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Generation-Independent Dimerization Behavior of Quadruple Hydrogen-Bond-Containing Oligoether Dendrons

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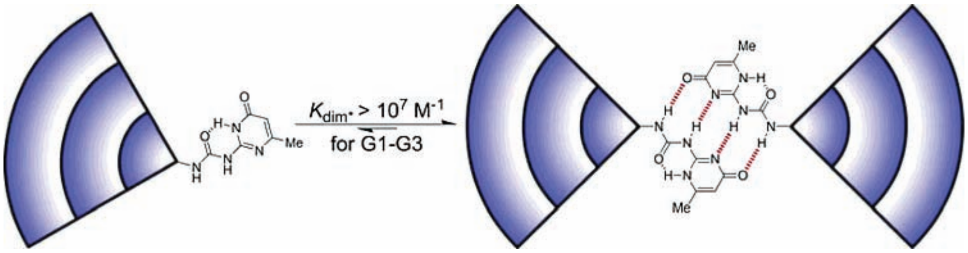
ABSTRACT



A new series of self-assembling G1–G3 dendronized dimers bearing oligoether dendrons and a dimeric 2-ureido-4-pyrimidinone (UPy) quadruple hydrogen-bonding core were prepared and characterized. It was found that the nonpolar microenvironment created by the dendrons preserved the UPy unit in its DDAA tautomeric form. As a result, the stabilities of the dimers were exceptionally strong for all three generations (K_{dim*} > 2 × 10^7 M^{-1} in CDCl$_3$ at 25 °C). Furthermore, the steric size of the dendrons did not exhibit a significant effect on their dimerization behavior.

Dendronized polymers belong to an important class of macromolecules that possess many applications due to their unique structural features. These applications have been successfully applied to areas such as catalysis,[1] light harvesting,[2] gene transfection,[3] optoelectronics,[4] and nanotechnology.[5] Most often, dendronized polymers were prepared by the covalent assemblies of the dendritic monomers.[6] However, such strategies were known to suffer from low degrees of polymerization (DP) and slow reaction rates because of steric congestions and kinetic problems associated with the polymerization process. Previously, we showed that polyfunctional amino acid-based dendrimers and dendrons formed nondiscrete nanoscopic-sized aggregates or dendritic gels via intermolecular hydrogen-bond interactions.[7] On the other hand, the preparation of discrete, cyclic dendritic supramolecular self-assemblies using dendritic monomers bearing preorganized multiple hydrogen-bonding units has been reported by Zimmerman.[8] We are therefore interested in

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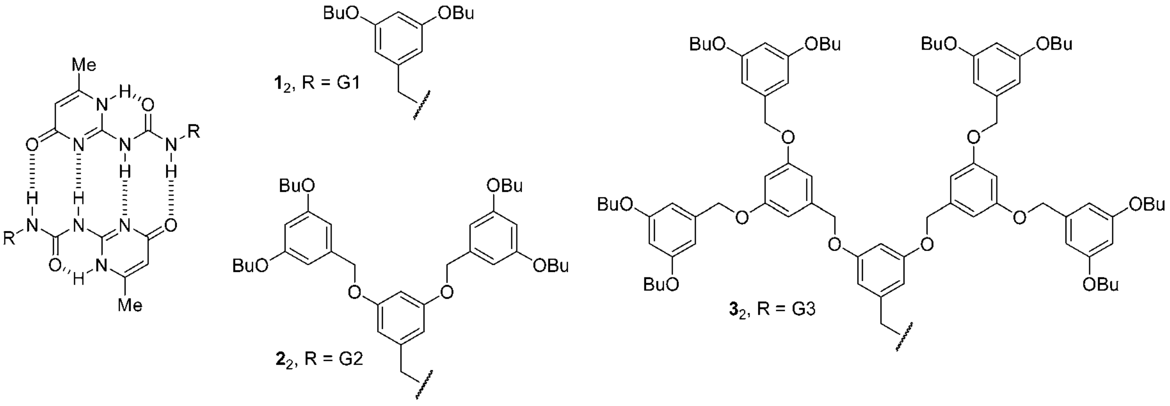
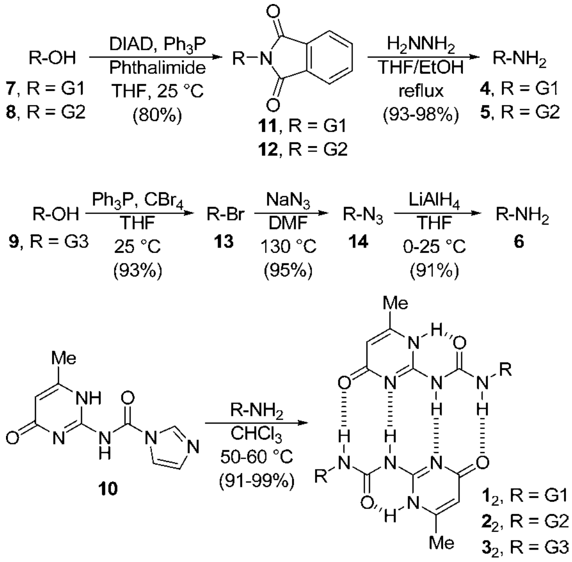


Figure 1. Structures of self-assembling dendronized dimers $\mathbf{1}_2$−$\mathbf{3}_2$.

using a self-assembling approach to synthesize high DP dendronized polymers using dendritic monomers bearing two nonpreorganized, self-complementary hydrogen-bonding units. This approach should also furnish dendronized polymers with tunable properties as the binding strength among the dendritic monomers is subjected to solvent and microenvironment effects.[9] However, the successfulness of this approach relies on the assumption that the binding constant between the subunits is not drastically reduced by the increasing size of the dendritic sectors; otherwise, oligomers instead of dendronized polymers will be formed as the major products. However, a recent report by Kaifer[10] on the dimerization behavior of a series of monofunctionalized dendrons bearing the 2-ureido-4-pyrimidinone[11] (UPy) quadruple hydrogen-bonding unit indicated a substantial decrease of the dimerization constant for the G3 dimer.[12] It was rationalized that this resulted from both the steric effect and the polar microenvironment exerted by the highly polar oligoamide dendrons. Their study, therefore, cast serious doubts on the feasibility of forming high DP self-assembling dendronized polymers using the hydrogen-bonding approach, especially for dendronized polymers constructed from higher generation monomeric units. However, we envisaged that one may restore the stability of the dimeric states by changing the microenvironment around the hydrogen-bonding units. Hence, we prepared a series of monofunctional, UPy-containing dendrons bearing nonpolar oligoether dendritic sectors $\mathbf{1}_2$−$\mathbf{3}_2$ (Figure 1) and studied their dimerization behavior. In contrast to Kaifer's findings, all of our dimers, irrespective of the generation, possess high dimerization constants ($K_{\mathrm{dim}*}$ > 2×10^7 M^{-1} in $\mathrm{CDCl_3}$ at 25 °C). Our studies show that the microenvironment of the dendrons is of paramount importance in dictating the strength of binding, and the binding strength is almost unperturbed by steric effects.

For the synthetic work, dendritic benzylamines **4**−**6** were prepared from their corresponding dendritic alcohols **7**−**9** via Mitsunobu-type Gabriel synthesis (for the G1 and G2 series) or $\mathrm{LiAlH_4}$ reduction of dendritic azide (for the G3 series).[13] Dendritic alcohols **7**−**9** were prepared from methyl 3,5-dihydroxybenzoate using a convergent approach. The resulting dendritic amines **4**−**6** were then coupled to imidazolide **10** to afford the corresponding dendronized dimers $\mathbf{1}_2$−$\mathbf{3}_2$ in high yields (Scheme 1).[14] The purities and structural identities of all dendritic compounds were fully characterized by ^{1}H and ^{13}C NMR, HRMS, GPC, and/or elemental analysis.

Scheme 1. Synthesis of Self-Assembling Dendronized Dimers



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(12) Recently, another series of a dendronized dimeric system has also been reported. However, no dimerization constants were given. See: Hahn, U.; González, J. J.; Huerta, E.; Segura, M.; Eckert, J.-F.; Cardinali, F.; de Mendoza, J.; Nierengarten, J.-F. *Chem.*−*Eur. J.* **2005**, *11*, 6666.

(13) See Supporting Information for details.

The dimerization properties were studied by ^{1}H NMR, ^{1}H NOESY/ROESY, vapor pressure osmometry (VPO), HRMS-ESI, and FT-IR. It was known that 4[1*H*]-pyrimidinone was a stronger dimerizing tautomer (via DDAA array) than pyrimidin-4-ol (via DADA array) because of attractive secondary interactions.[11b] Indeed, the ^{1}H NMR spectra of the dimers $\mathbf{1}_2$−$\mathbf{3}_2$ in $CDCl_3$ showed a set of characteristic NH signals (δ 13.0, 12.0, and 10.8 ppm) that were assigned to the 4[1*H*]-pyrimidinone tautomers (Figure 2).[11b] In contrast to Kaifer's dimers, the signals of the possible weaker DADA pyrimidin-4-ol tautomers were not observed in our dimers, indicating that the microenvironment in our system was significantly different from those of Kaifer's.[10,15] This preservation of the UPy unit in its DDAA tautomeric form was highly important, as it guaranteed a much stronger binding (10^7 vs 10^5 M^{-1}) between the quadruple hydrogen-bonding units.[11b] The sole presence of the 4[1*H*]-pyrimidinone tautomers was further supported by ^{1}H NOESY/ROESY correlation analysis.[13] The observed tautomeric behavior was identical to that reported in the literature.[11b] Additionally, the presence of dimers was confirmed by VPO measurements and by the presence of $[2M + H]^+$ peaks for dimers $\mathbf{1}_2$−$\mathbf{3}_2$ in HRMS-ESI studies (Table 1).

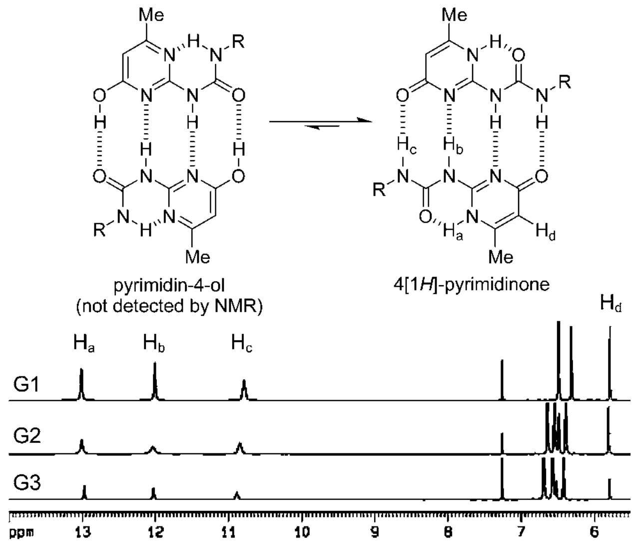


Figure 2. Partial ^{1}H NMR spectra (300 MHz) of $\mathbf{1}_2$−$\mathbf{3}_2$ in $CDCl_3$.

Table 1. Measured Molecular Weights of Dendronized Dimers $\mathbf{1}_2$−$\mathbf{3}_2$ by VPO and HRMS-ESI

	VPO[a]		HRMS-ESI $[2M + H]^+$	
dimers	theoretical	measured	theoretical	measured
$\mathbf{1}_2$	805	760 (±50)	805.4607	805.4606
$\mathbf{2}_2$	1518	1530 (±80)	1517.8582	1517.8585
$\mathbf{3}_2$	2944	2980 (±140)	2942.6532	2942.6473

[a] Solvent: $CHCl_3$. Temperature: 30.0 °C.

The absolute values of the dimerization constant (K_{dim*}) of the dendronized dimers in $CDCl_3$ could not be determined through ^{1}H NMR dilution studies because of the extremely large dimerization constants. However, no new peaks or shifting of existing peaks ($\Delta\delta < 0.01$ ppm) was observed for $\mathbf{1}_2$−$\mathbf{3}_2$ even at low concentrations (Figure 3).[13] Assuming more than 95% dimer formation at the lowest concentration studied (10 μM), we estimated that the lower limit of K_{dim*} was around 2×10^7 M^{-1} for all dendronized dimers $\mathbf{1}_2$−$\mathbf{3}_2$ (condition 1 in Table 2).[13] Furthermore, the ^{1}H NMR spectrum of a 1:1 mixture of $\mathbf{1}_2$ and $\mathbf{3}_2$ in $CDCl_3$ revealed the formation of a heterodimer **1·3** together with the

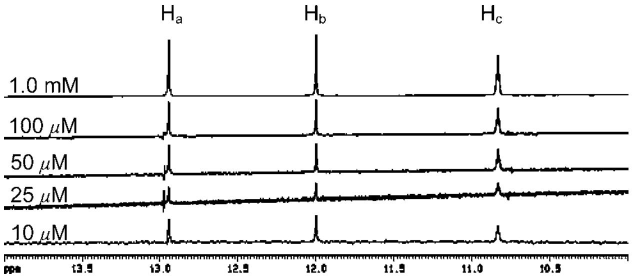
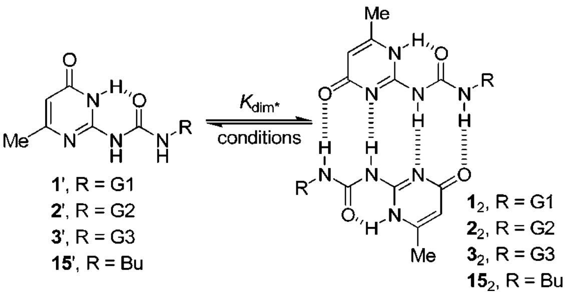


Figure 3. Stacked ^{1}H NMR spectra (600 MHz) of the hydrogen-bonding region of diluted samples (1.0 mM−10 μM) of G3 dimer $\mathbf{3}_2$ in $CDCl_3$ at 25 °C.

Table 2. Dimerization Constants of Dendronized Dimers $\mathbf{1}_2$−$\mathbf{3}_2$ and Nondendronized Dimer $\mathbf{15}_2$



	K_{dim*} (M^{-1})			
conditions	R = Bu	G1	G2	G3
(1) $CDCl_3$ at 25 °C	$6 \times 10^{7\,a}$	$>2 \times 10^7$	$>2 \times 10^7$	$>2 \times 10^7$
(2) 10% v/v DMSO-d_6 in $CDCl_3$ at 25 °C	2×10^2	1×10^2	2×10^2	2×10^2
(3) $CDCl_3$ at 50 °C	3×10^4	1×10^4	3×10^4	1×10^4

[a] See ref 18.

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homodimers $\mathbf{1}_2$ and $\mathbf{3}_2$ in a molar ratio of 2:1:1.[13] Hence, steric effect did not play a significant role in determining the dimerization constants in these oligoether-based dimers.

Comparative studies on the relative stabilities of dimers $\mathbf{1}_2-\mathbf{3}_2$ were conducted in 10% v/v DMSO-d_6 in $CDCl_3$ solution at 25 °C and in pure $CDCl_3$ at 50 °C (conditions 2 and 3 in Table 2). Under these conditions, the dimeric 4[1*H*]-pyrimidinone tautomers were found to be in equilibrium with the corresponding monomeric 6[1*H*]-pyrimidinone tautomers (i.e., **1′**−**3′**). In addition, a nondendronized analogue **15′** (i.e., R = Bu)[11b] was also included as a comparison. The values of $K_{\text{dim*}}$ under these conditions were calculated from the ratios of integrations of the relevant ^{1}H NMR signals.[16] The results indicated that dendronized dimers $\mathbf{1}_2-\mathbf{3}_2$ and the nondendronized analogue $\mathbf{15}_2$ possessed the same dimerization stabilities under identical conditions. In the presence of 10% v/v DMSO-d_6 in $CDCl_3$, the values of $K_{\text{dim*}}$ were in the order of 10^2 M^{-1} and were consistent with the literature values.[11b] As expected, the dimerization constants dropped to 10^4 M^{-1} at 50 °C in $CDCl_3$. We concluded here that (1) the relatively nonpolar microenvironment of the oligoether dendrons[17] did not disfavor the dimeric state and (2) the dimerization was not hindered by the largest G3 dendron.

Despite these findings, the branching pattern (nonaromatic AB_3 vs aromatic AB_2) and the branch length (4-atom vs 2-atom spacing) are different between Kaifer's and our dendrimers. Hence, it was difficult to compare directly the steric environment between these two series of compounds. Nonetheless, a significantly different microenvironment was established between these two classes of dendrons, and this factor led to the lowering of dimerization constants in Kaifer's oligoamide dendrons.

In the solid state, all dimers were shown to exist in the 4[1*H*]-pyrimidinone tautomeric form. The solid-state FT-IR spectra of dimers $\mathbf{1}_2-\mathbf{3}_2$ showed the characteristic peak pattern for the presence of this tautomer (1695, 1658, 1589, and 1523 cm^{-1}).[19] Furthermore, the absence of absorptions at 2500 cm^{-1} (O−H···O=C) and 3200−3260 cm^{-1} (intramolecular N−H···N) indicated that the pyrimidin-4-ol tautomer virtually did not exist in the solid state.[11b,20]

In summary, we disclosed a new series of UPy-containing oligoether dendrons which dimerize strongly even in the presence of a large G3 dendron ($K_{\text{dim*}} > 2 \times 10^7$ M^{-1} in $CDCl_3$ at 25 °C). These dimers used DDAA as the binding mode via the 4[1*H*]-pyrimidinone tautomers in $CDCl_3$ and in the solid state. Under certain monomer-favoring conditions, the dimerization constants of the various dendronized dimers were found to be nearly the same as that of the nondendronized dimer $\mathbf{15}_2$. These findings illustrated that the stabilities of dendronized dimers $\mathbf{1}_2-\mathbf{3}_2$ were not weakened by the steric effect imposed by the dendrons. It therefore appeared that the nonpolar microenvironment created by the oligoether dendrons played a much more important role in preserving the dimeric state. In contrast, the highly polar microenvironment imposed by Kaifer's oligoamide dendrons resulted in the destabilization of their dimeric structures.[10] Hence, a nonpolar dendritic environment is needed to ensure a high dimerization constant for the quadruple hydrogen-bonding unit. Work is now being carried out on the synthesis of these self-assembling dendronized polymers.

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Supporting Information Available: Details of synthetic procedures and ^{1}H and ^{13}C NMR spectra of all dendritic compounds and $\mathbf{15}_2$; ^{1}H NOESY/ROESY and FT-IR spectra of $\mathbf{1}_2-\mathbf{3}_2$; GPC measurements. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] The values of $K_{\text{dim*}}$ were determined from the ratios of integrations of the UPy−CH_3, C=CH, or CH_2N signals. It was noted that the volume factor was not taken into account in the equation that appeared in ref 11b. See Supporting Information for details.

[17] It was suggested that the microenvironment of the oligoether dendrons was very polar (comparable to the polarity of DMF). Our compounds, however, existed mainly in dimeric form in many organic solvents (e.g., $CDCl_3$, CD_2Cl_2, THF-d_8, acetone-d_6, and toluene-d_8). This indicated that oligoether dendrons are not so polar as suggested. See: Hawker, C. J.; Wooley, K. L.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1993**, *115*, 4375.

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