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# Conformational Control in the Cyclization of Hydrogen-Bonded Supramolecular Polymers

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***Abstract:*** Bifunctional 2-ureido-4[1H]-pyrimidinone (UPy) derivatives can form small cyclic oligomers as well as long supramolecular polymers in chloroform solutions using the quadruple hydrogen-bonding motif. Ring−chain equilibria of a set of supramolecular monomers containing methyl-substituted alkyl linkers between the hydrogen-bonding UPy moieties were investigated by $^1$H NMR spectroscopy and viscometry. The data were characterized in terms of critical concentration (CC, denoting the onset of polymerization) and equilibrium cyclic dimer concentration (EDC, representing preorganization of the monomer toward selective formation of cyclic dimer). Methyl substituents in the monomer were found to promote conformations favorable for cyclic dimerization, leading to an increase in both the EDC and the CC with respect to unsubstituted monomer. Furthermore, we observed an odd−even effect in the CC and EDC with increasing length of the linker between the hydrogen-bonding units. The combined results allow tuning of the critical concentration over a broad range and offer detailed information on the correlation between monomer structure, conformation, and polymerizability which may provide new insights for the study and design of other ring−chain equilibria or helix−random coil transitions.

## Introduction

In many chemical and biological systems, molecular conformations have a profound effect on the probability and rate of organic reactions as well as on the strength of supramolecular interactions by preorganization. By effective conformational design, functional groups in a molecule may be brought into close proximity to allow intramolecular reaction or into the correct arrangement for binding to a ligand or receptor.

Competition between linear chain extension and cyclization, which plays an essential role in many polymerization reactions, is also controlled by conformational preference. In the production of high molecular weight polymers by polycondensation or equilibrium ring-opening polymerization, a certain concentration of small cyclic oligomers always remains present after the reaction and strongly influences the properties of the polymeric material obtained by acting as plasticizer. Substituents are known to have a large influence on the polymerizability and the concentration of cyclic products formed. For example, poly($\epsilon$-caprolactam) polymerized in bulk at 260−270 °C contains around 7−8% residual monomer as well as 2% larger cyclic oligomers,[1,2] whereas equilibrium monomer concentrations of substituted lactam monomers increase with the bulk of the substituents, and very large or multiple substituents even prevent polymerization.[3,4] Similarly, an increase in equilibrium monomer concentration with the degree of substitution was observed for the ring-opening polymerization of substituted cyclic carbonates,[5,6] and analogous effects have been reported for other equilibrium ring-closing reactions.[7] This phenomenon has been attributed to a decrease in the change in gauche interactions upon ring-closure of the substituted monomer, thus reducing the enthalpy of cyclization.[8] In general, steric repulsion of substituents is usually larger in the polymer than in cyclic monomer and dimer. Furthermore, substituents may restrict rotation in the open chain compound, largely decreasing its entropy, whereas the entropy of the cyclic compound is not altered much, as compared to its unsubstituted analogue.

Examples of self-assembling systems in which preference for either cyclic or linear assemblies is determined by steric repulsions between substituents are also known.[9] However, most of these systems use more or less rigid building blocks, and steric interactions in the system affect the relative orientations of different components rather than the conformation of the

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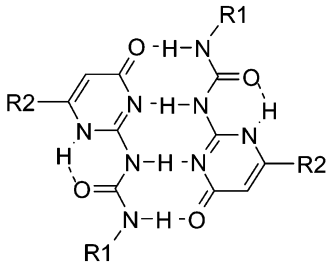

***Figure 1.*** Association of UPy derivatives by quadruple hydrogen bonding.

building blocks themselves. For example, Yang et al. reported that substituted isophthalic acid derivatives form hydrogen-bonded cyclic hexamers both in solution and in the solid state,[10] while similar compounds lacking the substituent produce linear polymers. Detailed model calculations of the stabilities of cyclic and linear melamine-cyanurate assemblies with different substituents were described by Bielejewska et al., who concluded that only steric groups directly affecting the internal energy of cyclic assemblies have a pronounced influence on the ring−chain equilibrium.[11] In addition, a number of groups have investigated ring−chain equilibria of flexible supramolecular polymers and have studied the effect of monomer length[12,13] and match or mismatch between the lengths of complementary monomers[14] on the concentration of the cyclic species formed.

Whether one would like to prevent cyclization as much as possible, as in conventional polymerization, or would like to optimize the yield of a specific cyclic structure, as is usually the case in self-assembled systems, understanding of the parameters involved in ring−chain equilibria is very important. In this paper, we demonstrate that supramolecular polymers based on the 2-ureido-4[1H]-pyrimidinone[15,16] (UPy) moiety (Figure 1) are ideal candidates for a detailed study into the effect of monomer structure and conformation on ring−chain equilibria. Bifunctional UPy derivatives are known to form long linear polymers as well as cyclic oligomers by strong quadruple hydrogen bonding ($K_a = 6 \times 10^7$ $M^{-1}$ in chloroform). Due to the reversibility of the monomer linkages, equilibration between different hydrogen-bonded aggregates is quite fast at room temperature.[16,19] Furthermore, it is relatively easy to make a broad series of UPy derivatives due to their good synthetic accessibility. In earlier studies, compounds based on linear, unsubstituted alkyl linkers were found to form long linear polymers in chloroform solution, while solutions of substituted UPy derivatives contained a mixture of cyclic oligomers and polymers.[17,18] Exclusive formation of cyclic dimers, both in solution and in the solid state, was observed for a bifunctional UPy derivative based on a *m*-xylylene linker, as a result of its very rigid preorganized structure.[19]

Theoretical distributions of cyclic and linear products in polycondensations have been described by Jacobson and Stockmayer,[20] who pointed out the existence of a critical concentration, below which the system is composed of cyclic products only. Ercolani et al. also investigated the subject and focused on dilute systems with a broad range of association constants.[21] The authors concluded that a true critical concentration, below which linear assemblies are virtually absent and above which the amount of cyclic species becomes constant, would only be observed for infinitely large values of the intermolecular association constant. Söntjens et al. established the existence of a critical concentration in solutions of UPy derivatives, showing that association between these molecules is sufficiently strong.[22] In the current study, we have used critical concentrations to quantify polymerizability of different monomers. In addition, we focused on selective preorganization toward cyclic dimerization by conformational effects and determined the equilibrium cyclic dimer concentration, or the maximum amount of cyclic dimers (the smallest possible cycles in our systems) formed by each monomer. Both parameters can be used as a measure for the tendency of a monomer to undergo polymerization in competition with cyclization, while the difference between the two values is related to the larger cyclic oligomers participating in the equilibrium.

In the equilibrium between polymers and small cyclic oligomers of substituted UPy derivatives, two different interactions were anticipated to play an important role. First, substituents in the monomer affect its conformational preference and, with this, the enthalpy and entropy of polymerization. Second, stacking interactions between UPy groups in small cyclic assemblies may have a stabilizing effect and also influence the ring−chain equilibrium. In this study, we have focused on the first issue and have used monomers based on methyl-substituted alkyl linkers, which are conformationally biased toward cyclization but still maintain enough flexibility to allow formation of long linear polymers at high concentrations. The substituents are anticipated to reduce the number of low energy conformers to produce preferential population of certain conformations. This subject has been studied in great detail by Hoffmann and coworkers,[23] who demonstrated that the conformational preference of molecules may be strongly biased by gauche interactions, *syn*-pentane interactions, or 1,3-allylic strain. We have used his approach to (1) study the conformational effect of substituents by X-ray diffraction analysis of carboxylic acid model compounds, and (2) analyze the equilibrium between cyclic and linear assemblies of different UPy derivatives quantitatively in solution by concentration-dependent viscometry and $^1$H NMR spectroscopy. By performing a detailed analysis of the ring−chain equilibrium of different UPy monomers, we aimed to gain a better understanding of the correlation between monomer

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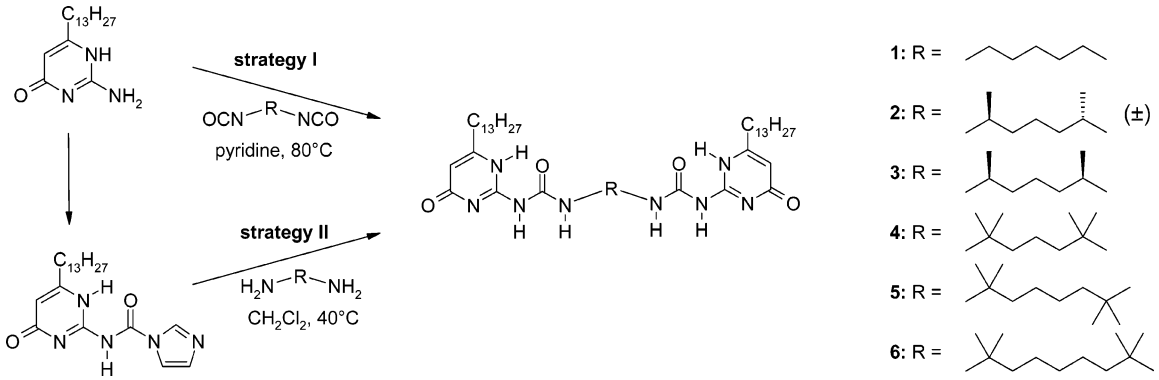
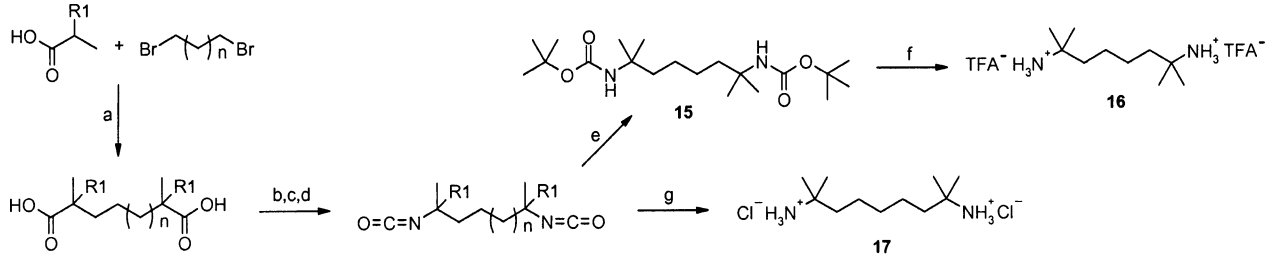
***Scheme 1.*** Synthetic Strategies for the Preparation of UPy Derivatives




***Scheme 2.*** Synthesis of Various Linker Precursors[a]




[a] (a) *i*-$Pr_2$NLi, THF, 0 °C; (b) EtOCOCl, $Et_3N$, THF, 0 °C; (c) $NaN_3$, $H_2O$, 0 °C; (d) toluene, 90 °C; (e) *t*-BuOH, *t*BuOLi, 90 °C; (f) TFA, $CH_2Cl_2$; (g) HCl, toluene, $H_2O$, 60 °C.

configuration, conformation, and cyclization, which allows tuning of the critical concentration and the design of responsive materials based on reversibly cyclizing UPy derivatives.

## Results

**Synthesis.**[24] A set of six different supramolecular monomers was selected for this study, to investigate both the effect of the substitution pattern and the length of the linker moiety on conformational preference and ring−chain equilibrium (Scheme 1). UPy derivatives **1**−**6** were synthesized via two different routes: either by reaction of alkyl diisocyanates with 6-tridecylisocytosine (strategy I) or by reaction of alkyl diamines with an "activated" 6-tridecylisocytosine (strategy II). Although strategy II requires more synthetic steps, it was found to be the preferred method, due to both the ease of purification of the intermediate products and the milder reaction conditions that minimize side reactions.[25]

Diacid model compounds and precursors for the linker moieties (**7**−**10**) were synthesized by reaction of propionic acid or isobutyric acid with α,ω-dibromoalkanes[26] (Scheme 2) and were obtained pure after recrystallization from ethyl acetate/hexane (yields 62−100%). Diisocyanate analogues **11**−**14** were prepared from the diacid compounds by reaction with sodium azide and subsequent Curtius rearrangement. Products **11** and **12** were isolated in 70% and 76% yield, respectively. Compounds **13** and **14** were not isolated, but were directly converted into the corresponding diamines. Product **16** was obtained as bis(trifluoroacetate) salt in 45% yield by reaction of **13** with *tert*-butyl alcohol and subsequent deprotection using trifluoroacetic acid. Diamine **17** was prepared by direct hydrolysis of **14** using hydrochloric acid and was obtained as pure bis-hydrochloride salt in 88% yield by precipitation in diethyl ether.

UPy derivatives **2** and **3** were synthesized as a diastereomeric mixture via strategy I starting from precursor **11**. Flash column chromatography yielded both pure products (overall yields 19% and 5%) as well as a mixed fraction (40%). Monomer **4** was also prepared according to strategy I (50% yield), while compounds **1**, **5**, and **6** were obtained via strategy II in 60%, 92%, and 89% yield, respectively. All monomers were carefully purified by flash column chromatography and subsequent precipitation in acetone or ethyl acetate and characterized by $^1$H and $^{13}$C NMR spectroscopy, as well as by MALDI-TOF or ESI mass spectroscopy.

**X-ray Crystal Structure Analysis.** Diacid precursors **8**−**10** were used as model compounds to study the effect of the methyl substitution on the conformation of the molecules. Similar to the UPy derivatives, these compounds can dimerize by hydrogen bonding through their carboxylic end groups and form cyclic as well as linear aggregates. After synthesis, single crystals suitable for X-ray analysis were obtained by slow diffusion of hexane vapor into ethyl acetate solutions (**8** and **10**) or ethanol solutions (**9**) of the diacids. Determined crystal structures of **8**, **9**, and **10** (Figure 2) were compared to the crystal structures of their unsubstituted analogues (Figure 3), described by Thalladi et al.[27] For all compounds, association by hydrogen bonding is observed in the solid state. However, while the unsubstituted

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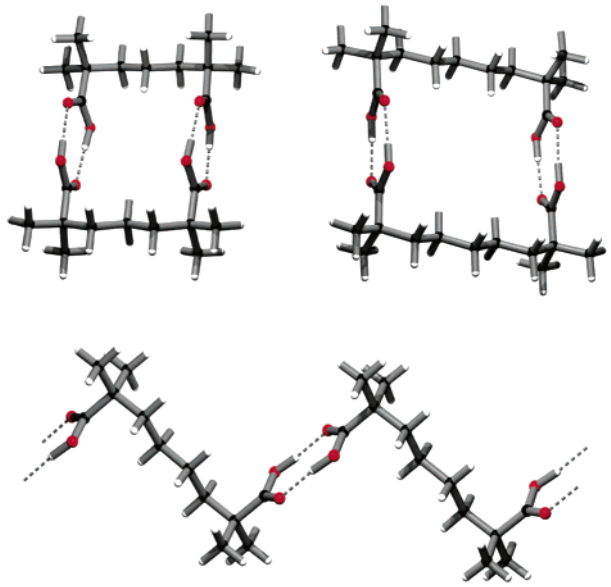

***Figure 2.*** Crystal structures of **8** (top left), **9** (bottom), and **10** (top right).

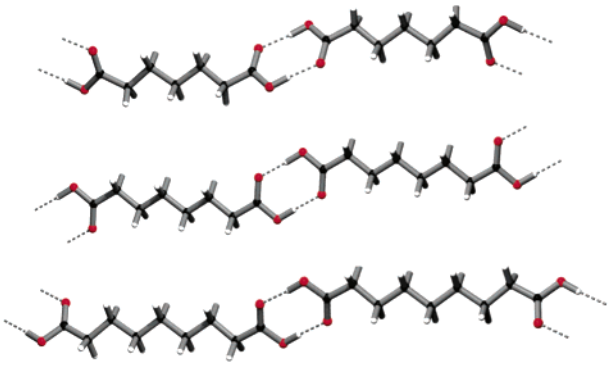

***Figure 3.*** Crystal structures of unsubstituted pimelic acid (top), suberic acid (middle), and azelaic acid (bottom).[27]

molecules are in an all-trans conformation and form infinite linear hydrogen-bonded chains through carboxylic acid dimers, methyl substitution of the alkyl linkers in **8**, **9**, and **10** results in a preferred conformation in which one of the methyl groups on each side of the molecule is in the trans position with respect to the rest of the linker and the carboxylic acid end groups are placed perpendicular to the linker.

In **8** and **10**, which contain an odd number of carbon atoms in the linker moiety, this leads to a parallel arrangement of the carboxylic end groups, promoting the formation of hydrogen-bonded cyclic dimers. Derivative **9** forms long chains by hydrogen bonding as a result of the even number of carbon atoms between the end groups. The difference in molecular structure between the odd and even diacids was also reflected in the solubility of the compounds. While **8** and **10** could easily be dissolved in various organic solvents such as ethyl acetate and chloroform, compound **9** was only sparingly soluble in those solvents. Only by addition of hydrogen-bond competing solvents such as ethanol or dimethyl sulfoxide could concentrated solutions be obtained.

A similar conformation of the linker was observed in the crystal structure of **18**, which is an analogue of monomer **2**,

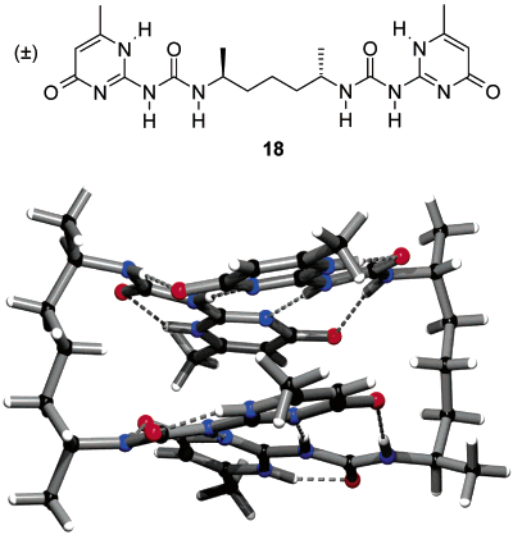


***Figure 4.*** Cyclic dimers in crystals of **18**.[28]

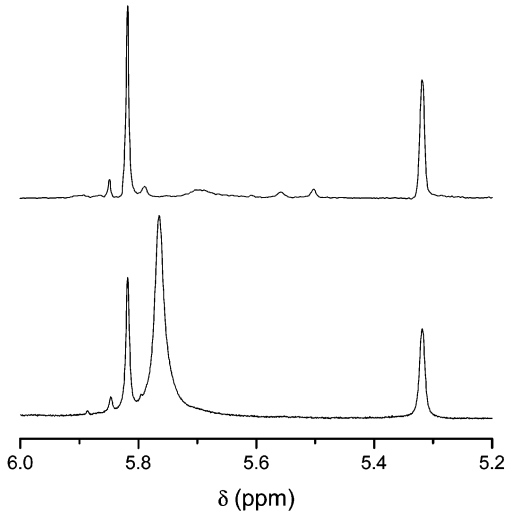


***Figure 5.*** Part of the $^1$H NMR spectrum of **4** at 5 mM (top) and 300 mM (bottom) in $CDCl_3$.

lacking the long tails on the pyrimidinone ring (Figure 4).[28] One of the methyl groups is arranged trans relative to the linker, and the hydrogen-bonding units are again placed in a parallel position. The obtained conformation induces the formation of a cyclic dimer, which is proposed to be stabilized further by stacking interactions between the pyrimidinone rings, leading to some bending of the UPy units.

**$^1$H NMR Spectroscopy of UPy Derivatives.** Ring−chain equilibria of supramolecular monomers **1**−**6** were studied in chloroform-$d_1$ solution. The presence of different hydrogen-bonded assemblies was established by $^1$H NMR spectroscopy, as the assemblies give rise to small changes in chemical shift for the UPy proton signals.[17,19,22,29] Figure 5 shows part of the $^1$H NMR spectrum of **4** at 5 and 300 mM in $CDCl_3$, containing the signals of the pyrimidinone alkylidene proton between 5 and 6 ppm. At 5 mM, two major peaks of equal intensity were observed at 5.83 and 5.33 ppm. These signals were assumed to originate from an asymmetric cyclic dimer in which one part

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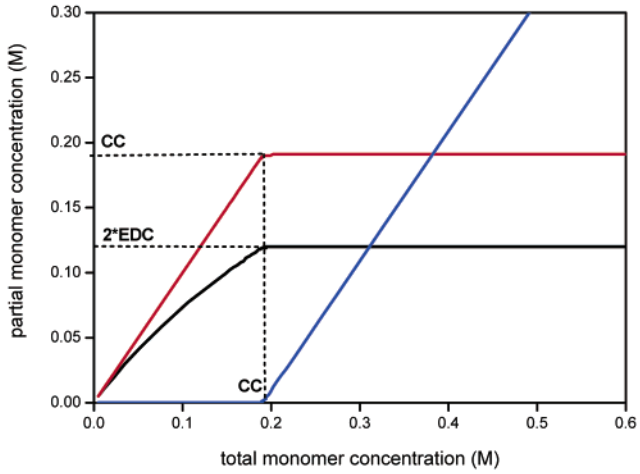


***Figure 6.*** Partial concentrations of linear polymers (blue), cyclic dimers (black), and the total of all cyclic assemblies (red), calculated for a hypothetical system of equilibrating UPy assemblies;[30] CC is defined as the critical concentration of all cyclic assemblies, and EDC is defined as the maximum concentration of monomer in cyclic dimers divided by 2.

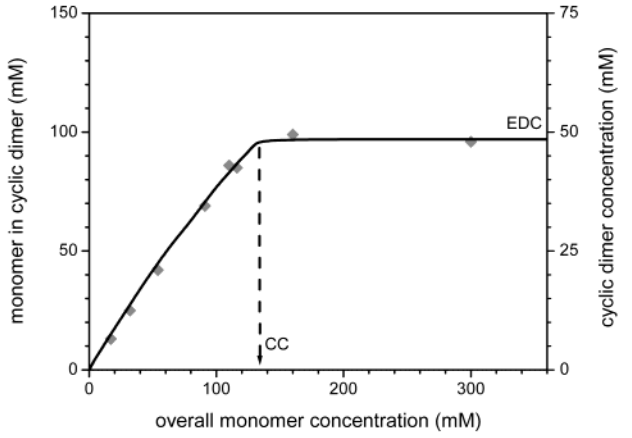


***Figure 7.*** Partial concentration of monomer **4** present in cyclic dimers in $CDCl_3$ solution, calculated from $^1$H NMR spectra (9−10 ppm range).

of each monomer is the 4[1H]-pyrimidinone tautomer and the other half is the pyrimidin-4-ol tautomer. A similar structure has been found for a bifunctional UPy derivative based on a *m*-xylylene linker.[19] The presence of substantial amounts of enol tautomer in dilute solutions of **4** was confirmed by FTIR spectroscopy ($\nu$ = 2595 (w), 2519 (w), 1612 (s) cm$^{-1}$).

At concentrations well above 100 mM, an additional broad peak was present at 5.76 ppm, corresponding to a different hydrogen-bonded assembly. $^1$H NMR diffusion measurements demonstrated that this aggregate has a much lower diffusion coefficient. Therefore, the peak at 5.76 ppm was assigned to polymeric aggregates in equilibrium with the cyclic dimers. Comparable concentration-dependent effects were observed for peaks corresponding to the other UPy protons of monomer **4**.

Monomers **1**, **2**, **3**, **5**, and **6** were investigated in a similar manner. Based on concentration-dependent $^1$H NMR spectroscopy and $^1$H NMR diffusion experiments, monomers **1**, **3**, **5**, and **6** were also found to form mixtures of small cyclic and large polymeric aggregates in chloroform solution. Because molecular models showed that the molecules could not form cyclic monomers and because two-fold symmetry was again observed for some of the cyclic species, cyclic dimers were assumed to be the predominant cyclic species in all cases. Two different tautomeric forms of cyclic dimers were detected in $CDCl_3$ solutions of **3**, in a concentration-independent ratio. For compound **2**, only one set of signals was observed for the UPy protons over the entire concentration range (5−300 mM), indicating that **2** is present in solution as a single type of hydrogen-bonded assembly, which was assigned to be a cyclic dimer on the basis of its relatively high diffusion coefficient. Moreover, cyclic dimerization was found to occur enantioselectively, both in chloroform solution as well as in racemic crystals.[28]

**Critical Concentration.** As stated before, the high association constant of the UPy derivatives allows for the occurrence of a critical concentration. A corresponding theoretical distribution[30] of cyclic and linear products in a hypothetical system of equilibrating UPy assemblies is plotted in Figure 6. In this plot, the concentration of the different assemblies is expressed as the amount of monomer present in certain aggregates (partial monomer concentration). The critical concentration (CC) of the system is indicated as the concentration where the amount of all cyclic species (dimers and others) reaches a maximum and also as the maximum partial monomer concentration for all cyclic assemblies. In this system, a value of 0.19 M is obtained, depending on the choice of cyclization constants. The equilibrium cyclic dimer concentration (EDC) is defined as the maximum concentration of monomer in cyclic dimers divided by 2 (the number of monomers in a cyclic dimer), yielding a value of 0.06 M for the selected system.

As it is possible to distinguish between cyclic dimers and other assemblies of the UPy derivatives by $^1$H NMR spectroscopy, we used this technique to determine the CC and EDC of the different monomers. Partial concentrations of monomer present in cyclic dimers were determined by integration of the corresponding peaks in the $^1$H NMR spectra. For each monomer, one of the UPy protons was selected for which the overlap of the peaks was minimal, and, additionally, deconvolution was used to determine peak areas accurately.

Partial monomer concentrations of cyclic dimers of **4**, calculated from the signals of one of the urea protons (between 9 and 10 ppm), are plotted against the total monomer concentration in Figure 7. While at low concentrations cyclic dimers are the predominant species in solution, the amount of monomer present in cyclic dimers becomes constant upon increasing the concentration above 160 mM, and other assemblies are being formed, confirming the existence of a critical concentration. On the basis of the results displayed in Figure 7, the CC of monomer **4** was estimated at 130 ± 10 mM, and the EDC was be determined to be 48 ± 1 mM.

EDCs and CCs of monomers **1**, **2**, **3**, **5**, and **6** were evaluated in a manner similar to that described above, and the results are presented in Figure 9. As no evidence of polymeric aggregates in solutions of **2** was found in the concentration range studied, the EDC for monomer **2** was assumed to be above 150 mM, and the CC was assumed to be above 300 mM. The EDC obtained for monomer **3** is the sum for the two tautomeric cyclic dimers. Due to strong overlap between different peaks in the $^1$H NMR spectra of **6**, determination of an accurate EDC and CC for this monomer proved difficult. Between 5 and 200 mM, no changes for the UPy protons were observed in the $^1$H NMR

(30) Calculations were based on equations derived in ref 21; $K_{inter} = 6 \times 10^7$, effective molarities arbitrarily chosen: $EM_1 = 0$, $EM_2 = 0.06$, $EM_{3-6} = 0.15 \cdot i^{-5/2}$.

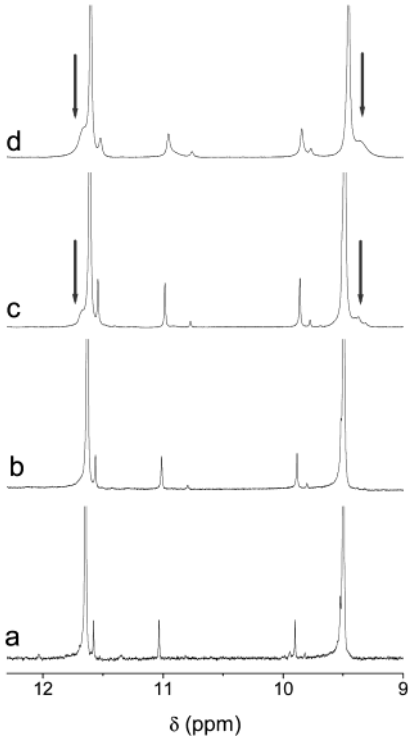


***Figure 8.*** Part of the $^1$H NMR spectrum of **6** at 5 mM (a), 182 mM (b), 295 mM (c), all at 298 K, and 295 mM at 318 K (d); arrows indicate signals corresponding to polymeric aggregates.

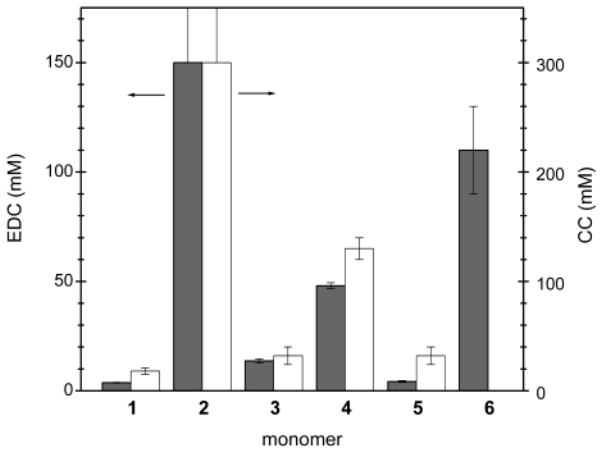


***Figure 9.*** Equilibrium cyclic dimer concentrations (EDC, gray, left axis) and critical concentrations (CC, white, right axis) of UPy derivatives **1**−**6** in $CDCl_3$ solution, as determined by $^1$H NMR analysis.

spectra. In more concentrated solutions (and even more pronounced at elevated temperatures), the spectra broadened and small shoulders could be observed next to the signals of the UPy protons (Figure 8), indicating the formation of polymeric assemblies. By deconvolution of the $^1$H NMR spectrum at 295 mM, the EDC was estimated at 110 ± 20 mM. Due to the broadness and overlap of the different peaks, the obtained value is less accurate than that of the other monomers, reflected in the relatively large error.

From Figure 9, it is clear that methyl substitution strongly influences the tendency toward cyclization of the UPy derivatives. Methyl-substituted monomers **2**, **3**, and **4** display an increase in EDC and CC with respect to the unsubstituted analogue **1**, completely in line with the hypothesis of introducing

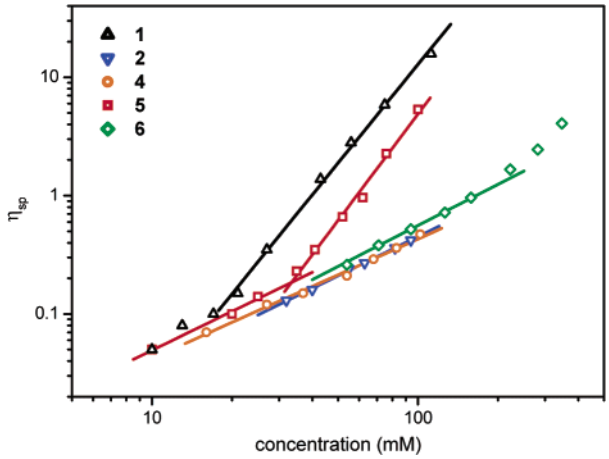


***Figure 10.*** Specific viscosity of chloroform solutions of **1**, **2**, **4**, **5**, and **6** versus the concentration (293 K).

a conformational bias toward cyclization by substitution. Moreover, the ring−chain equilibrium is highly dependent on the exact pattern of substitution. When **2** and **3** are compared, the reversal of just one stereocenter in the linker moiety leads to an increase in CC and EDC by at least a factor of 8−9.

Comparing monomers **4**−**6**, we can conclude that variation in the length of the linker moiety leads to an odd−even effect in the preference for cyclization. High EDCs were observed for monomers **4** and **6**, while the EDC for **5** is much lower. In other words, monomer **5** is less inclined to form a hydrogen-bonded cyclic dimer, due to its even number of linker atoms. The factor of 2 difference observed in EDCs of monomers **4** and **6** coincides with a strong difference in the tautomeric form of the UPy moiety; while monomer **4** primarily forms asymmetric cyclic dimers containing both 4[1H]-pyrimidinone and pyrimidin-4-ol tautomers, **6** is present in its cyclic dimers almost exclusively as the 4[1H]-pyrimidinone tautomer.

**Viscometry.** A characteristic property of polymeric structures, which distinguishes them from small cycles, is their relatively high solution viscosity. Specific viscosities of UPy derivatives **1**−**6** in chloroform were measured as a function of concentration. A double logarithmic representation of the data is given in Figure 10. Toward low concentration, all curves approach a slope of around 1, demonstrating a linear relation between specific viscosity and concentration, which is characteristic for noninteracting assemblies of constant size. These results confirm the presence of cyclic dimers in dilute solutions. Upon an increase in the concentration, a sharp rise in the viscosity is observed for some of the compounds. The stronger concentration dependence (slopes of 2.8 and 3.0 were found for compounds **1** and **5**, respectively) indicates the formation of entangled polymers of increasing size.

From Figure 10, critical concentrations were determined from the onset of the steeper plots, yielding values of 18 and 33 mM for **1** and **5**, respectively. Solutions of **2** and **4** remained low viscous up to 100 mM, denoting critical concentrations above 100 mM. For compound **6**, a deviation from linear behavior was observed around 200 mM, indicating that the critical concentration lies in this range.

## Discussion and Conclusions

Using $^1$H NMR spectroscopy and viscometry, we were able to study the ring−chain equilibria of supramolecular monomers

***Table 1.*** Crystallographic Data for Crystal Structure Determinations of **8**, **9**, and **10**

| compound | **8** | **9** | **10** |
|---|---|---|---|
| | Crystal Data | | |
| formula | $C_{11}H_{20}O_4$ | $C_{12}H_{22}O_4$ | $C_{13}H_{24}O_4$ |
| molecular weight | 216.27 | 230.30 | 244.32 |
| crystal system | monoclinic | monoclinic | monoclinic |
| space group | $P2_1/c$ (No. 14) | $P2_1/c$ (No. 14) | $P2_1/c$ (No. 14) |
| $a$, Å | 9.9354(10) | 6.1700(9) | 12.488(2) |
| $b$, Å | 11.882(2) | 9.9686(15) | 11.018(2) |
| $c$, Å | 12.041(2) | 12.025(3) | 11.207(2) |
| $\beta$, deg | 115.247(11) | 118.864(16) | 112.319(10) |
| $V$, Å$^3$ | 1285.7(4) | 647.7(2) | 1426.5(4) |
| $D_{calc}$, g cm$^{-3}$ | 1.117 | 1.181 | 1.138 |
| $Z$ | 4 | 2 | 4 |
| $F$(000) | 472 | 252 | 536 |
| $\mu$ (Mo K$\alpha$), cm$^{-3}$ | 0.084 | 0.087 | 0.083 |
| crystal size, mm | 0.2 × 0.2 × 0.4 | 0.08 × 0.20 × 0.25 | 0.2 × 0.2 × 0.4 |
| | Data Collection | | |
| X-ray exposure, h | 3.4 | 3.4 | 2.8 |
| $\theta_{min}$, $\theta_{max}$, deg | 1.6, 27.4 | 1.0, 27.6 | 1.6, 27.5 |
| data set ($hkl$) | −12:12, −15:15, −15:15 | −8:7, −12:12, −15:15 | −16:16, −13:14, −14:14 |
| total data | 25 681 | 10 524 | 24 532 |
| total unique data | 2920 | 1483 | 3264 |
| $R_{int}$ | 0.0336 | 0.1211 | 0.0394 |
| | Refinement | | |
| no. of refined params | 196 | 78 | 226 |
| final R1[a] | 0.0356 [2530$I > 2\sigma(I)$] | 0.0540 [829$I > 2\sigma(I)$] | 0.0359 [2759$I > 2\sigma(I)$] |
| final wR2[b] | 0.0911 | 0.1380 | 0.0919 |
| goodness of fit | 1.072 | 1.011 | 1.062 |
| $w^{-1}$ [c] | $\sigma^2(F^2) + (0.040P)^2 + 0.30P$ | $\sigma^2(F^2) + (0.0654P)^2$ | $\sigma^2(F^2) + (0.0350P)^2 + 0.40P$ |
| min. and max. residual density, e Å$^{-3}$ | −0.24, 0.25 | −0.20, 0.22 | −0.20, 0.25 |

[a] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $wR2 = [\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]]^{1/2}$. [c] $P = (\max(F_o^2,0) + 2F_c^2)/3$.

**1**−**6** in chloroform solution. The equilibria were characterized in terms of equilibrium cyclic dimer concentrations, which give information on the selective preorganization toward cyclic dimers by substituent effects, and critical concentrations, representing the onset of polymerization. Values obtained for CCs by $^1$H NMR spectroscopy and viscometry are in very good agreement. EDCs have only been determined by $^1$H NMR spectroscopy, as this technique distinguishes between cyclic dimers and other hydrogen-bonded aggregates due to small differences in chemical shift for the UPy protons. A strong correspondence exists between the CC and EDC of individual monomers, as is clear from Figure 9, and both parameters can be used to compare different monomers.

Results obtained for monomers **1**−**4** show that substitution of the alkyl linkers with methyl groups next to the UPy moieties strongly increases the concentration of cyclic dimer formed in solution. Although crystal structures cannot be interpreted as a direct reflection of conformational preference in solution, the X-ray crystal structure analyses of model compounds **8**, **10**, and **18** strongly support the hypothesis that methyl substituents promote conformations in which the hydrogen-bonding groups are oriented more or less perpendicular to the linker moiety. This in turn will lead to an increased preference for cyclic dimerization. In concentrated solutions of **3** and **4**, significant amounts of polymeric assemblies are formed, demonstrating that the conformational preference induced by the substituents does not fully exclude conformations leading to linear association, in agreement with the results of Hoffmann et al.[23] Complete explanation of the differences in CC and EDC among the methyl-substituted compounds, for example, the more than 8-fold difference between **2** and **3**, is difficult, and a detailed analysis should take into account the conformational preference of the linker, as well as the preferred relative orientation of UPy groups in either of the tautomeric forms observed. Whereas the former preference may be predicted using the rules set out by Hoffmann, the latter requires a detailed computational study.

Another important result is the observation of an odd−even effect in the critical concentration of monomers **4**−**6**, which is again consistent with the analysis of corresponding model compounds **8**−**10**: while even-membered diacid **9** was found to crystallize into linear hydrogen-bonded chains, odd-membered derivatives **8** and **10** form hydrogen-bonded cyclic dimers in the solid state. This effect originates from the requirement of two hydrogen-bonding units facing the same direction to form a cyclic assembly. The remarkable difference in critical concentration between monomers **4** and **6** again emphasizes the importance of tautomerism and stacking interactions on the stability of cyclic dimers of different UPy derivatives.

The conformational preference of the monomer induced by substituents, combined with stacking interactions between neighboring UPy groups, results in a very high stability of the hydrogen-bonded cyclic dimers, which contributes to the sharpness of the ring−chain transition in these systems. This study provides new insight into the relation between monomer configuration, conformation, and cyclization equilibria for bifunctional UPy derivatives. By choosing the desired substitution pattern and length of the linker moiety, it is possible to tune the critical concentration over a broad concentration range. Furthermore, the results may offer valuable information for the study of other (covalent as well as noncovalent) ring−chain transitions as well as for the design of helical polymers, foldamers, and tunable materials.

## Experimental Section

**Materials.** Details of the synthesis and characterization of monomers **1**−**6** are given in the Supporting Information. Chloroform (AR) and deuterated chloroform used in NMR spectroscopy and viscometry experiments were obtained from Biosolve and Cambridge Isotope Laboratories, respectively, and were used as received.

**Single-Crystal X-ray Structure Analyses.** Pertinent data for the structure determinations are given in Table 1. Data were collected at 150 K on a Nonius KappaCCD diffractometer on rotating anode (graphite monochromated Mo Kα radiation, $\lambda = 0.71073$ Å). The unit-cell parameters were checked for the presence of higher lattice symmetry.[31] Structures were solved with direct methods using SHELXS86[32] and were refined on $F^2$ using SHELXL-97.[33] No observance criterion was applied during refinement. For compound **9**, the hydrogen atoms bonded to carbon were included in the refinement on calculated positions riding on their carrier atoms. The methyl groups of **9** were allowed to rotate along the C−C bond. The carboxylic acid hydrogen atoms of **9** and all hydrogen atoms of **8** and **10** were located on difference Fourier maps, and their coordinates were included as parameters in the refinement. The non-hydrogen atoms of all of the structures were refined with anisotropic displacement parameters. The hydrogen atoms were refined with a fixed isotropic displacement parameter linked to the value of the equivalent isotropic displacement parameter of their carrier atoms. Neutral atom scattering factors and anomalous dispersion corrections were taken from the International Tables for Crystallography.[34] Validation, geometrical calculations, and illustrations were performed with PLATON.[35]

**NMR Spectroscopy.** $^1$H NMR spectra were recorded on a Varian Inova 500, Varian Mercury Vx 400, or Varian Gemini 300 spectrometer. Chemical shifts are reported in ppm downfield of TMS. Deconvolution of overlapping peaks was performed using routines incorporated in the VNMR software.

**Viscometry.** Solution viscosities were measured using Schott-Geräte Ubbelohde microviscometers with a suspended level bulb in automated setups with Schott-Geräte AVS/S measurement tripods and AVS 350 measurement devices. The microviscometers were thermostated in a water bath. Samples were filtered over 5 $\mu$m filters before measurement.

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**Supporting Information Available:** Synthetic procedures and characterization of all new compounds; further details of the structure determinations of compounds **8**, **9**, and **10**, including atomic coordinates and displacement parameters in crystallographic information format (CIF); displacement ellipsoid plots for compounds **8**, **9**, and **10** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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