

# Unsymmetric Dendrimers Containing a Single Ureidopyrimidine Unit: Generation-Dependent Dimerization via Hydrogen Bonding

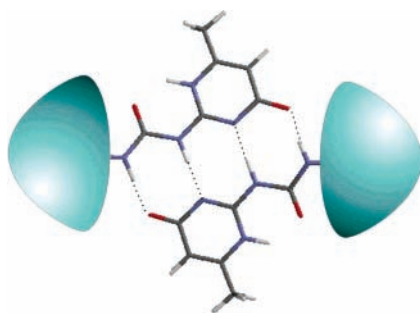
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## ABSTRACT



A new series of unsymmetric Newkome-type dendrimers have been prepared and characterized. These dendrimers contain a single ureidopyrimidine residue covalently attached to their apical positions. In low polarity solvents, the first and second generation dendrimers form highly stable dimers via hydrogen bonding of their AADD ureidopyrimidine units, whereas the third generation dendrimer dimerizes to a very low extent.

Dendrimers are attractive nanoscale building blocks for self-assembly. As compared to the assembly of smaller molecular units, the large molecular sizes of dendrimers facilitate structure building with decreased entropic cost, since fewer components need to be held together to achieve the desired size.<sup>1</sup> Our group has recently demonstrated the redox-controlled dimerization of viologen-containing dendrimers mediated by the host cucurbit[8]uril.<sup>2</sup> Although many other methods have been developed to elicit the self-assembly of dendrimers, the directionality and reversibility inherent to

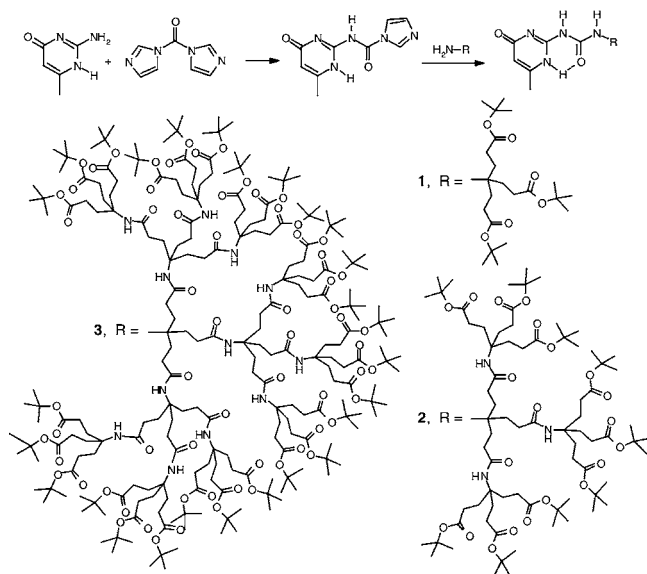
hydrogen bonding interactions<sup>3</sup> have prompted their frequent utilization in dendrimer self-assembly.<sup>4</sup> To drive the formation of stable hydrogen-bonded assemblies, a suitable combination of several hydrogen bonds is required. In this regard the self-complementary acceptor-acceptor-donor-donor (AADD) motif present in ureidopyrimidine units has proven to be quite useful.<sup>5</sup> In this work, we present preliminary results on the synthesis, characterization, and self-assembly (dimerization) through hydrogen bonding of a new series of Newkome-type dendrimers<sup>6</sup> containing a single ureidopyrimidine residue covalently attached to their

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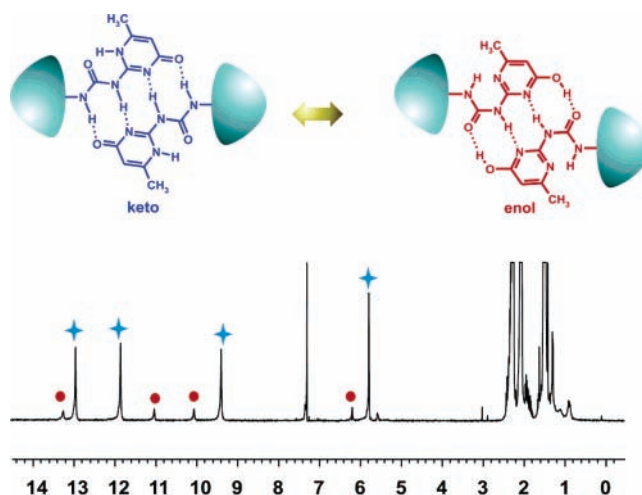


**Figure 1.** Synthesis and structure of uridopyrimidine dendimers 1–3.

apical positions (see Figure 1). Remarkably, these dendrimers exhibit a pronounced generational effect on the stability of their hydrogen-bonded dimers.

The preparation of dendrimers **1–3** started by the activation of 6-methylcytosine, as described by Meijer and co-workers,<sup>7</sup> to 2-(1-imidazolylcarbonylamino)-6-methyl-4[1*H*]-pyrimidinone, which was subsequently treated with the corresponding amine building blocks (Newkome-type dendrons) previously described by our group<sup>6b</sup> to yield dendrimers **1–3** in moderate yields. The dendrimers were characterized by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopies, as well as by MALDI-TOF mass spectrometry to guarantee monodispersity. Interestingly, peaks assigned to dendrimer dimers, presumably due to hydrogen bonding, were readily observed in the MALDI-TOF mass spectra of dendrimers **1** and **2** (Supporting Information).

The  $^1\text{H}$  NMR spectrum of dendrimer **1** in  $\text{CDCl}_3$  shows two sets of signals for the NH protons (Figure 2). The first



**Figure 2.** Partial  $^1\text{H}$  NMR spectra (400 MHz) of 8.0 mM **1** in  $\text{CDCl}_3$  solution.

set of signals at 12.93, 11.84, and 9.38 ppm is assigned to the 4[1*H*]-pyrimidinone tautomer.<sup>5e</sup> A second set of less intense signals at 13.26, 11.02, and 10.04 ppm is assigned to the pyrimidin-4-ol tautomer. The large downfield shifts from the usual chemical shift values of the urea NH protons are consistent with their involvement in strong hydrogen bonds. The observation of peaks for both known tautomers reveals their slow exchange in the NMR time scale.

We attempted to determine the dimerization equilibrium constant ( $K_{\text{dim}}$ ) of the first generation dendrimer by recording NMR spectra at progressively lower concentrations of **1** in CDCl<sub>3</sub> solutions. However, no significant signal displacements were observed down to an absolute concentration of 10<sup>-5</sup> M, reflecting the large thermodynamic stability of the dimer ( $K_{\text{dim}} > 10^6 \text{ M}^{-1}$  in CDCl<sub>3</sub>).<sup>5f</sup> The relative amounts of the pyrimidin-4-ol and 4[1*H*]-pyrimidinone tautomers were measured from the relative integration of peak areas. The results are shown in Table 1.

**Table 1.** Keto:Enol Tautomer Ratio Determined from  $^1\text{H}$  NMR Spectroscopy in  $\text{CDCl}_3$  and Toluene- $d_8$  Solutions

dendrimer	chloroform- <i>d</i>	toluene- <i>d</i> <sub>8</sub>
<b>1</b>	6:1	3:1
<b>2</b>	99:1	7:1

As is evident from these data, the pyrimidinone (keto) tautomer predominates in all cases, but the relative abundance of the pyrimidinol tautomeric form is larger in the less polar solvent toluene. These findings are in agreement with previous literature reports.<sup>5e</sup> We performed semiempirical and ab initio calculations on both tautomeric forms of a simple ureidopyrimidinone compound ( $R = CH_3$  in Figure 1) and found that the dipole moment of the pyrimidinone tautomer is substantially larger than that of the pyrimidinol tautomer (see Table 2), which is consistent with the larger abundance

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**Table 2.** Dipole Moments Calculated for Model Ureidopyrimidinone Compound ( $R = CH_3$  in Figure 1) Using Semiempirical and ab Initio Methods as Implemented in the Titan and Gaussian Software Packages

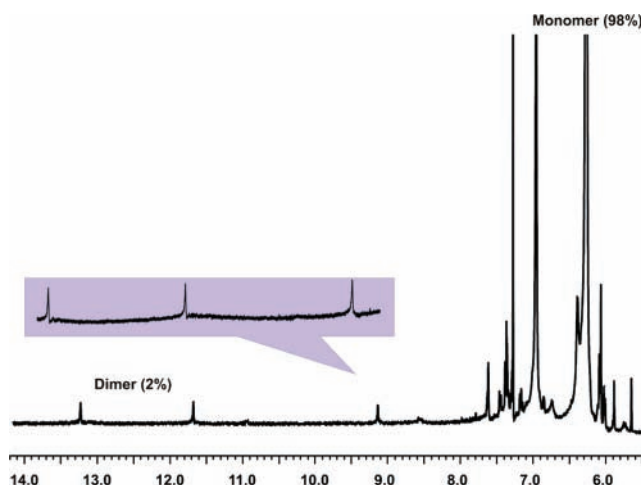
form	dipole moments (debyes)	
	Titan (PM3 method)	Gaussian (Hartree–Fock, 6-31G basis set)
keto	7.342	7.584
enol	3.249	3.672

of the latter form in solvents of lower polarity. The larger abundance of the more polar tautomer in dimer **2**<sub>2</sub> as compared to **1**<sub>2</sub> probably reflects the growth of the dendritic components, since the inner phases of these dendrimers exhibit a polarity greater than those of the two solvents used in our experiments.<sup>6d,e</sup>

The extensive dimerization of dendrimers **1** and **2** was also verified by effective molecular weight determinations using vapor pressure osmometry in toluene solutions.<sup>8</sup> For instance, solutions of **1** in toluene in the 3–50 mM concentration range showed decreased vapor pressure compared to that of pure toluene, corresponding to the presence of a solute with an average molecular weight of 1,173 g/mol. This value is within 3% of the calculated molecular weight of the **1**<sub>2</sub> dimer (1,134 g/mol). Similar experiments with dendrimer **2** yielded an average molecular weight of 3,108 g/mol, which is within 2% of the calculated value for the **2**<sub>2</sub> dimer (3,180 g/mol). As control experiments, vapor pressure osmometric measurements in ethanol solutions<sup>8</sup> yielded molecular weights for **1** and **2** of 559 and 1,570 g/mol, respectively, both of which are within 1% of the calculated molecular weights for the monomers (567 and 1,590 g/mol, respectively). These results provide clear and independent confirmation for the quantitative dimerization of **1** and **2** in toluene solutions, while they confirm the lack of dimerization in the more polar ethanol solutions.

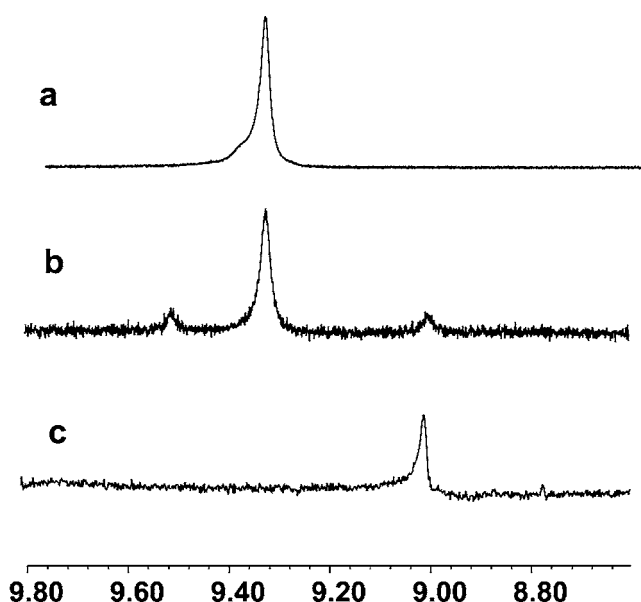
In contrast with **1** and **2**, dendrimer **3** dimerizes to a very limited extent. Figure 3 shows the <sup>1</sup>H NMR spectrum of **3** in CDCl<sub>3</sub> solution. Integration of the corresponding peak areas reveals that only ca. 2% of the dendrimer undergoes dimerization ( $K_{\text{dim}} = 2.6 \text{ M}^{-1}$ ). This is a very surprising result in lieu of the quantitative dimerization observed with the smaller dendrimers **1** and **2**. Steric hindrance exerted by the larger dendritic component in **3** may play a significant role. An alternative rationalization would rely on the relative microenvironment polarities created by the dendritic components. Dendron growth from the second to the third generation may give rise to a microenvironment polar enough to weaken hydrogen bonding between the ureidopyrimidine subunits of the two dendrimers.

To address the relative importance of these two factors we performed a number of heterodimerization experiments. In the <sup>1</sup>H NMR spectrum of an equimolar mixture of



**Figure 3.** Partial <sup>1</sup>H NMR spectra (400 MHz) of 8.0 mM **3** in CDCl<sub>3</sub> solution.

dendrimers **1** and **2** one can observe signals corresponding to the NH protons of the **1**<sub>2</sub> and **2**<sub>2</sub> homodimers, as well as new signals that are ascribed to heterodimers **1**•**2**. As an illustration, the region of the NMR spectrum corresponding to the hydrogen-bonded NH urea proton adjacent to the dendron provides clear evidence for the presence of two heterodimers, presumably formed by the keto and enol forms of the dendrimers (see Supporting Information). The spectroscopic data clearly reveal that both **1** and **2** fully engage in homodimer and heterodimer formation in solutions containing both compounds.



**Figure 4.** Partial <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) spectra of (a) dendrimer **1**, (b) 1:1 mixture of dendrimers **1** and **3**, and (c) dendrimer **3**. The resonances shown correspond to the NH urea proton adjacent to the dendron.

(8) Osmometric data for the molecular weight calibration plots were obtained with standard solutions of the dendritic building blocks shown in Figure 1 having either -NO<sub>2</sub> or -NH<sub>2</sub> groups at their apical positions.

In contrast to these results, Figure 4b shows the same spectral region for a solution containing an equimolar mixture of **1** and **3**. Notice that in addition to the signal (at 9.32 ppm) corresponding to the NH proton of **1**<sub>2</sub>, the spectrum only shows two additional low intensity signals corresponding to the heterodimer **1**·**3** (at 9.50 ppm) and the homodimer **3**<sub>2</sub> (at 9.02 ppm). Integration of these signals reveals that only about 5% of **3** is engaged in dimerization with itself or with the first generation dendrimer **1**, whereas 95% of **3** remained in the monomeric form.

Previous results from our group<sup>6c</sup> have clearly demonstrated that growth of the Newkome dendrons used in this work leads to an effective increase in the polarity of the microenvironment surrounding the functional residue attached to the dendron's apical position. This microenvironment effect seems to be important to the understanding of the low stability of dimer **3**<sub>2</sub>, since our experimental data suggest relatively moderate steric hindrance effects. Furthermore, the increasing polarity of the microenvironment around the ureidopyrimidine residue in going from dendrimer **1** to **3** is also consistent with the keto:enol ratios shown in Table 1 for dimers formed by dendrimers **1** and **2**.

Our group has investigated extensively the binding interactions between synthetic hosts and structurally similar dendrimers containing a single guest residue attached to the apical position.<sup>9</sup> Generally, the stability of the host–guest

complex tends to decrease as the size of the dendron increases. The results presented here constitute a sharp extreme of this general behavior, as the stability of the hydrogen-bonded dimer goes from very high ( $K_{\text{dim}} \geq 10^6 \text{ M}^{-1}$ ) in the first and second generation to quite low in the third generation ( $K_{\text{dim}} = 2.6 \text{ M}^{-1}$ ). This generational dendrimer effect is so pronounced that even hydrogen bonding of **3** with smaller partners, such as dendrimer **1**, takes place to a very modest extent.

In conclusion, we have prepared and characterized a new series of dendrimers containing a focal ureidopyrimidine hydrogen bonding subunit, which gives rise to the formation of highly stable hydrogen-bonded dimers at the first and second generations of dendron growth (compounds **1** and **2**). A pronounced discontinuity on the stability of the hydrogen-bonded dimers was observed, since growth of the dendron component to the third generation strongly hinders the dimerization of compound **3**.

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**Supporting Information Available:** MALDI-TOF spectra for compounds **1** and **2**, NMR spectra of mixtures of **1** and **2**, and synthetic details for the preparation of **1**–**3**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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