield region,[10,11] compound **2** showed only limited solubility (*ca.* 5 mM), high viscosity, and a broad, ill-defined spectrum. Addition of a trace of trifluoroacetic acid greatly decreased the viscosity, resulting in full solubilization of the species, and a well resolved spectrum compatible with monomer **2** emerged. It is likely that linear oligomers or polymers $\mathbf{2_n}$ were favored over the desired, though rigid and crowded, cyclic tetramer $\mathbf{2_4}$. CPK modeling studies[12] gave a clearer insight into the explanation for this observation. With the UPy moieties attached directly to the carbazole ring, flexibility would be a significant factor when considering the formation of hydrogen bonds between the monomers. The assembly of a flat, rosette-like structure would ultimately result in twisting of the structure (torsional strain) and subsequent unfavorable hydrogen-bonding angles due to the presence of the undecyl chains at the inner region of the rosette. This is highly unfavorable due to steric interactions, and models show that there is clearly not sufficient space inside a flat rosette to accommodate the long alkyl chains. Therefore, the assembly of linear oligomers or polymers is likely to dominate.

To increase the flexibility, a methylene group was inserted between the UPy subunits and the carbazole spacer. Thus compound **4** and the corresponding control **3** were prepared. In **4**, the UPy subunits can adopt multiple conformations (Figure 2) that could generate cyclic oligomers of various sizes and shapes. Once again, model inspection clearly shows that a flat trimer or tetramer cannot be built for torsional and steric reasons. On the contrary, folded structures can easily be arranged. Indeed, model optimizations[12] for either cyclic trimers or tetramers are fully compatible with propeller-like shapes where both UPy subunits in each monomer are pointing to opposite sides (Figure 3a and 3b). In the case of the tetramer, a very favorable, sterically unhindered tubular (belt-like) shape can be generated with both UPy subunits being mirror images pointing to the same side of the carbazole spacer (Figure 3c).

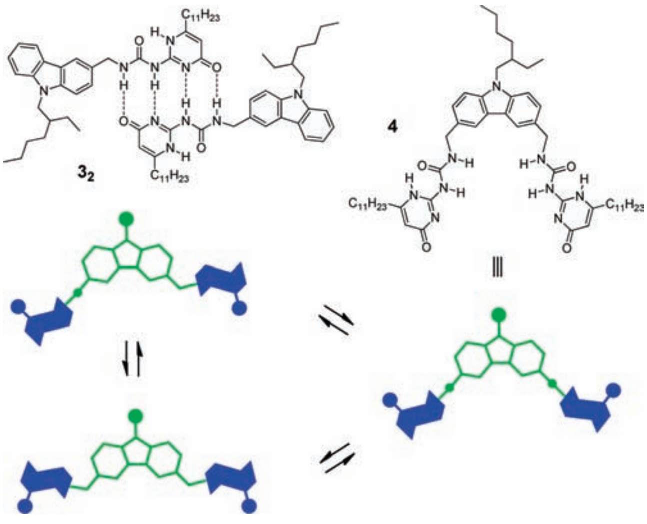

Figure 2. Mono- and disubstituted carbazoles **3** ($\mathbf{3_2}$ dimer shown) and **4** (monomer), and schematic representation of conformations around the UPy subunits.

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In this arrangement, all alkyl chains at both edges of the hydrogen bonded belt orient away from the assembly (Figure 3d and 3e), and into the bulk solvent, thus providing greater solubility and reduced steric hindrance compared to the flat systems.

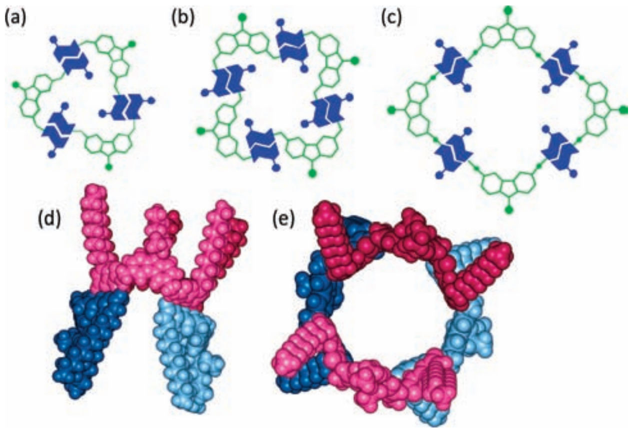

Figure 3. Schematic representation of cyclic aggregates from **4**. (a) Propeller-shaped trimer. (b) Propeller-shaped tetramer. (c) Tubular-shaped tetramer. Side (d) and top (e) views of optimized tubular-shaped $\mathbf{4_4}$ aggregates.

Spectroscopic data were in full agreement with our predictions of a tubular belt-like assembly. Unlike **2**, both compounds **3** and **4** showed sharp ^{1}H NMR signals in $CDCl_3$ with three well-defined singlets for the UPy's NH signature (compound **3**: 13.03, 11.96, and 10.82 ppm; compound **4**: 13.03, 12.07, and 10.83 ppm). Also, compound **4** showed increased solubility ($>$40 mM in $CDCl_3$) relative to **2**, and the viscosity of the solution was almost the same as that of the solvent itself.

Molecular masses of the trimer and the tetramer were clearly observed by MALDI-TOF$^+$ (m/z 2761 and 3682, respectively), accompanied by the monomer and the dimer, but no peaks were observed for higher aggregates (Figure 4 and Supporting Information; see Figure SS22).

Also, the DOSY spectrum ($CDCl_3$) at different concentrations showed a well-defined signal on the D axis, indicating the presence of a discrete species in solution at the NMR time scale (Figure 5). The spectra show the slight change of D with the concentration increase, which favors cyclic oligomers.[2]

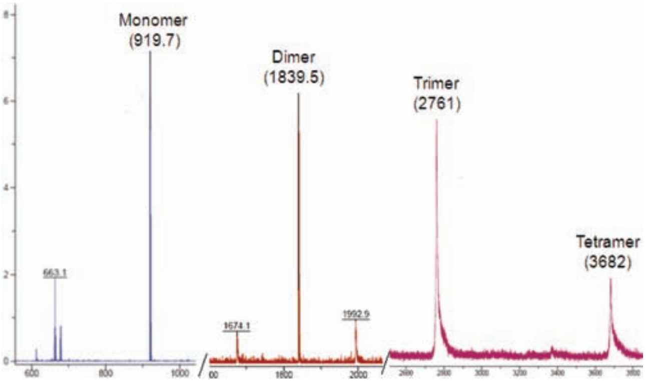

Figure 4. MALDI-TOF$^+$ Mass spectrum of compound **4** showing the presence of the monomer, dimer, trimer, and tetramer.

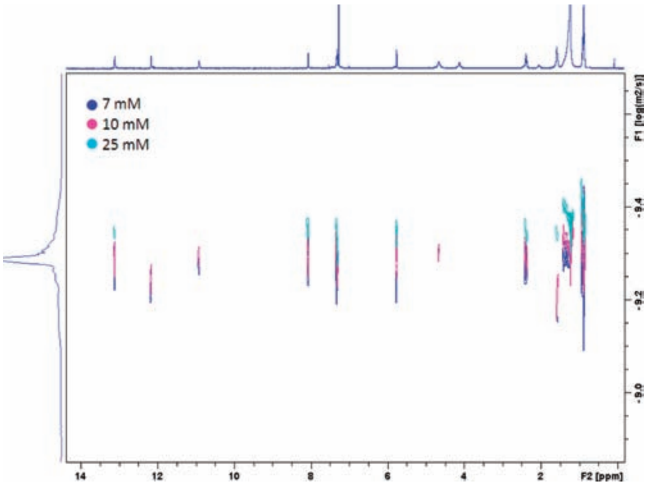

Figure 5. DOSY spectrum of compound **4** ($CDCl_3$) at 7 mM (blue), 10 mM (pink), and 25 mM (light blue) concentrations.

Using the Stokes–Einstein equation, the experimentally found diffusion coefficients can be converted to an approximate hydrodynamic radius.[13] Thus, a value of 9.29 Å results at a 25 mM concentration, which translates into a "sphere" volume of 3358 Å^3. This experimental value for the hydrodynamic radius can be compared with a theoretical one, which can be approximately calculated by taking the average of the length, width, and height of the dissolved species,[14] as measured on the optimized models for the different cyclic oligomers.[12] The average estimated radii/volumes for a tetramer (9.95 Å/ 4126 Å^3) and a pentamer (11.8 Å/6882 Å^3) strongly point toward a tetramer as the dominant species in solution.

Low temperature NMR allowed us to unequivocally assign the structure shown in Figure 3d and 3e for the most populated aggregate. At 213 K (10 mM in $CDCl_3$), the spectrum shows a unique set of sharp signals for the UPy subunits, accounting for a symmetric structure with a plane of symmetry bisecting the carbazole core. As expected, the methylene protons attached to the carbazolyl

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(12) Structures were minimized *in vacuo* by molecular mechanics using Augmented MM3 parameters (OG_MM-MM3 protocol) within the SCIGRESS 7.7.0.47 software (Fujitsu Ltd.)

(13) $r_h = k_b T/(6\pi\eta D)$, in which the solute is a spherical species.

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core split into two doublets, accounting for a rigid structure with different environments for each proton (Figure 6). These findings strongly point to a belt-shaped tetrameric assembly, like that shown in Figure 3d and 3e. In good agreement with this geometry, the NOESY spectrum at 213 K shows contacts between H^1 and the 4-carbazolyl proton as well as with the urea protons (Figure 6, arrows c, g, and f). H^2, however, is coupled with the 2-carbazolyl proton and also to the urea protons, but to a lesser extent than H^1. This indicates that both hydrogen-bonded edges are oriented *anti* with respect to the carbazolyl *N*-substituent.

In summary, we have demonstrated that 2-ureido-4-[1*H*]-pyrimidinone (UPy) subunits attached to a 3,6-carbazolyl core self-assemble into tubular cyclic tetramers, in which substituents are oriented to both edges of the ring. Due to the possibility of carbazole-based polymers displaying interesting optical and electrical properties,[15] it is likely that modification of the central cores to allow self-assembly of a second array of UPy partners would provide an easy access to polymeric carbazolyl nanotubes possessing interesting optical and electrical properties. We are currently exploring these possibilities.

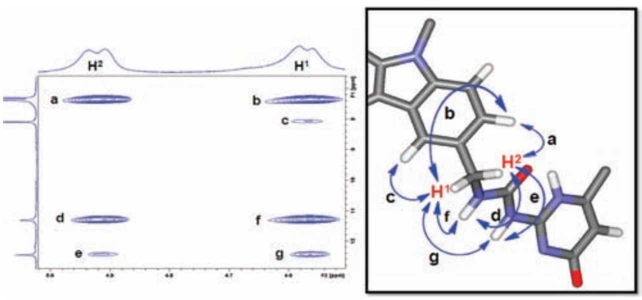

Figure 6. Low temperature ($CDCl_3$, 213 K) NOESY spectrum of compound **4** (partial section showing contacts with methylene H^1 and H^2 protons).

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Supporting Information Available. Experimental details, characterization and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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