N,*N*′-Disubstituted Ureas: Influence of Substituents on the Formation of Supramolecular Polymers

Frédéric Lortie,[a] Sylvie Boileau,[a] and Laurent Bouteiller*[b]

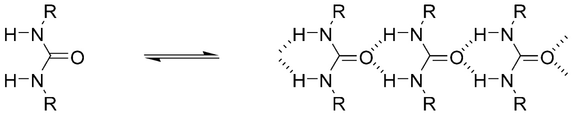
Abstract: Symmetrical *N*,*N*′-disubstituted ureas have been synthesized and characterized. Among them, the branched dialkylureas prepared are highly soluble in organic media. Moreover, the solutions obtained are very viscous in heptane, if the branched alkyl groups are not too bulky (i.e. a methyl group on the α carbon, or an ethyl group on the β carbon). Due to the strong, bifurcated hydrogen bonds between the urea moieties, linear supramolecular polymers are formed. The degree of association of these supramolecular polymers has been determined by FTIR spectroscopy.

Keywords: IR spectroscopy · polymers · self-assembly · supramolecular chemistry

Introduction

Supramolecular polymers are chains of small molecules held together through reversible noncovalent interactions.[1–3] This reversibility is responsible for the appearance of new properties, as compared to those of usual covalent polymers. For instance, the molecular-weight dependence of supramolecular polymers on concentration, solvent polarity, and temperature leads to unusual rheological properties.

In the case of supramolecular polymers held together by hydrogen bonds, the *N*,*N*′-disubstituted urea moiety is often used, for example in compounds such as bis-ureas[4] or tetra-ureas.[5] The same chemical function is also used in the closely related field of organogelators.[6–10] This ubiquity of the *N*,*N*′-disubstituted urea moiety can be ascribed to its relatively strong bifurcated hydrogen bonds, which lead to the formation of linear chains (Scheme 1). This association pattern of mono-ureas has been thoroughly demonstrated in the solid state,[11–14] but surprisingly few quantitative studies in solution have been published.[4a, 15, 16] This apparent lack of interest is probably due to the fact that, in solution, the connection between repeat units should involve more than two hydrogen bonds if very long chains are sought. However, we think that a good knowledge of the behavior of mono-ureas in solution can help understand more complex systems such as bis-ureas. Accordingly, we present here results on the self-association of several disubstituted mono-ureas in nonpolar solvents. It is shown that there is a large influence of the substituents on the strength of the association.



Scheme 1. Association pattern of *N*,*N*′-disubstituted ureas.

Results and Discussion

Description of aliphatic ureas: Investigations of *N*,*N*′-dialkylurea solutions have established the association pattern shown in Scheme 1,[15, 16] but they have been limited to dilute solutions in carbon tetrachloride and benzene because the ureas used, such as diethylurea (**EU**), are poorly soluble in low polarity solvents. However, to study the formation of long supramolecular chains, solutions at higher concentrations and in solvents of the lowest possible polarity are required. Consequently, a range of dialkylureas was synthesized (Scheme 2) in order to obtain heptane-soluble compounds. Three classes of substituents were investigated: linear alkyls (**MU**, **EU**, **PU**, **OU**, **ODU**) and branched alkyls with branching either on the α carbon (**MHU**, **DMHU**) or on the β carbon (**EHU**, **MPHU**, **DPHU**). Both the size of the substituents and the distance between the urea function and the branching point were varied because they were expected to have an influence on the strength of the association. Moreover, no heteroatom was included in order to avoid intramolecular

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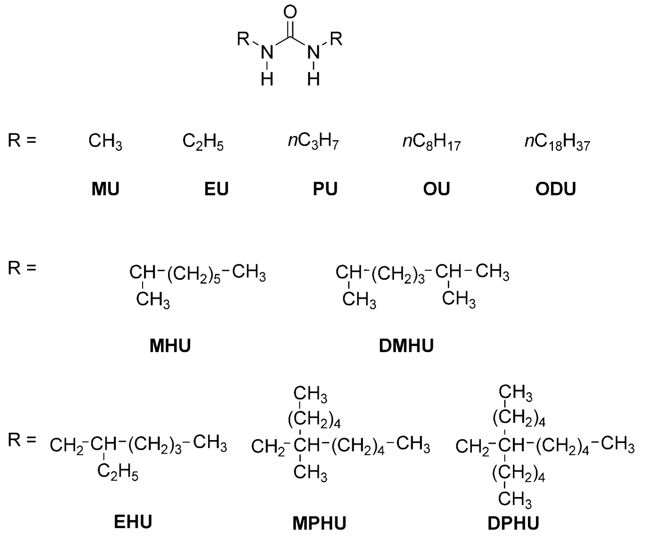
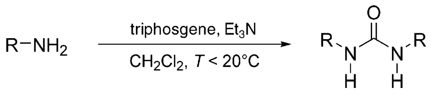
hydrogen bonding with the urea function. Computer simulations showed that for all these disubstituted ureas, the most stable conformation of the urea moiety in the isolated molecule is the *trans–trans* conformation, which allows self-assembly according to Scheme 1.

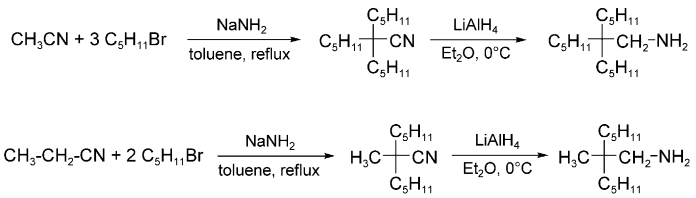


Scheme 2. Structures of *N,N'*-dialkylureas studied.

The ureas were obtained in high yields by treating primary amines with triphosgene (Scheme 3), which is a safe analogue of phosgene.[17] Only two amines were not commercially available and were thus synthesized according to Scheme 4. In the first step, a branched nitrile was obtained by base-catalyzed substitution of acetonitrile or propionitrile. In the second step, the nitrile was reduced to the corresponding amine.



Scheme 3. Synthesis of disubstituted ureas from primary amines.



Scheme 4. Synthesis of two primary amines.

The present set of substituted ureas was then tested for solubility (at 10 $g\,L^{-1}$ and at room temperature) in heptane and carbon tetrachloride (Table 1). As expected, branching increases the solubility: while none of the linear-alkyl-substituted ureas is significantly soluble in heptane, all the branched-alkyl-substituted ureas are highly soluble in this solvent.

Table 1. Solubility of *N,N'*-dialkylureas in carbon tetrachloride and heptane.[a]

	MU	EU	PU	OU	ODU	MHU	DMHU	EHU	MPHU	DPHU
carbon tetrachloride	I	S	I	I	I	S	S	S	S	S
heptane	I	I	I	I	I	S	S	S	S	S

[a] I: insoluble, S: soluble. Solubility was tested at a concentration of 10 $g\,L^{-1}$ and at room temperature.

Association of aliphatic ureas: The supramolecular association of the substituted ureas was investigated by capillary viscosimetry. Figure 1a shows the relative viscosity of heptane solutions of the three ureas branched on the β carbon. Among them, **EHU** displays the highest viscosity: at 40 $g\,L^{-1}$, the viscosity of the solution is six times that of the pure solvent. This viscosity value is remarkable, bearing in mind the relatively low concentration and the simplicity of the compound. Increasing the number and the size of the branches on the β carbon is responsible for a strongly reduced viscosity in the case of **MPHU** and **DPHU**. The relative viscosity values of the ureas branched on the α carbon are shown in Figure 1b and are compared to those of **EHU**. Below a concentration of 25 $g\,L^{-1}$, solutions of the three ureas **EHU**, **MHU**, and **DMHU** have very similar viscosities. However, at higher concentrations significant differences appear, and the viscosity increases in the order **DMHU** < **MHU** < **EHU** at a given concentration.

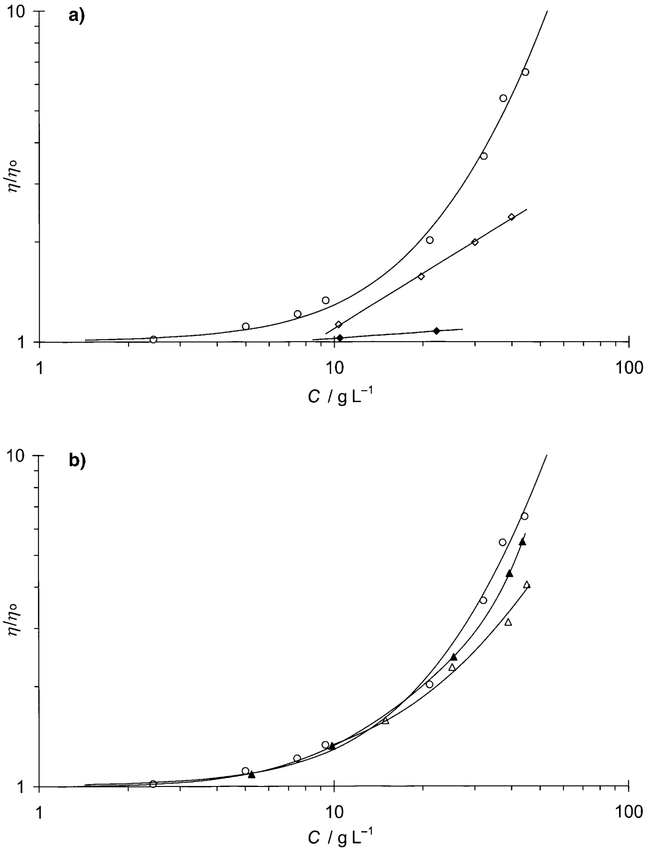


Figure 1. Relative viscosity of a) **EHU** (○), **MPHU** (◇) and **DPHU** (◆) and b) **EHU** (○), **MHU** (▲) and **DMHU** (△) versus concentration in heptane at 25 °C. The curves are a guide for the eye only.

Correlation of these results with the molecular structure is not straightforward, because the viscosity of the solutions can be expected to depend not only on the length of the supramolecular chains, but also on their flexibility and their interactions with the solvent. Indeed, by analogy with covalent polymers, the viscosity should be higher in a good solvent than in a theta solvent.

To decouple these different contributions, other techniques must be used. In the case of dialkylureas, it has been shown that FTIR spectroscopy is particularly well suited to determining the association constants of the equilibria involved,[16] and thus the length of the associated species. Unfortunately, heptane is not transparent enough in the relevant IR region, consequently carbon tetrachloride was used as a solvent. Figure 2 shows the FTIR spectra of a 10^{-2} mol L^{-1} solution of **EHU** in carbon tetrachloride at different temperatures: two N−H and two C=O stretching vibrations are observed, and can be attributed to the free and hydrogen-bonded groups.[18] As shown by their relative evolution, an increase in temperature results in dissociation of the supramolecular polymer. After cooling down the solution, an identical spectrum is obtained, thus proving the reversibility of the association. The values of the frequencies of the four vibrations for the different substituted ureas are reported in Table 2. First of all, the values of free N−H and C=O stretching vibrations show that for all compounds considered here, the conformation of the urea moiety is *trans*−*trans*, thus allowing self-assembly according to Scheme 1.[19] This proves that the steric bulk due to the branched alkyls does not change the conformation of the monomer, even in the case of **DPHU**. This point is worth mentioning because *N*,*N*′-di-*t*butylurea has been shown to be partly in an out−*trans* conformation,[20, 21] that is, one of the N−H groups is out of the plane of the urea function, due to repulsion between the *tert*-butyl substituents and the carbonyl group. Secondly, the displacement of the N−H and C=O stretching vibrations due to hydrogen bonding is similar in the cases of **EU**, **MHU**, **DMHU**, **EHU**, and **MPHU**; this shows qualitatively that the strengths of the hydrogen bonds formed are comparable. In the case of **DPHU** however, the displacement of the N−H and C=O stretching vibrations due to hydrogen bonding is much smaller; this proves that hydrogen bonds are formed, but that they are of lower stability than for the other compounds.

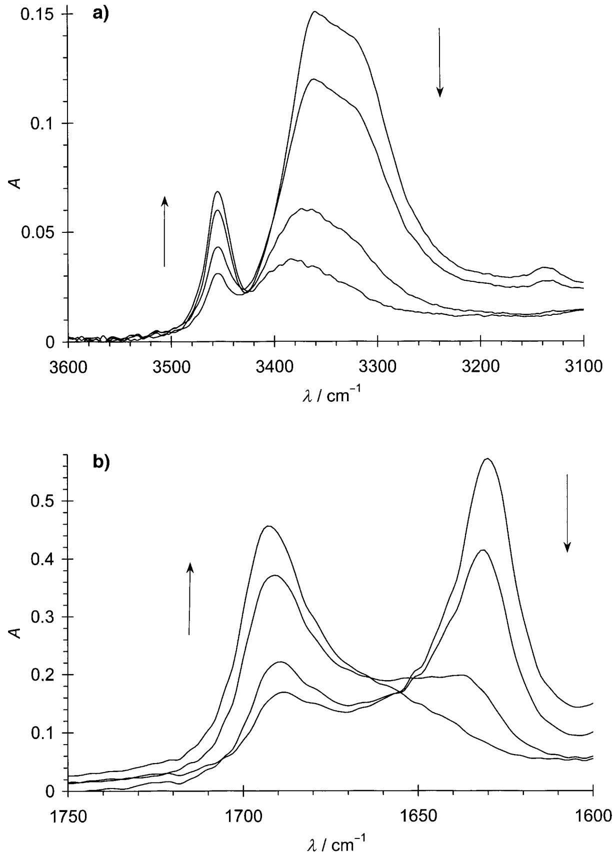


Figure 2. FTIR spectra of a 2.34 g L^{-1} (10^{-2} mol L^{-1}) solution of **EHU** in carbon tetrachloride versus temperature (15, 30, 45, and 60 °C). Spectral regions characteristic of a) N−H and b) C=O. Arrows indicate the direction of change with increasing temperature.

A quantitative analysis of the spectra was performed according to Jadzyn et al.,[16] and was based on the measurement of the intensity of the free N−H stretching vibration (ν_f^{N-H}). The molar extinction coefficient is obtained at very low concentration (about 10^{-4} mol L^{-1}, Table 2), and then used at higher concentrations to derive the fraction of free N−H groups (Figure 3). This Figure shows that at a given concentration, the length of the supramolecular polymers increases in the order **DPHU** $\ll$ **MPHU** $<$ **DMHU** $\approx$ **MHU** $\approx$ **EHU** $<$ **EU**. Moreover, the association can be modeled by considering an infinite set of equilibria (Scheme 5). The simplest (isodesmic) model (i.e. $K_n = K$, for $n \geq 2$)[22] does not yield a good description of the data, as already reported for **EU**,[16] but the second simplest model ($K_2 \neq K = K_n$, for $n \geq 3$) yields an excellent fit for all the data sets. The values of the constants derived are reported in Table 2. In the case of **EHU** $K_2 \ll K$, this shows that the association is cooperative in the sense that the formation of higher oligomers is favored relative to the formation of dimers. The origin of this

Table 2. Characteristics of solutions of *N*,*N*′-dialkylureas in carbon tetrachloride at room temperature.

	EU	MHU	DMHU	EHU	MPHU	DPHU
ν_f^{N-H} [a]	3448	3437	3437	3455	3456	3454
ν_b^{N-H} [a]	3300−3400	3300−3390	3300−3390	3300−3400	3320−3410	3360−3410
$\nu_f^{C=O}$ [a]	1689	1684	1684	1689	1691	1691
$\nu_b^{C=O}$ [a]	1633	1630	1630	1632	1633	1655
ε_f^{N-H} [b]	98 ± 3	80 ± 2	82 ± 2	82 ± 2	107 ± 2	102 ± 2
K_2 [c]	17 ± 7	10 ± 4	9 ± 4	11 ± 4	23 ± 6	30 ± 11
K [c]	467 ± 22	330 ± 17	325 ± 19	350 ± 14	156 ± 6	26 ± 1

[a] N−H and C=O stretching frequencies (ν_b: hydrogen bonded; ν_f: free) in cm^{-1}. [b] Molar extinction coefficient of the free N−H stretching vibration, in L mol^{-1} cm^{-1}. [c] Dimerization (K_2) and multimerization (K) constants in L mol^{-1}.

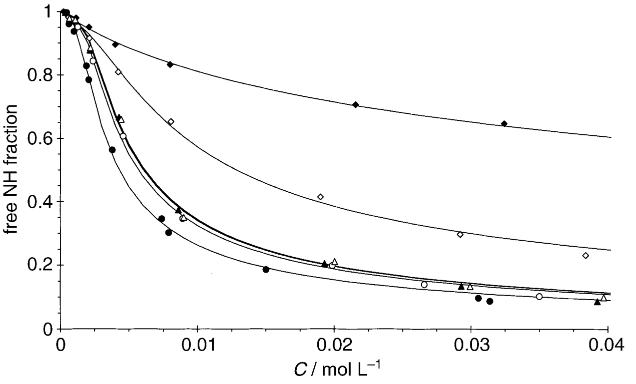
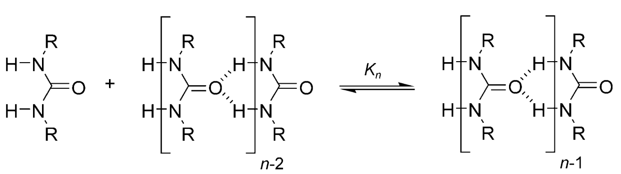


Figure 3. Fraction of free NH groups of **EU** (●), **EHU** (○), **MHU** (▲), **DMHU** (△), **MPHU** (◇), and **DPHU** (◆) versus concentration in carbon tetrachloride at room temperature. The curves are calculated according to ref. [16], with the constants reported in Table 2.



Scheme 5. Definition of the association constant K_n, $n \geq 2$.

cooperativity is the polarization of the urea function subsequent to dimerization.[23] All other compounds investigated here show this behavior, except **DPHU**. The multimerization constants (K) increase in the order **DPHU** $\ll$ **MPHU** < **DMHU** $\approx$ **MHU** $\approx$ **EHU** < **EU**; this is obviously related to the steric bulk of the substituents. More surprisingly, the dimerization constants (K_2) increase in the order **DMHU** $\approx$ **MHU** $\approx$ **EHU** $\leq$ **EU** < **MPHU** < **DPHU**; this means that the substituents of **DPHU** are not large enough to inhibit dimerization, but are bulky enough to destabilize higher oligomers. Moreover, the increased stability of the dimer of **DPHU** compared with the other dimers could be due to a micropolarity effect, because the large dipentylheptyl group reduces the number of solvent molecules that can approach the urea function.

This two-constant model ($K_2 \neq K = K_n$, for $n \geq 3$) is an approximation because the association constants for the formation of trimers and higher oligomers are probably not strictly equal to each other. However, knowledge of the association constants of this simple model makes it possible to compute an approximation of the whole distribution of oligomers, as a function of concentration. For example, Figure 4 shows the distribution of oligomers for **EHU** and **DPHU** at a concentration of 10^{-2} mol L^{-1}. At this concentration, a **DPHU** solution mainly contains monomers, dimers, and trimers. The behavior of **EHU** is quite different: together with a significant monomer fraction, there is a broad oligomer fraction centered around the decamer. The bimodality of this distribution is a consequence of the cooperativity of the association, which imposes a low dimer concentration. From the distributions, the average degree of polymerization can be calculated (Figure 5). Coming back to the interpretation of Figure 1a, it is now clear that the strong decrease in viscosity going from **EHU** to **MPHU** and to **DPHU** is due to a decrease in the degree of association.

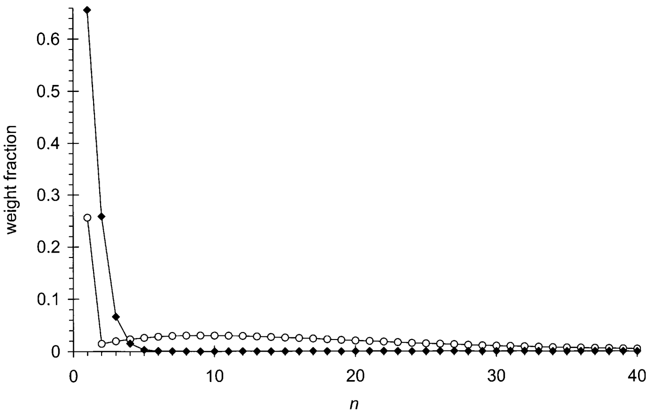


Figure 4. Calculated *n*-mer distribution in a 10^{-2} mol L^{-1} solution of **EHU** (○) and **DPHU** (◆). (The values of the constants used are in Table 2.)

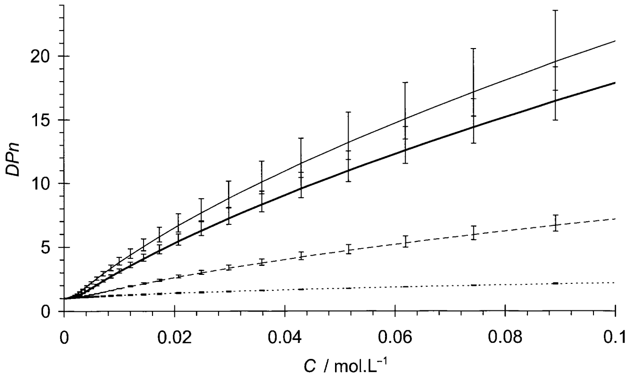
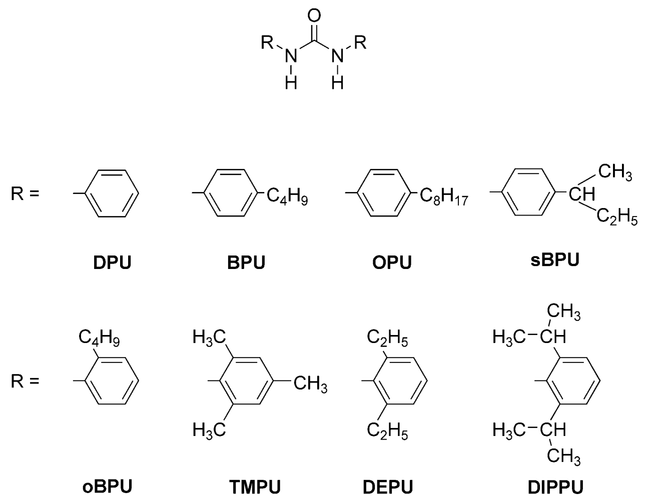


Figure 5. Calculated number-average degree of polymerization versus concentration, in a solution of **EU** (——), **EHU** (——) **MPHU** (– – –), and **DPHU** (···). (The values of the constants used are in Table 2.)

Description of aromatic ureas: *N*,*N*′-diarylureas were also investigated because the electron-withdrawing effect of the aromatic ring is expected to strengthen the association.[15] Due to the very low solubility of diphenylurea (**DPU**) in nonpolar solvents, several compounds were synthesized to improve solubility (Scheme 6). The *para* position of the benzene ring was substituted with linear (**BPU**, **OPU**) or branched (**sBPU**) alkyl groups. Alternatively, one (**oBPU**) or both (**TMPU**, **DEPU**, **DIPPU**) *ortho* positions were substituted with alkyl groups of increasing size. Despite these substitutions, none of the present *N*,*N*′-diarylureas is significantly soluble in heptane. Moreover, only **DIPPU** is soluble in carbon tetrachloride.

Association of DIPPU: Computer simulations showed that the *trans–trans* conformation of an isolated molecule of **DIPPU** is, in fact, less stable than the *cis–trans* conformation by 8.3 kJ mol^{-1}. The association of **DIPPU** was nevertheless investigated (Figure 6) and compared to the association of **EHU** and **DPHU**. The low viscosity is in agreement with the absence of supramolecular chains in solution. Moreover, FTIR spectroscopy (Figure 7) definitely proves that the association does not proceed according to Scheme 1. At the



Scheme 6. Structures of *N,N'*-diarylureas studied.

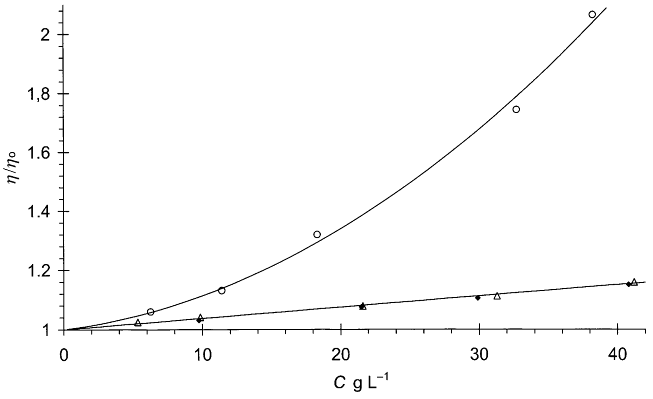


Figure 6. Relative viscosity of **EHU** (○), **DIPPU** (△) and **DPHU** (◆) versus concentration in carbon tetrachloride at 25 °C.

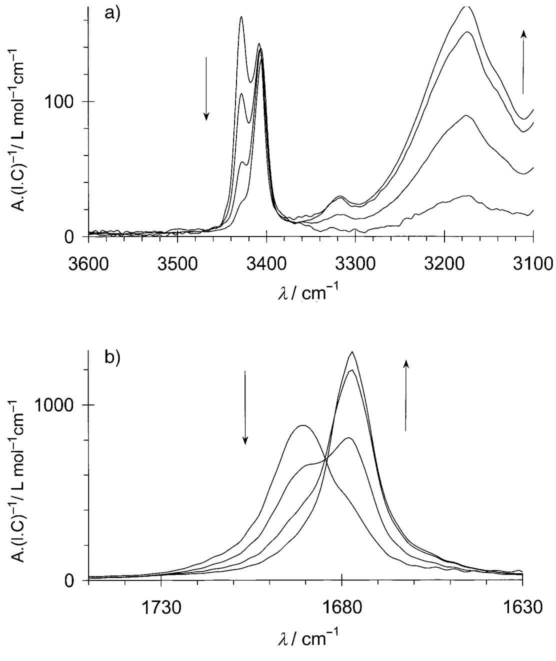
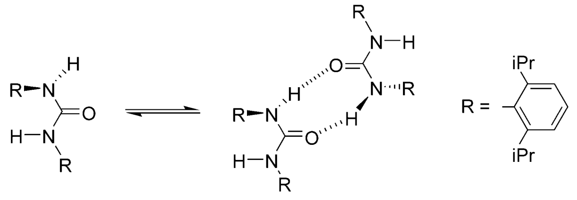


Figure 7. Normalized FTIR spectra of solutions of **DIPPU** in carbon tetrachloride versus concentration (10^{-4}, 10^{-3}, 10^{-2}, and 10^{-1} mol L^{-1}). Spectral regions characteristic of a) N–H and b) C=O. Arrows indicate the direction of change with increasing concentration.

lowest concentration investigated (10^{-4} mol L^{-1}), two free N–H vibrations are detected at 3428 and 3408 cm^{-1} and are probably due to two different conformations. We tentatively assign them to the out and *trans* conformations, respectively.[24] When the concentration is increased, the intensity of the free N–H out band decreases and a hydrogen-bonded N–H band appears at 3170 cm^{-1}. The fact that the maximum of the hydrogen-bonded N–H band does not depend on concentration indicates that finite aggregates are formed and not indefinite chains, because in this case, the value of the maximum should increase with concentration.[25] In the same concentration range, the free N–H *trans* band is not affected and the free C=O vibration (1690 cm^{-1}) is progressively replaced by a hydrogen-bonded band (1677 cm^{-1}). These different results are in agreement with **DIPPU** being in the out–*trans* conformation and with the formation of dimers through hydrogen bonding of the N–H groups in the out conformation (Scheme 7).



Scheme 7. Proposed association pattern for **DIPPU**.

Conclusion

Symmetrical *N,N'*-disubstituted ureas have been synthesized and characterized. Among the eight diarylureas prepared, only **DIPPU** is soluble in carbon tetrachloride. Moreover, this compound does not form a supramolecular polymer. All the branched dialkylureas synthesized are highly soluble in heptane and carbon tetrachloride. If the branched alkyl groups are not too bulky, then the corresponding dialkylureas (**MHU**, **DMHU**, **EHU**) self-assemble to form supramolecular polymers in solution.

Experimental Section

Synthesis: *N,N'*-Dimethylurea (**MU**), *N,N'*-dipropylurea (**PU**), *N,N'*-dioctadecylurea (**ODU**), and *N,N'*-diphenylurea (**DPU**) (Aldrich) were used as received. *N,N'*-Diethylurea (**EU**) (Aldrich) was recrystallized in heptane. The synthesis of *N,N'*-di(2-ethylhexyl)urea (**EHU**) has been previously reported.[4a] Unless specified, all reagents were from Aldrich and were used as received. Yields are not optimized.

6-cyano-6-methylundecane: The synthesis was adapted from previous literature.[26] A mixture of 1-propionitrile (10.5 g, 0.19 mol), 1-bromopentane (66.5 g, 0.44 mol), and sodium-dried toluene (70 mL, SDS) was placed in a 500 mL flask fitted with a condenser and a 500 mL dropping funnel. A suspension of sodium amide (50 % wt in toluene, 29.5 g, 0.43 mol) was placed in the dropping funnel and diluted with more toluene (50 mL). The flask was placed under nitrogen and warmed to 80 °C. The sodium amide suspension was added at such a rate that gentle refluxing resulted (the dropping funnel must be large enough to avoid plugging by the suspension). After the addition was completed, the reaction mixture was stirred and heated under reflux for two additional hours. The flask was cooled in an ice bath, and water (200 mL) was added. The organic phase was separated, then washed with water until neutral pH was reached, dried over magnesium sulfate and concentrated, leading to a crude oil. Purification was performed by silica gel column chromatography with cyclohexane/toluene (50:50) as the eluent (yield: 60%). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.5$ (m, 7H), 1.3 (m, 12H), 0.9 (t, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta =$ 124.8, 39.4, 36.7, 31.8, 24.5, 24.0, 22.5, 14.0; IR (neat): $\tilde{\nu} = 2230\ cm^{-1}$.

6-cyano-6-pentylundecane: The synthesis was analogous to the previous one, starting with a mixture of acetonitrile (6 mL, 0.115 mol) and 1-bromopentane (60 g, 0.40 mol). Purification was performed by silica gel column chromatography with toluene as the eluent (yield: 40%). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.5$ (m, 6H), 1.3 (m, 18H), 0.9 (t, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 125.2$, 40.5, 36.0, 31.8, 23.8, 22.3, 13.8; IR (neat): $\tilde{\nu} = 2230\ cm^{-1}$.

2-methyl-2-pentylheptylamine: The synthesis was adapted from previous literature.[27] A solution of 6-cyano-6-methylundecane (18.3 g, 94 mmol) in diethyl ether (100 mL) was slowly added under nitrogen to a cooled (ice bath) solution of lithium aluminium hydride (100 mL, 1 mol L^{-1} in diethyl ether) diluted in sodium-dried diethyl ether (100 mL). After the mixture had been stirred for 2 h, water (4 mL), 20% sodium hydroxide (3 mL), and water (4 mL) were added successively, with continued cooling and vigorous stirring. The inorganic residue was filtered, and the ether fraction was concentrated. Purification was performed by distillation (95 °C, 3 mm Hg). Yield: 79%; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.4$ (s, 2H), 1.2 (m, 16H), 1.0 (brs, 2H), 0.9 (t, 6H), 0.8 (t, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 50.4$, 37.1, 36.6, 32.9, 23.1, 22.7, 22.6, 14.1.

2,2-dipentylheptylamine: The synthesis was analogous to the previous one. Purification was performed by distillation (75 °C, 2 mm Hg). Yield: 55%; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.4$ (s, 2H), 1.0 (m, 26H), 0.8 (t, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 47.3$, 38.8, 34.5, 32.8, 22.6, 22.5, 14.0.

***N,N′*-di(2-methyl-2-pentylheptyl)urea (MPHU)**: MPHU was prepared according to a slightly modified version of a procedure described previously.[28] Trisphosgene (1.6 g, 5.4 mmol) in dichloromethane (20 mL) was slowly added under nitrogen to a stirred solution of 2-methyl-2-pentylheptylamine (6 g, 30 mmol) and triethylamine (Merck, 4.5 mL, 32 mmol) in dichloromethane (50 mL; SDS, distilled over phosphorus pentoxide) in an ice-cooled flask. The ice bath was removed, and the mixture was stirred for 2 h before aqueous HCl (60 mL, 0.1N) was added. The organic phase was separated, then washed with water until neutral pH was reached, dried over magnesium sulfate, and concentrated, leading to a white powder. Purification was performed by recrystallization in acetonitrile. Yield: 82%; m.p. 160 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 5.0$ (brs, 2H), 2.9 (d, 4H), 1.2 (m, 32H), 0.8 (m, 18H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 159.0$, 48.3, 37.0, 36.5, 32.5, 22.4, 21.5, 14.1; IR (KBr): $\tilde{\nu} = 3345$, 1625 cm^{-1}; elemental analysis calcd (%) for $C_{27}H_{56}N_2O$: C 76.35, H 13.29, N 6.60, O 3.77; found C 76.06, H 13.43, N 6.75, O 3.76.

***N,N′*-di(2,2-dipentylheptyl)urea (DPHU)**: DPHU was synthesized analogously to **MPHU**. Purification was performed by recrystallization in ethanol/water (5:1). Yield: 75%; m.p. 130 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 4.4$ (t, 2H), 2.9 (d, 4H), 1.2 (m, 48H), 0.8 (t, 18H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 158.5$, 45.6, 38.3, 35.0, 32.8, 22.6, 22.3, 14.0; IR (KBr): $\tilde{\nu} = 3365$, 1633 cm^{-1}; elemental analysis calcd (%) for $C_{35}H_{72}N_2O$: C 78.29, H 13.51, N 5.22, O 2.98; found C 78.36, H 13.45, N 5.15, O 3.05.

***N,N′*-di(1-methylheptyl)urea (MHU)**: MHU was synthesized analogously to **MPHU**. Purification was performed by recrystallization in acetonitrile. Yield: 77%; m.p. 70 °C (lit. 48 °C);[29] ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 4.1$ (d, 2H), 3.6 (m, 2H), 1.2 (m, 20H), 1.1 (d, 6H), 0.8 (t, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 154.0$, 42.8, 34.3, 28.5, 25.9, 22.7, 19.2, 18.3, 10.7; IR (KBr): $\tilde{\nu} = 3330$, 1630 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{36}N_2O$: C 71.77, H 12.75, N 9.85, O 5.62; found C 71.53, H 12.86, N 9.86, O 5.74.

***N,N′*-di(1,5-dimethylhexyl)urea (DMHU)**: DMHU was synthesized analogously to **MPHU**. Purification was performed by silica gel column chromatography with dichloromethane/ethyl acetate (90:10) as the eluent. Yield: 65%; m.p. 51 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 4.2$ (d, 2H), 3.6 (m, 2H), 1.4 (m, 2H), 1.2 (m, 12H), 1.0 (d, 6H), 0.8 (d, 12H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 157.4$, 46.1, 38.9, 37.9, 27.9, 23.8, 22.6, 21.7; IR (KBr): $\tilde{\nu} = 3330$, 1630 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{36}N_2O$: C 71.77, H 12.75, N 9.85, O 5.62; found C 71.59, H 12.82, N 9.82, O 5.77.

***N,N′*-di(4-butylphenyl)urea (BPU)**: BPU was synthesized analogously to **MPHU**. Purification was performed by recrystallization in ethanol. Yield: 77%; m.p. 188 °C (lit. 200 °C);[30] ^{1}H NMR (200 MHz, [D_6]DMSO): $\delta = 8.5$ (s, 2H), 7.3 (d, 4H), 7.0 (d, 4H), 2.4 (m, 4H), 1.5 (m, 4H), 1.2 (m, 4H), 0.8 (t, 6H); ^{13}C NMR (50 MHz, [D_6]DMSO): $\delta = 152.5$, 137.3, 135.5, 128.3, 118.1, 34.0, 33.1, 21.5, 13.6; IR (KBr): $\tilde{\nu} = 3310$, 1640 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{28}N_2O$: C 77.74, H 8.70, N 8.63, O 4.93; found C 77.76, H 8.75, N 8.77, O 4.73.

***N,N′*-di(4-octylphenyl)urea (OPU)**: OPU was synthesized analogously to **MPHU**. Purification was performed by recrystallization in ethanol. Yield: 73%; m.p. 179 °C; no suitable solvent for NMR analysis has been identified; IR (KBr): $\tilde{\nu} = 3310$, 1635 cm^{-1}; elemental analysis calcd (%) for $C_{29}H_{44}N_2O$: C 79.77, H 10.16, N 6.42, O 3.66; found C 79.66, H 10.15, N 6.60, O 3.58.

***N,N′*-di(4-*s*butylphenyl)urea (sBPU)**: sBPU was synthesized analogously to **MPHU**. Purification was performed by recrystallization in heptane. Yield: 55%; m.p. 238 °C; ^{1}H NMR (200 MHz, [D_6]DMSO): $\delta = 7.4$ (s, 2H), 7.2 (d, 4H), 7.0 (d, 4H), 2.5 (m, 2H), 1.5 (m, 4H), 1.2 (d, 6H), 0.8 (t, 6H); ^{13}C NMR (50 MHz, [D_6]DMSO): $\delta = 154.2$, 143.1, 136.0, 127.8, 121.3, 41.2, 31.3, 21.9, 12.3; IR (KBr): $\tilde{\nu} = 3310$, 1640 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{28}N_2O$: C 77.74, H 8.70, N 8.63, O 4.93; found C 77.39, H 8.71, N 8.73, O 5.16.

***N,N′*-di(2-butylphenyl)urea (oBPU)**: oBPU was synthesized analogously to **MPHU**. Purification was performed by recrystallization in ethanol. Yield: 77%; m.p. 196 °C; ^{1}H NMR (200 MHz, [D_6]DMSO): $\delta = 8.1$ (s, 2H), 7.6 (d, 2H), 7.1 (m, 4H), 6.9 (t, 2H), 2.5 (t, 4H), 1.5 (m, 4H), 1.5 (m, 4H), 1.3 (m, 4H), 0.9 (t, 6H); ^{13}C NMR (50 MHz, [D_6]DMSO): $\delta = 153.5$, 138.9, 133.5, 129.2, 125.9, 123.5, 123.4, 31.6, 30.5, 21.9, 13.6; IR (KBr): $\tilde{\nu} = 3310$, 1640 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{28}N_2O$: C 77.74, H 8.70, N 8.63, O 4.93; found C 77.02, H 8.62, N 8.53, O 5.84.

***N,N′*-di(2,4,6-trimethylphenyl)urea[31] (TMPU)**: TMPU was synthesized analogously to **MPHU**. Purification was performed by recrystallization in ethanol. Yield: 78%; m.p. 201 °C; no suitable solvent for NMR analysis has been identified; IR (KBr): $\tilde{\nu} = 3290$, 1640 cm^{-1}; elemental analysis calcd (%) for $C_{19}H_{24}N_2O$: C 76.99, H 8.16, N 9.45, O 5.40; found C 76.73, H 8.14, N 9.27, O 5.86.

***N,N′*-di(2,6-diethylphenyl)urea (DEPU)**: DEPU was synthesized analogously to **MPHU**. Purification was performed by recrystallization in ethanol. Yield: 39%; m.p. 290 °C (lit. 288 °C);[32] ^{1}H NMR (200 MHz, [D_6]DMSO): $\delta = 7.7$ (s, 2H), 7.1 (m, 6H), 2.6 (m, 8H), 1.1 (t, 12H); IR (KBr): $\tilde{\nu} = 3270$, 1630 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{28}N_2O$: C 77.74, H 8.70, N 8.63, O 4.93; found C 77.63, H 8.81, N 8.51, O 5.05.

***N,N′*-di(2,6-diisopropylphenyl)urea (DIPPU)**: DIPPU was synthesized analogously to **MPHU**. Purification was performed by recrystallization in heptane. Yield: 69%; m.p. 230 °C (lit. 229.5 °C);[33] ^{1}H NMR (200 MHz, [D_6]DMSO): $\delta = 7.3$–7.1 (m, 6H), 5.9 (s, 1H), 5.4 (s, 1H), 3.4 (t, 2H), 3.0 (t, 2H), 1.3 (d, 6H), 1.1 (s, 18H); ^{13}C NMR (50 MHz, [D_6]DMSO): $\delta = 156.5$, 148.2, 146.6, 131.2, 131.0, 129.2, 128.0, 124.0, 123.3, 28.5, 25.5, 23.8, 22.1; elemental analysis calcd (%) for $C_{25}H_{36}N_2O$: C 78.90, H 9.53, N 7.36, O 4.20; found C 78.92, H 9.61, N 7.32, O 4.15.

Capillary viscosimetry: Measurements were performed at 25 ± 0.1 °C with a Cannon–Manning semimicro viscometer. Solutions in heptane (SDS) or carbon tetrachloride (SDS) were prepared 1 day prior to the measurements and filtered through Millex membranes ($\Phi = 0.45\ \mu m$). Solvents were used as received.

IR spectroscopy: Infrared spectra were recorded at room temperature on a Perkin–Elmer 1760 spectrometer in KBr cells of 0.05 to 2.5 cm path length. The temperature-controlled measurements were performed with a heating device (P/N 21525) from Specac. Solutions in carbon tetrachloride (SDS) were prepared 1 day prior to the measurements. Preliminary tests showed that solutions obtained from carbon tetrachloride that had been saturated with water or dried on molecular sieves yielded the same spectrum. Consequently, carbon tetrachloride was used as received. Quantitative data analysis was based on the N–H vibration, because the intensity of the C=O vibration was not precise enough, due to high solvent absorption at this wavelength. The molar extinction coefficient of the free N–H stretching vibration was determined on sufficiently dilute solutions, such that only the free component was detected. At higher concentrations, after deconvolution of the N–H vibration curve, the height of the free component was used to derive the fraction of free N–H groups.[16] Then, the association constants were determined by nonlinear curve fitting. The main source of uncertainty (which is mentioned in Table 2 and Figure 5) is due to the uncertainty of the deconvolution, because the shape of the hydrogen-bonded N–H band is ill-defined. The values of the association constants obtained for **EU** (Table 2) are significantly different from the values reported previously ($K_2 = 110\ \mathrm{L\,mol^{-1}}$, $K = 780\ \mathrm{L\,mol^{-1}}$),[16] but these latter values are certainly less precise because the molar extinction coefficient of the free N–H band was determined by extrapolation from solutions containing a fraction of hydrogen bonded N–H groups.

Computer modeling: Molecular-modeling calculations were done using the Consistent Valence Force Field as implemented in the software Insight II from Molecular Simulations Incorporated. All calculations were done in the gas phase with a dielectric constant of 1 and with no cut-off.

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[24] The other possibility, in agreement with previous data,[21] is to assign the N–H vibrations detected at 3428 and 3408 cm^{-1} to the *trans* and *cis* conformations, respectively. However, computer simulations of an isolated **DIPPU** molecule show that, in the *cis–trans* conformation, the *trans* N–H group is completely buried within the molecule and is not accessible for hydrogen bonding. Consequently, this alternative assignment is in conflict with the evolution of the FTIR spectrum at higher concentrations.

[25] See, for example, Figure 2 in ref. [4a].

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