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Conformational control of hydrogen bonded aromatic bis-ureas

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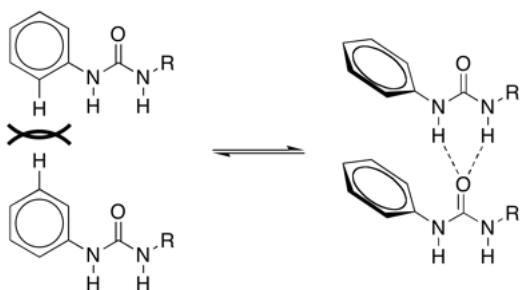
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ABSTRACT The phenylurea moiety is a ubiquitous synthon in supramolecular chemistry because it contains strong complementary hydrogen bonding groups and is synthetically very accessible. Here we investigate the possibility to strengthen self-association by conformational preorganization of the phenylurea moiety. In fact, we show that it is possible to strongly enhance intermolecular interactions between hydrogen bonded aromatic bis-ureas by substitution at the ortho positions of the phenylurea groups. Ortho substituents enforce a non-coplanar conformation of the urea and phenyl moieties better suited for hydrogen bonding. Substitution by methyl groups is more efficient than with larger groups, probably because of reduced steric hindrance. These effects have been demonstrated in the case of two different supramolecular architectures, which points to the probable generality of the phenomenon. In addition, this study has led to the discovery of a new bis-urea able to form very stable self-assembled nanotubes in toluene up to high temperatures (boiling point) or low concentrations (10^{-7} M) and in chloroform down to 3×10^{-4} M.

Introduction

The phenylurea moiety (Scheme 1) is a ubiquitous synthon in supramolecular chemistry because it contains both a hydrogen bond acceptor and hydrogen bond donors, which are complementary and relatively strong. Moreover, its straightforward synthetic accessibility allows the incorporation of this synthon in a wide variety of molecular scaffolds. For instance, the hydrogen bond donor ability of phenylureas has been exploited in the fields of anion complexation¹⁻³ and foldamer conformational control.⁴ Most importantly, the self-complementarity of the phenylurea synthon is a reliable design element in crystal engineering^{5,8} and the main driving force for the self-assembly of numerous organogelators,⁹⁻¹² liquid crystals,¹³ supramolecular polymers,¹⁴⁻²³ nanostructured polymers,²⁴⁻²⁹ self-assembled monolayers³⁰⁻³² and dimeric capsules.³³⁻³⁶

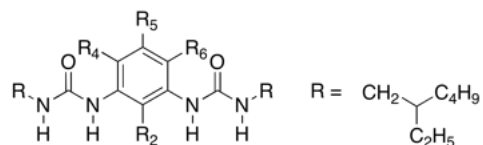


Scheme 1. Schematic conformations for the phenylurea moiety (trans-trans conformation).

Interestingly, the phenylurea moiety can display a strong conformational change on self-assembly. Molecular simulation studies and gas phase experiments show that several conformations are possible in the monomeric state (mainly trans-trans and cis-trans). When the urea group is in trans-trans conformation (Scheme 1), the urea and the phenyl groups are close to coplanar, because this conformation is stabilized by the possibility of extended conjugation and also by a weak hydrogen bond between the C=O group and the neighboring ortho hydrogen on the phenyl ring.^{37,38} However, upon self-assembly the N-C_{phenyl} bond has to rotate to avoid steric clash between the aromatic groups and to allow some π -stacking interaction (Scheme 1).³⁹⁻⁴² It is therefore remarkable that no systematic study has yet been performed to assess to what extent it is possible to improve the preorganization of the phenylurea synthon for self-assembly. Indeed, enforcing a non-coplanar conformation in the monomer should strengthen self-association for both enthalpic and entropic reasons.

A natural approach to such a conformational control is to introduce bulky substituents on the phenyl ring, in ortho positions to the urea. The efficiency of this design has been amply demonstrated in the cases of benzamides^{43,44} and phenyloxalamides⁴⁵ and other aromatic structures.⁴⁶ In this article, we show that it is possible to extend this strategy to aromatic bis-ureas and vastly improve the stability of the assemblies.

Results and Discussion



	R ₂	R ₄	R ₅	R ₆
Φ	H	H	H	H
4Me Φ	H	CH ₃	H	H
4Et Φ	H	C ₂ H ₅	H	H
4,6diMe Φ	H	CH ₃	H	CH ₃
4,6MeEt Φ	H	C ₂ H ₅	H	CH ₃
4,6diEt Φ	H	C ₂ H ₅	H	C ₂ H ₅
4,5,6triMe Φ	H	CH ₃	CH ₃	CH ₃
2,4,6triMe Φ	CH ₃	CH ₃	H	CH ₃

Scheme 2. Structure of bis-urea monomers.

Bis-urea **4Me Φ** (Scheme 2) was shown to self-assemble through hydrogen bonding into two distinct supramolecular structures of high molar masses.⁴⁷ In toluene both structures have similar stabilities and are in fast dynamic exchange.⁴⁸⁻⁴⁹ Therefore, it is possible to switch the assembly from one structure to the other by changing the temperature: the high-temperature structure is a long filament with a single bis-urea in the cross-section,¹⁶ while the low-temperature structure is a very long and rigid tube with three bis-ureas in the cross-section (Figure 1).^{50,51} The latter structure is particularly interesting as the entanglements between the nanotubes are responsible for the formation of viscoelastic gels^{22,51-54} and the presence of a tubular cavity opens the door to ultramicroporous materials.²⁷ In a preliminary attempt to control the monomer conformation and stabilize the nanotube supramolecular assembly, bis-urea **2,4,6triMe Φ** was synthesized.⁵⁵ However, it was shown that the nanotube assembly was actually less

stable for bis-urea **2,4,6triMe Φ** than for bis-urea **4Me Φ** . Molecular simulations showed that the three methyl groups indeed preorganize the urea groups better for intermolecular hydrogen bonding, but that this effect is more than compensated by the increased steric strain in the nanotube interior, which is due specifically to the methyl group in position 2 (Figure 1).⁵⁵ Therefore, we engaged in a systematic investigation of the influence of alkyl substituents in positions 4 and 6 on the phenyl ring, while keeping a hydrogen atom in position 2, to avoid filling the cavity of the nanotubes. Bis-ureas shown in Scheme 2 were synthesized by dinitration of the corresponding alkylbenzenes followed by reduction and reaction with 2-ethylhexylisocyanate, except **Φ** and **4Me Φ** for which the aromatic diisocyanate is commercially available (see Supporting Information).

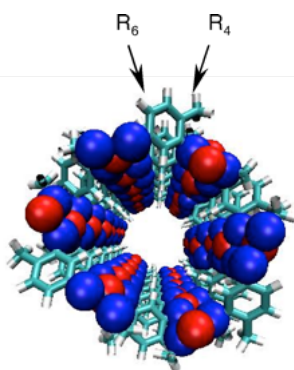


Figure 1. Optimized nanotube structure for bis-urea **4Me Φ** determined by molecular mechanics.⁵⁵ The ethylhexyl side chains were replaced by methyl groups for clarity.

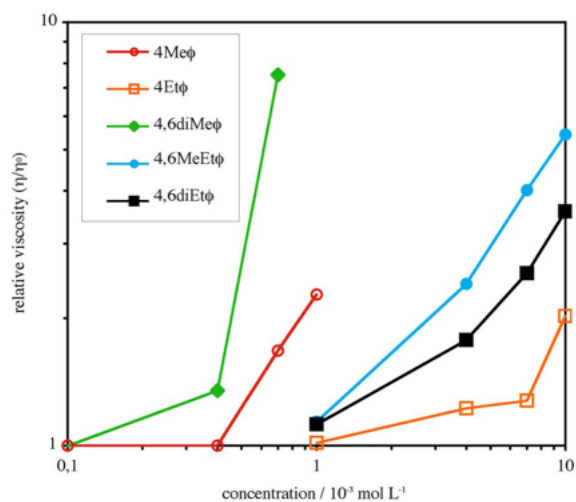


Figure 2. Relative viscosity versus concentration for bis-urea solutions in toluene at 25°C.

Most bis-ureas synthesized dissolve in toluene, except **4,5,6triMeΦ** (which dissolves only at high temperature and forms an opaque gel after cooling) and **Φ** (which is insoluble even at high temperature). All solutions display a significant increase in viscosity with concentration, revealing the large size of the assemblies (Figure 2). Moreover, the strong influence of the substituents on the assemblies is clearly demonstrated by the huge differences in viscosity of the solutions. The concentration at which these large assemblies form varies by almost two orders of magnitude, and it increases in the order **4,6diMeΦ** < **4MeΦ** < **4,6MeEtΦ** < **4,6diEtΦ** < **4EtΦ**.

The fact that hydrogen bonding is involved in the formation of these assemblies was verified by FTIR spectroscopy. Figure S1 shows that at 10mM in toluene, all bis-ureas have two absorption bands in the range 3250 - 3350 cm⁻¹ corresponding to hydrogen bonded aromatic and aliphatic N-H groups, and they show no contribution at larger wavenumbers where free N-H groups would absorb.^{16,56}

The structure of the assemblies was then examined by Small Angle Neutron Scattering (SANS). Figure 3 shows the scattered intensity for solutions in deuterated toluene. The low angle region shows a q⁻¹ dependence over more than a decade, which is characteristic for long and rigid fibrillar objects.⁵⁷ In principle, the characteristic dimensions of the scattering objects can be deduced from a fit to a form factor calculated according to a suitable geometrical model. In the present case, the use of a form factor for infinitely long rigid filaments with a circular cross-section and a uniform scattering length density profile,^{47,58} affords an excellent fit over the whole q range except for **4,6MeEtΦ** (Figure 3). In the case of **4,6MeEtΦ** the fit is still characteristic for long fibrillar objects in the large q region, while at lower q some additional scattered intensity is seen. It is most probably due to a lower rigidity of the objects (lower persistence length) or to a presence of aggregates (see Supporting Information). The values deduced from the fits are summarized in Table 1. According to these results, bis-ureas **4EtΦ**, **4,6MeEtΦ** and **4,6diEtΦ** form similar assemblies, with a relatively low linear density ($n_L \approx 0.25 \text{ \AA}^{-1}$). This linear density is compatible with the presence of a single bis-urea in the cross-section and is characteristic of the previously described filament structure.^{47,59} In contrast, bis-ureas **4MeΦ** and

4,6diMe Φ form assemblies with a linear density two to three times larger than the others. Linear density values for **4Me Φ** in this range ($0.52 \leq n_L \leq 0.70 \text{ \AA}^{-1}$) have previously been attributed to the tube structure (Figure 1) with three bis-ureas in the cross-section,^{47,50,51} because this structure is the simplest structure compatible with a previously demonstrated host-guest effect.⁵⁰ Furthermore, we assume that **4,6diMe Φ** forms the same tube structure, because of the similar linear density measured ($n_L = 0.68 \text{ \AA}^{-1}$).

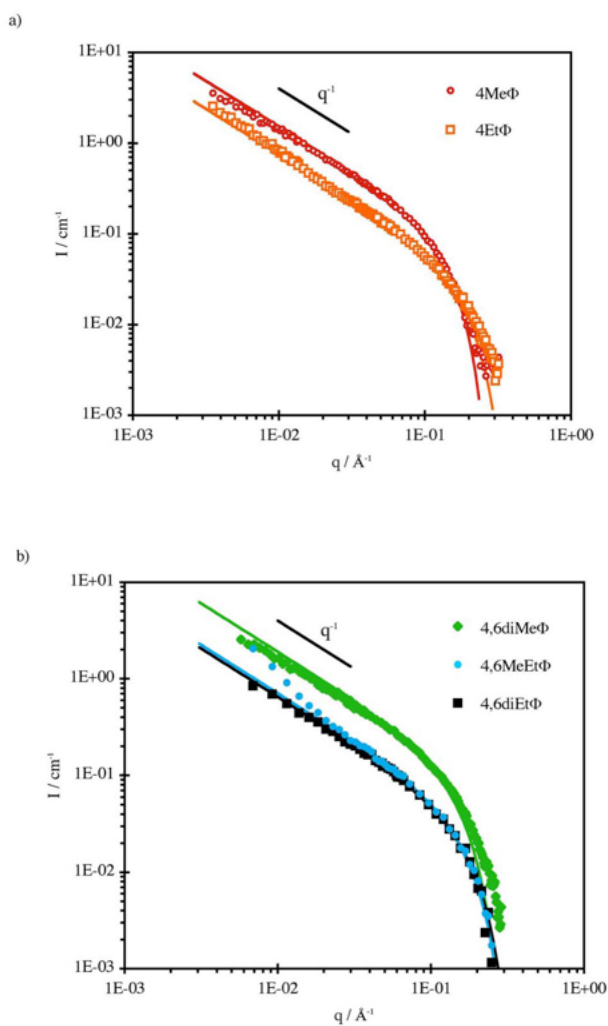


Figure 3. SANS intensity (I) versus scattering vector (q) for bis-urea solutions in d_8 -toluene at 5g/L (12mM) and 22°C. The plain curves are fits according to a model for long rigid filaments with a circular cross-section (characteristic dimensions in Table 1).

At this stage, one can conclude that the tube to filament equilibrium is shifted in favor of the filament for **4EtΦ**, **4,6MeEtΦ** and **4,6diEtΦ** compared to **4MeΦ**. Therefore, the addition of an ethyl group and/or the substitution of a methyl group by an ethyl group in positions 4 or 6 of the aromatic ring stabilizes the filament structure or destabilizes the tube structure. In contrast, the addition of a methyl group in position 6 of the aromatic ring induces a less obvious perturbation, because both **4MeΦ** and **4,6diMeΦ** form the same tube structure. To assess more precisely the effect of a methyl group in position 6 of the aromatic ring, the comparison between **4MeΦ** and **4,6diMeΦ** was extended to higher temperatures. In the case of **4MeΦ** in toluene, the tube structure is known to lose stability at about 45°C in favor of the filament structure (at concentrations larger than 1mM). This transition is easily detected by DSC, SANS and FTIR.^{47,60} In the case of **4,6diMeΦ**, no transition is detected by DSC, SANS (Figure S5) or FTIR (Figure S2) up to a temperature of 105°C. Therefore one can conclude that the addition of a methyl group in position 6 of the aromatic ring strongly stabilizes the tube relative to the filament structure. Remarkably, the FTIR experiment (Figure S2) also shows the absence of absorption in the 3450 - 3400 cm⁻¹ range corresponding to free N-H groups, which means that the tube to monomer equilibrium is strongly in favor of the tubes, even at 105°C.

Table 1. Geometrical radius (r) and linear density (n_l) of the fibrillar objects, deduced from the fit shown in Figure 3.

Bis-urea	r (Å)	n_l (Å ⁻¹)
4MeΦ	13	0.55
4EtΦ	10	0.27
4,6diMeΦ	12	0.68
4,6MeEtΦ	12	0.26
4,6diEtΦ	11	0.23

Up to now, we have only probed the *relative* stability of the tube and filament structures. Therefore, in order to reach more definite conclusions, we investigated the filament to monomer and tube to monomer equilibria. To do so, one has to dilute the solutions until the assemblies dissociate into monomers. Such dilution experiments can conveniently be monitored by Isothermal Titration

Calorimetry (ITC).⁶¹ Figure 4 shows the heat effect produced when a drop of a solution containing a self-assembled bis-urea is diluted into pure solvent. The endothermic signal results from the breaking of hydrogen bonds due to the dilution. Qualitatively, it is possible to see that the dilution of **4MeΦ** and **4EtΦ** produce similar heat effects, whereas **4,6diMeΦ**, **4,6MeEtΦ** and **4,6diEtΦ** yield very small heat effects. This means that the self-association of **4,6diMeΦ**, **4,6MeEtΦ** and **4,6diEtΦ** is much stronger than that of **4MeΦ** and **4EtΦ**. To quantify this effect, the experiments were reproduced with optimized initial concentrations and injection volumes (see Table S5 for conditions) and then the heat signal was integrated and plotted versus the concentration in the calorimetric cell (Figure 5). From these curves, it is first possible to determine the critical concentration (c^*) below which the assemblies dissociate into monomers.⁶⁰ Table 2 shows that the stability of the assemblies increases very strongly from **4MeΦ** and **4EtΦ** ($c^* = 30\mu\text{M}$) to **4,6MeEtΦ** and **4,6diEtΦ** ($c^* \approx 5\mu\text{M}$) and to **4,6diMeΦ** ($c^* < 0.1\mu\text{M}$). Moreover, the exact shape of the titration curves can be accounted for by a simple mass action law model describing the evolution of the concentration of monomers (M) and filaments (F_n) of any degree of polymerization (n) (Figure 6).⁶¹ The values deduced from the fit for the association constants and the enthalpy of association are reported in Table 2. The validity of this treatment has been carefully checked in the case of **4MeΦ** in various solvents and in a large temperature range.^{60,61} Still, it is of interest to see if the application of this model to the ITC data yields parameters that are compatible with the model-free viscosity data. For each bis-urea, the parameters in Table 2 were used to compute the average degree of polymerization of the supramolecular assembly versus concentration. Figure S8 shows that, in the concentration range 10^{-4} to 10^{-2} mol L⁻¹, the average degree of polymerization increases in the order **4EtΦ** < **4,6diEtΦ** < **4,6MeEtΦ** << **4MeΦ**. In fact, Figure 2 shows that the viscosity of the solutions increases in exactly the same order, thus confirming the qualitative agreement between the ITC derived thermodynamic parameters and viscosity data.

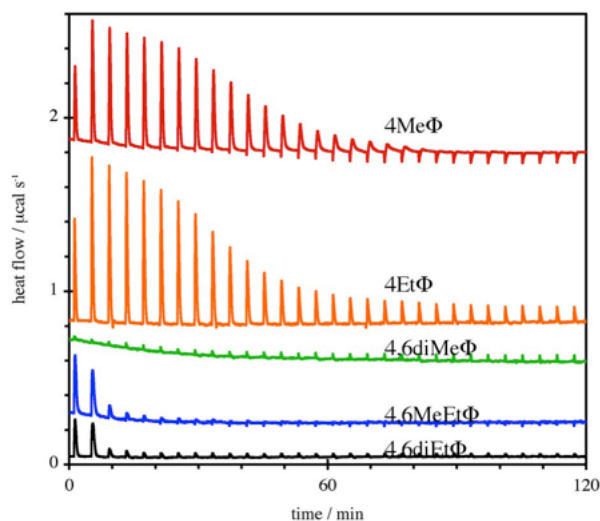


Figure 4. Heat effect (ITC) produced by injecting 3 μL aliquots of a 0.5 mM bis-urea solution in toluene into toluene ($T = 25^\circ\text{C}$).

The data in Table 2 now allows an unambiguous analysis of the influence of the bis-urea structure on the self-assembly. The first observation is that the presence of two alkyl groups in positions 4 and 6 (instead of a single alkyl) strongly favors intermolecular interactions, whatever the nature of the alkyl (methyl or ethyl) and whatever the structure (filament or tube). Indeed, the association constant for the filament growth (k) is an order of magnitude larger in the case of **4,6MeEt Φ** or **4,6diEt Φ** than in the case of **4Me Φ** or **4Et Φ** . As far as the tube formation is concerned, the association constant for **4,6diMe Φ** is too strong to be determined, but it is much stronger than for **4Me Φ** . This first effect is in line with our expectation that the presence of ortho substituents should enforce a non-coplanar conformation in the monomer and thus better preorganize it for self-association. The second observation is that a methyl group enhances intermolecular interactions more efficiently than an ethyl group. This can be seen by comparing the association constant of **4Me Φ** versus **4Et Φ** or of **4,6MeEt Φ** versus **4,6diEt Φ** . This second effect is probably due to the increased steric bulk of the ethyl group compared to methyl.

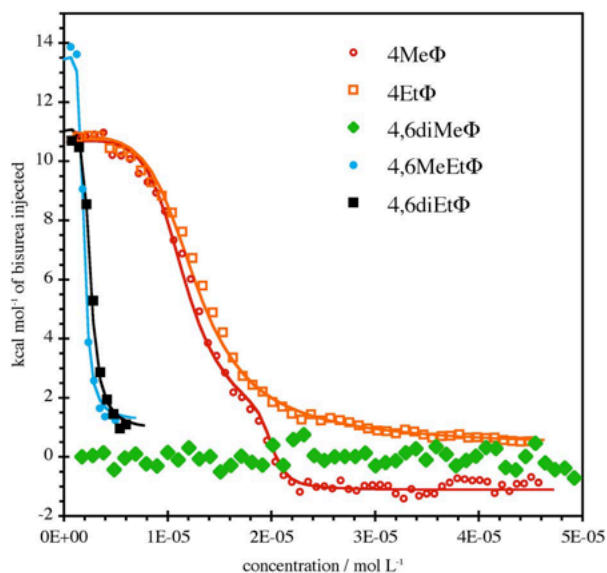


Figure 5. ITC enthalpograms for bis-urea solutions in toluene injected into toluene versus total bis-urea concentration in the cell ($T = 25^{\circ}\text{C}$). Experimental conditions are reported in Table S5.

As far as the stabilization of the nanotube supramolecular structure is concerned, we have identified a particularly efficient monomer (**4,6diMeΦ**). In order to test it further, we characterized its behavior in a more polar solvent (chloroform), i.e. in conditions where hydrogen bonds are weaker.⁶² FTIR spectroscopy shows that, at a concentration of 10mM, **4,6diMeΦ** is fully hydrogen bonded, in contrast to the other bis-ureas which display a weak absorption in the range $3430 - 3450 \text{ cm}^{-1}$ corresponding to free N-H groups (Figure S3). Moreover, SANS shows that **4,6diMeΦ** self-assembles into the tube structure, whereas the other bis-ureas self-assemble into the filament structure (Figure S6 and Table S4). Finally, the stability of the assemblies was probed by ITC. The enthalpograms are shown in Figure S7, and the results of the fit with the self-association model of Figure 6 are summarized in Table 3. The ITC results highlight the exceptional stability of the hydrogen bonded assemblies formed by bis-urea **4,6diMeΦ**: the nanotube structure is stable in chloroform at concentrations as low as $c^* = 0.3 \text{ mM}$. Moreover, ITC also confirms the conclusions previously derived from the experiments in toluene. (i) The presence of two alkyl groups in positions 4 and 6 favors intermolecular interactions, whatever the nature of the alkyl (methyl or ethyl), because the association constant for the filament growth (k) increases in the order $\Phi < 4\text{Et}\Phi < 4,6\text{diEt}\Phi$, but also $\Phi < 4\text{Me}\Phi$, or $4\text{Et}\Phi < 4,6\text{MeEt}\Phi$. (ii) A methyl

group enhances intermolecular interactions more efficiently than an ethyl group, as shown by the increasing association constant in the order $4\text{Et}\Phi < 4\text{Me}\Phi$ or $4,6\text{diEt}\Phi < 4,6\text{MeEt}\Phi$.

Table 2. Parameters deduced from ITC experiments in toluene at 25°C (Figure 5).

Bis-urea	c^{*a} (mol L ⁻¹)	k_2^b (L mol ⁻¹)	k^b (L mol ⁻¹)	ΔH^c (kcal mol ⁻¹)
4MeΦ	$3 \cdot 10^{-5}$	800 0.24 ^d	77000 87000 ^d	-12 -13 ^d
4EtΦ	$3 \cdot 10^{-5}$	1100	70000	-12
4,6diMeΦ	$< 10^{-7}$			
4,6MeEtΦ	$4 \cdot 10^{-6}$	3500	550000	-14
4,6diEtΦ	$5 \cdot 10^{-6}$	3800	400000	-12

^a concentration below which the assemblies dissociate into monomers.⁶⁰

^b association constant for filament growth (Figure 6).

^c enthalpy for filament growth (Figure 6).

^d association constant or enthalpy for tube growth. Data from reference 60.



Figure 6. Association equilibria between monomer (M) and filaments (F_n) of degree of polymerisation (n).

Table 3. Parameters deduced from ITC experiments in chloroform at 20°C (Figure S7).

Bis-urea	c^{*a} (mol L ⁻¹)	k_2^b (L mol ⁻¹)	k^b (L mol ⁻¹)	ΔH^c (kcal mol ⁻¹)
Φ	1.6×10^{-3}	25	1100	-7.8
4MeΦ	1.0×10^{-3}	58	1700	-8.3
4EtΦ	1.2×10^{-3}	87	1300	-9.3

4,6diMeΦ	3x10 ⁻⁴	8 ^a	8000 ^a	-8.3 ^a
4,6MeEtΦ	5.0x10 ⁻⁴	36	3700	-8.5
4,6diEtΦ	6.5x10 ⁻⁴	39	2900	-8.5

^a concentration below which the assemblies dissociate into monomers.⁴⁰

^b association constant for filament growth (Figure 6).

^c enthalpy for filament growth (Figure 6).

^d association constant or enthalpy for tube growth. The equilibrium between monomer and tubes was described according to the model in Figure S9).

Conclusion

In conclusion, we have shown that it is possible to strongly enhance intermolecular interactions between hydrogen bonded aromatic bis-ureas by substitution at the ortho positions of the phenylurea groups. Ortho substituents enforce a non-coplanar conformation of the urea and phenyl moieties and thus probably better preorganize the monomer for hydrogen bonding. Substitution by methyl groups is more efficient than with larger groups, probably because of reduced steric hindrance. The fact that these effects have been demonstrated in the case of two different supramolecular architectures points to the probable generality of the phenomenon. In addition, this study has led to the discovery of a new bis-urea (**4,6diMeΦ**) able to form very stable self-assembled nanotubes in toluene up to high temperatures (boiling point) or low concentrations (10⁻⁷ M) and in chloroform down to 3x10⁻⁴ M.

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SUPPORTING INFORMATION AVAILABLE Synthesis and characterization of bis-ureas; additional solubility, viscosimetry, SANS, FTIR, DSC and ITC data. This information is available free of charge via the Internet at <http://pubs.acs.org/>.

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