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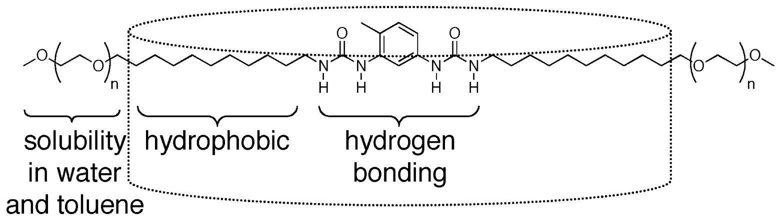

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ARTICLES

Both Water- and Organo-Soluble Supramolecular Polymer Stabilized by Hydrogen-Bonding and Hydrophobic Interactions

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Abstract: A new bis-urea based supramolecular polymer is reported and shown by viscosimetry, neutron scattering (SANS), and calorimetry (ITC) to self-assemble in a wide range of solvents, encompassing the polarity scale from water to toluene. The presence of both hydrogen-bonding and hydrophobic groups ensures that self-assembly occurs in water, aprotic polar solvents, and nonpolar solvents. Both the driving force for the assembly and the exact structure of the filaments is solvent dependent, but whatever the solvent, long rigid filaments are formed in dynamic equilibrium with the monomer.

Introduction

Since the pioneering works in the field of hydrogen-bonded liquid crystals,[1] supramolecular polymer chemistry has demonstrated that tailoring the position and strength of intermolecular forces within macromolecules makes it possible to control the structure and thus the properties of polymeric materials.[2,3] Within this context, a particular class of supramolecular polymers also called reversible polymers are chains of low molar mass monomers held together by reversible and highly directional noncovalent interactions.[4] In suitable experimental conditions they can display polymer-like rheological or mechanical properties because of their macromolecular architecture. However, the chains can break and recombine at room temperature, and there is a continuous exchange of bound and free monomers. If breaking and recombination of bonds occur on experimental time scales, this reversibility brings additional features compared to usual polymers, such as improved processing, self-healing behavior, or stimuli responsiveness. The design of a supramolecular polymer can involve three main classes of reversible interactions (hydrogen bonding,[5] metal−ligand complexation,[6] or hydrophobic interaction[7]), and the choice of a particular interaction usually dictates the range of solvents where the supramolecular polymer can self-assemble. Indeed, hydrogen bonds are used in low-polarity solvents, where they are the strongest, metal−ligand complexes are restricted to polar solvents because of solubility reasons, and hydrophobic interactions obviously occur in water. In contrast, it would be highly desirable to have a single supramolecular polymer able to self-assemble in a wide range of solvents, encompassing the polarity scale from water to hydrocarbons. This would be advantageous in formulations where mixtures of solvents are used, and it would open up new possibilities such as use of supramolecular polymers in biphasic processes. Toward this aim we decided to combine hydrogen-bonding and hydrophobic interactions so that the driving force for association may withstand both highly polar and nonpolar environments. The bioinspired concept of protecting hydrogen bonds in hydrophobic pockets has been fruitfully exploited in the field of low molar mass hydrogelators,[8,9] and use of hydrogen bonds in combination with another interaction is also known in the field of supramolecular

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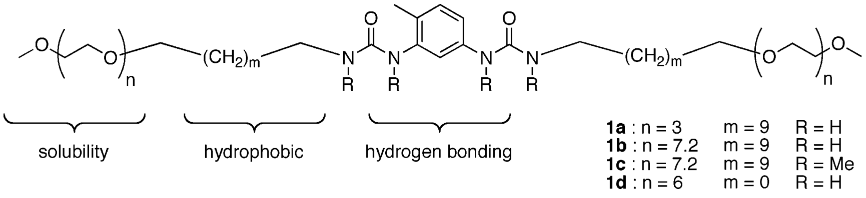
Chart 1. Design and Structure of Bis-ureas **1a** and **1b** and Reference Compounds **1c** and **1d**

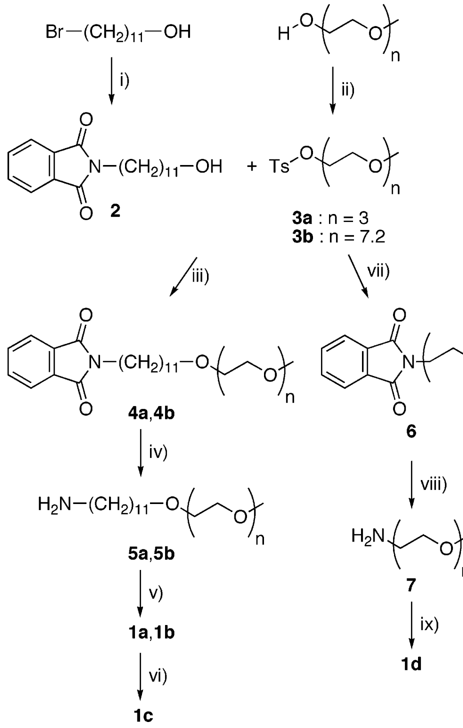


polymers,[10] but it has never been applied to purposefully increase the range of solvents where self-assembly is possible. In this paper we report the first dynamic supramolecular polymer which spontaneously self-assembles in a wide variety of solvents ranging in polarity from water to toluene.[11]

Results and Discussion

Design and Synthesis. The design is apparent in Chart 1: (1) the center of the molecule is a bis-urea motif well known to form strong hydrogen bonds. In contrast to other known bis-urea motifs which lead to slow hydrogen-bond dynamics,[9,12] this particular bis-urea moiety has been successfully used to obtain dynamic supramolecular polymers in nonpolar solvents.[13] (2) The hydrogen-bonding group is linked to alkylene spacers expected to stabilize the association in water by hydrophobic interactions and provide a low-polarity microenvironment for the hydrogen bonds. (3) Finally, ethylene oxide oligomers are hydrophilic but also have good solubility in several low-polarity organic solvents. Consequently, such oligomers were chosen for the outer part of the molecule, which is supposed to be in direct contact with the solvent. Straightforward organic synthesis (Scheme 1) afforded two potential candidates **1a** and **1b** differing in the number of ethylene oxide units. Reference compounds **1c** and **1d**, without a hydrogen-donating group or hydrophobic part, respectively, were also prepared in order to assess the relative influence of these particular interactions. Bis-urea **1a** is soluble in toluene, chlorinated solvents, and alcohols (see Supporting Information, Table S1) but not in water. Increasing the ethylene oxide chain from 3 to ca. 7 units significantly improves the solubility in polar solvents (water and acetonitrile) without losing the solubility in toluene. Consequently, only bis-urea **1b** was considered for further characterization.

Scheme 1. Synthesis of Bis-ureas **1a**−**d**[a]



[a] (i) Potassium phthalimide, DMF, 60 °C, 88%; (ii) TsCl, NaOH, THF/H_2O, 5 °C, 90−84%; (iii) tBuOK, tBuOH, reflux, 43−14%; (iv) $MeNH_2$, H_2O, RT, 71−76%; (v) toluene 2,4-diisocyanate, CH_2Cl_2, RT, 86−77%; (vi) MeI, NaH, THF, RT, 75%; (vii) potassium phthalimide, THF, reflux, 84%; (viii) $MeNH_2$, H_2O, RT, 50%; (ix) toluene 2,4-diisocyanate, THF, RT, 40%.

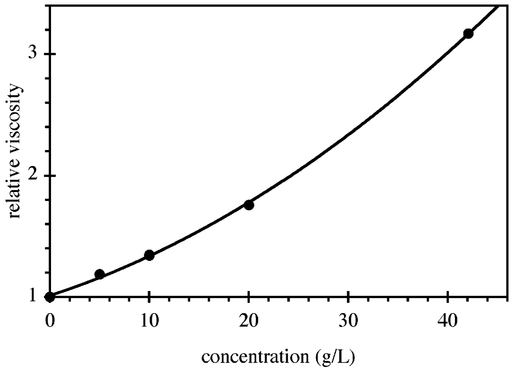


Figure 1. Relative viscosity (η/η_0) of water solutions versus concentration of **1b** (at 25 °C).

Capillary viscosimetry is a convenient way to qualitatively test the propensity of a monomer to self-assemble into large aggregates. Figure 1 shows the viscosity of aqueous solutions of **1b** obtained by simply stirring **1b** and water together for a few minutes at room temperature. The strong viscosity increase with concentration can only be due to formation of large anisotropic aggregates. Figure 2 shows that self-assembly also

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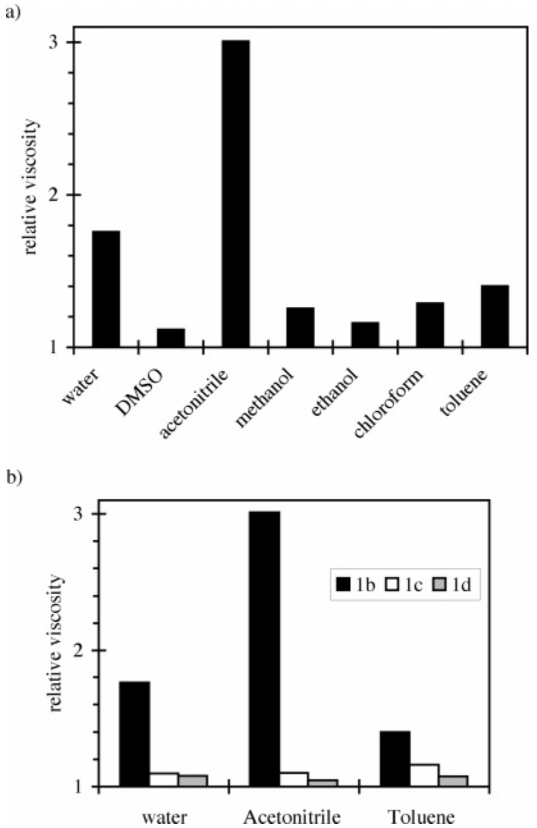

Figure 2. (a) Relative viscosity (η/η_0) of solutions of **1b** in several solvents (20 g/L, 16 mM, 25 °C). (b) Comparison with solutions of reference compounds **1c** and **1d** (16 mM, 25 °C).

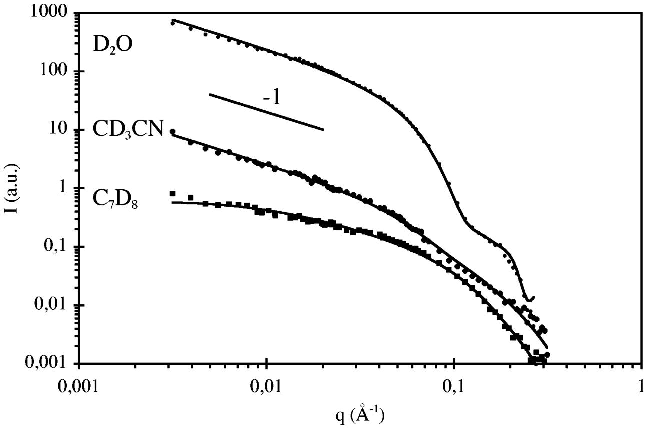

Figure 3. SANS intensity (I) versus scattering vector (q) for solutions of **1b** in D_2O, d_3-acetonitrile, and d_8-toluene at 5 g/L (4 mM) and 22 °C. The plain curves are fits according to a model for long rigid filaments with an elliptical cross-section (see Supporting Information). The data have been moved vertically to avoid overlapping (CD_3CN, multiplied by 5; D_2O, multiplied by 20).

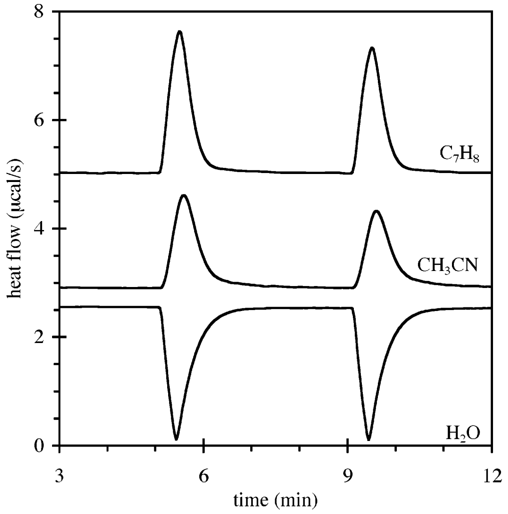

Figure 4. Heat effect produced by injecting aliquots of solutions of **1b** in a given solvent into the same pure solvent (T = 25 °C). Toluene and acetonitrile, 10 μL injections at 4 mM; water, 8 μL injections at 33 mM. The complete traces are shown in the Supporting Information (Figure S5).

Table 1. Dimensions of Assemblies in **1b** Solutions Deduced from the Fit Shown in Figure 3

solvent	2*a (Å)[a]	2*b (Å)[b]	L (Å)[c]	M_L (g mol^{-1} Å^{-1})[d]	n[e]
D_2O	54	86	≫300	1400	5.3
d_3-acetonitrile	13	84	≫300	120	0.5
d_8-toluene	18	44	130	130	0.5

[a] Short cross-section diameter of the filament [b] Long cross-section diameter of the filament. [c] Length of the filament. [d] Mass per unit length. [e] Number of **1b** molecules in the cross-section, assuming a repeat distance of 4.6 Å (which is the distance between hydrogen-bonded urea groups in 1,3-dimethylurea crystals).[16]

occurs in other solvents, in particular, in aprotic polar solvents (acetonitrile) and nonpolar solvents (toluene). The fact that both the urea groups and the alkylene spacers are necessary for this self-assembly to occur is shown by the very low viscosities displayed by reference compounds **1c** and **1d** (Figure 2b).

Structure. Three representative solvents (water, acetonitrile, and toluene) were selected for more precise characterization, and the structure was probed by small angle neutron scattering (SANS). Figure 3 shows the scattered intensity for solutions of **1b** in the three deuterated solvents. Very dilute solutions were selected to ensure that no interaction between scattering objects is present in the q range considered.[13a] In water and acetonitrile the low-angle region shows a perfect q^{-1} dependence over more than a decade, which is characteristic for long and rigid fibrillar objects. 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, use of a form factor for infinitely long rigid filaments with an elliptical cross-section[14] afforded an excellent fit over the whole q range (Figure 3).[15] The values deduced from the fits are summarized in Table 1.

According to this analysis the solutions contain very long filaments with a largest cross-section (2*b) that is similar to the largest dimension of a **1b** molecule in a fully extended conformation (85 Å). The model also gives an order of magnitude of the number of molecules in the cross-section (deduced from the mass per unit length of the filament). In the case of the acetonitrile solution, the filaments have a nearly monomolecular cross-section. This fact together with the strong shape anisotropy of the molecule explains why the cross-section is elliptical rather than circular. In water, however, the filaments contain several molecules in the cross-section. On the basis of these data it is possible to propose a schematic representation of the assembly of **1b** (Chart 2). Hydrogen bonds are supposed to lie along the filament direction, explaining the anisotropy of

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(15) Use of a form factor for infinitely long filaments with a circular cross-section afforded a poor fit in the high q region (see Supporting Information).

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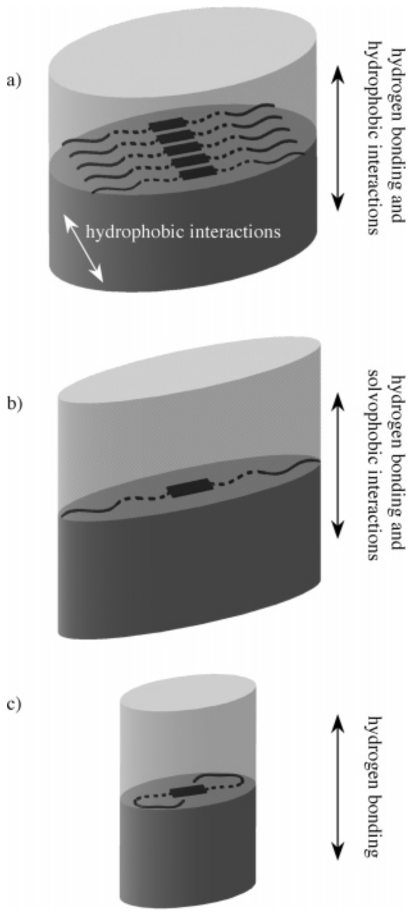
Chart 2. Schematic Structure for the Cross-Section of Filaments of **1b** in Water (a), Acetonitrile (b), and Toluene (c)[a]



[a] The bis-urea, alkylene spacer, and oligoethylene oxide fragments are represented as a rectangle, dotted line, and continuous line, respectively.

the filaments. Within the cross-section, only solvophobic interactions are then possible. In water, they are responsible for the lateral packing of several molecules, but in acetonitrile, they are not strong enough.

In the case of the toluene solution, the fit with the same geometrical model is not satisfactory because at low angle the scattered intensity does not decrease as fast as q^{-1} (Figure 3 and Supporting Information). This can be explained by a lower average length of the filaments in toluene than in acetonitrile, which is also in agreement with the fact that the viscosity of the toluene solution is lower than the viscosity of the other solutions (Figure 2). Consequently, a model for moderately long and polydisperse filaments (keeping an elliptical cross-section) was considered.[14,17] The fit (Figure 3) is indeed very satisfactory. The values deduced from the fit (Table 1) show, first, that the cross-section is close to monomolecular, as in the case of the acetonitrile solution. However, the largest cross-section (2*b) of the filaments in toluene is twice as low as the largest cross-section (2*b) of the filaments in the other solvents (Chart 2). This more compact conformation may be related to the absence of solvophobic interactions because the absence of interaction among alkylene spacers gives more flexibility to the side chains. Alternatively, this more compact conformation in toluene may be due to the presence of intramolecular hydrogen bonds involving ether oxygens, which are clearly identified in chloroform solutions (see Supporting Information).

To summarize the SANS results, it is clear that the assemblies formed by **1b** in the three solvents do not have identical structures but are all in agreement with the formation of elongated filaments whose cross-sections are close to the molecular dimensions of **1b**.

Driving Force and Dynamics. The stability of the filaments was investigated by isothermal titration calorimetry (ITC). The experiment consists of injecting aliquots of the supramolecular polymer solution into the pure solvent, placed within a calorimetric cell. Dilution of the supramolecular polymer leads to its partial dissociation, so that the heat flow measured is directly related to the self-assembly process.[18] Qualitative information can be derived from these experiments (Figure 4). First, in the three solvents tested the exchange of heat is a fast process: after each injection, the trace smoothly reaches the baseline within a minute. It proves that the self-assembly is indeed dynamic, and it is in agreement with the fact that solutions of **1b** in the three solvents form spontaneously within a few minutes (unlike a similar system,[9] no sonication step is required to assemble the filaments). The dynamic character of the present system constitutes a major difference with usual hydro- and organogelators which form strong crystal-like fibers that are not in dynamic exchange at room temperature.[19] Here, the fact that the cross-section of the filament is close to the molecular dimension is obviously related to this dynamic character. The second piece of information contained in the ITC experiment is the sign of the heat exchanged. The negative signal for the dilution experiment in water shows that the dissociation of **1b** generates heat ($\Delta H_{\text{dissoc}} < 0$). Consequently, the association is entropy driven ($\Delta H_{\text{assoc}} > 0$ and thus $\Delta S_{\text{assoc}} > 0$), which shows that hydrophobic interactions are the main driving force for the assembly of **1b** in water.[20] On the contrary, the positive signal for the dilution experiment in toluene or acetonitrile shows that association of **1b** in these organic solvents is enthalpy driven ($\Delta H_{\text{assoc}} < 0$), confirming the strong role of hydrogen bonding in these two solvents. To summarize: in water, self-assembly of **1b** is mainly driven by hydrophobic interactions because $\Delta H_{\text{assoc}} > 0$, but hydrogen bonding also plays a role, as shown by the low viscosity of **1c** in water (Figure 2b). In toluene, the only interaction involved is hydrogen bonding because toluene is a good solvent for all parts of the **1b** molecule. However, the alkylene spacer improves the association because the viscosity of **1d** in toluene is significantly lower than that for **1b**. This effect is due to a reduced tendency for intramolecular hydrogen bonding for **1b** (see Figure S3, Supporting Information). Finally, in acetonitrile, it is possible that self-assembly of **1b** is driven by both hydrogen-bonding and solvophobic interactions. This could explain why the strongest viscosity is measured in acetonitrile (Figure 2).

Conclusion

We reported the synthesis and characterization of a new supramolecular polymer able to self-assemble in a wide range of solvents, encompassing the polarity scale from water to

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(17) The polydispersity in length is assumed to be exponential as is the case for isodesmic association.

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toluene. The presence of both hydrogen-bonding and hydrophobic groups ensures that self-assembly occurs in water, aprotic polar solvents, or nonpolar solvents. Both the driving force for the assembly and the exact structure of the filaments depend on the particular solvent, but whatever the solvent, long rigid filaments are formed in dynamic equilibrium with the monomer. Moreover, the cross-section of the filaments is close to the molecular dimension of the monomer, which explains their dynamic character.

Experimental Section

Solvents were used as received. Solutions were prepared under stirring at least 2 h prior to use.

Viscometry. Measurements were performed with Cannon-Manning semi-microcapillary viscometers. The solutions were filtered on Millex membranes ($\Phi = 0.45$ μm).

SANS. Measurements were made at the LLB (Saclay, France) on the Pace instrument at three distance−wavelength combinations to cover the 3×10^{-3} to 0.3 Å^{-1} q range, where the scattering vector q is defined as usual, assuming elastic scattering, as $q = (4\pi/\lambda)\sin(\theta/2)$, where θ is the angle between the incident and scattered beam. Collimation details are provided in the Supporting Information. Data were corrected for the empty cell signal and the solute and solvent incoherent background. A light water standard was used to normalize the scattered intensities to cm^{-1} units.

ITC. Heats of dissociation were measured using a MicroCal VP−ITC titration microcalorimeter. The experimental conditions have been described previously.[18]

Acknowledgment. Cognis Company is acknowledged for financial support.

Supporting Information Available: Synthesis and characterization of compounds **1a−d**; additional solubility, FTIR, SANS, and ITC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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