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Synthesis and organogelating ability of bis-urea pseudopeptidic compounds

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ABSTRACT

A large family of amphiphilic pseudopeptidic derivatives in which the aliphatic tails are connected to the pseudopeptidic moiety through urea functionalities have been prepared with excellent yields. The synthetic procedure is simple and very efficient and allows a modular variation of a large number of structural parameters. The self-assembling properties of the resulting compounds has been studied under different conditions and using different media. Very interestingly, many of the compounds obtained have revealed to act as very efficient organogelators at low concentrations. The resulting gels provide some unusual properties. Of particular relevance are the broad scope of organic solvents that can be gelated and the high thermal stability of the resulting gels. Gels that are stable up to temperatures close to 100 °C can be obtained in some instances.

1. Introduction

The preparation of chemical structures with high tech applications have been attracted the interest among chemists. Molecular gels are one of these new functional materials,[1–8] and the design of compounds that are able to form robust and stable gels is a challenge for scientist.[9–16]

Technological and industrial applications reported for organogelators[17,18] are very broad and those include their use in fields, such as cosmetics,[19–26] development of separation processes,[27,28] novel NMR techniques based on residual dipolar coupling[29–32] or controlled drugs release.[19,33–35] Other applications are related to the preparation of intelligent materials being responsive to external stimuli,[36–44] biocompatible[33,45–47] or having a structured porosity.[17,27] Essential properties of the gels, particularly organogels, are mainly based on several parameters: on the one hand, the variety of solvents in which the gelation process can take place and the minimum concentration of compound that are able to form the gel.[48–50] On the other hand, an additional parameter to be considered is the stability of the gels under different external stimuli.[51–53] In general, a broad range of compounds that can form organogels at 1% weight–volume or even lower concentrations. However, most reported families of organogelator are only appropriate to gelate a limited number of organic solvents. In the same way, organogels present, very often, a limited thermal stability, which can preclude their technical application in different fields such as cosmetics or drug release.[54] So, the synthesis of new low molecular weight organogelators displaying a good stability for the gels formed in different media and at relatively high temperatures is still a challenge.[55–58]

In recent years, the gelation ability of urea derivatives has been deeply investigated.[6,59–70] Urea and their derivatives have been playing a central role in the field of Supramolecular Chemistry. In this regard, the urea group contains a number of desirable features, including its rigidity, planarity, polarity, and hydrogen bonding capacity.[59,71] Thus, for instance, different urea derivatives have proven to be good receptors for the recognition of anions in solution[72–83] or in the gel state.[60,84]

Moreover, their potential self-assembling based on the hydrogen bonding capacity of the urea group makes this type of compounds useful for the design of new materials.[9,10,85] Molecular gels formed by low molecular weight organogelators or hydrogelators are one of these new functional materials.[1–6,86–88] In recent years, the gelation ability of urea derivatives has been deeply investigated.[6,59–69]

Recently, we have prepared and studied different amphiphilic pseudopeptides containing long aliphatic tails bound to the two nitrogen atoms of a C_2 symmetric pseudopeptides.[89] This family of compounds has shown some interesting properties in terms of their self-assembly in the solid state,[90] as well as in the self-assembly with quantum dots, allowing their solubilisation in water.[90] Although, in this case, strong organogelating properties were not found, the utility of amphiphilic peptides to build up strong biocompatible gelator systems has been demonstrated by different groups.[45,91–99] In this regard, our research group has investigated how different C_2 symmetric pseudopeptides have interesting properties as organogelators.[100–103] Here, we present the development of a new family of amphiphilic in which the long aliphatic tails are bound to the nitrogen amino atoms of a C_2 symmetric pseudopeptide through

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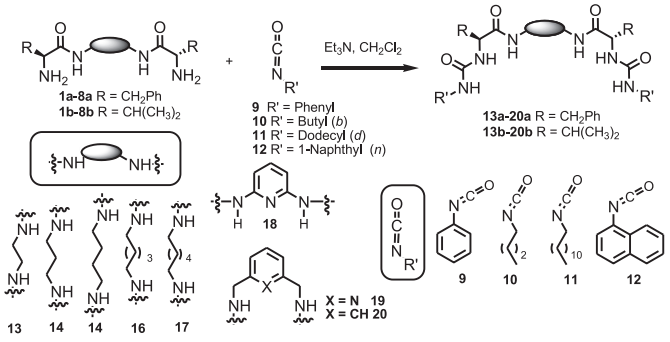
a urea linkage. Those compounds not only present interesting self-assembling properties in the solid state, but also provide a new family of strong organogelators with improved properties.

2. Results and discussion

2.1. Design and synthesis of the bis-urea pseudopeptidic compounds

The bis-urea pseudopeptidic compounds were designed to enhance the potential for hydrogen bonding and other polar and non-polar intermolecular interactions, taking advantage of the properties of the urea group. The general structure of those compounds contains two amino acid moieties connected through their acid ends by a flexible spacer, two urea groups at both amino termini with two hydrophobic tails connected to them, rendering an overall C_2 symmetry. This design allows a implementation of the different structural elements in order to optimize their potential for establishing intermolecular interactions (H-bond, dipole–dipole, π–π stacking, hydrophobic contacts, etc.).

The synthesis of the proposed enantiomerically pure bis-urea pseudopeptidic compounds was carried out following a simple procedure as depicted in Scheme 1. First of all, the corresponding C_2 symmetrical bis(amidoamines) were obtained using previously reported procedures.[104] From those starting materials, the bis-urea compounds were prepared by a reaction with 2 equiv of different isocyanates (Scheme 1),[105] leading to the expected compounds in good to excellent yields (Table 1). These yields do not seem dependent on the structural variations of the starting isocyanate or the bis(amino amide). In this regard, only in a single case the yield was low (entry 14 in Table 1), but, most likely this can be associated with its high solubility in most solvents, which seems to make difficult, the purification process according to the standard procedure developed.



Scheme 1. General procedure for the synthesis of the bis-urea pseudopeptidic compounds. Prefixes *b*-, *d*-, and *n*- are used to denote the nature of the aliphatic tails (butyl, dodecyl, 1-naphthyl); when no prefix is present, a phenyl group is present in that position.

As can be seen in Table 1, it was possible to synthesize a large variety of gemini amphiphilic pseudopeptides having both aliphatic and aromatic components in three key structural elements: the central spacer, the amino acid side chain and the substituent at the amino nitrogen atoms.[89]

2.2. Ultrastructure in the solid state

The ability of the current knowledge of chemistry for the design and proper understanding of the structure–properties relationships in low molecular weight compounds clearly favor the development of this kind of gelators. The self-assembling process leading to the formation of the fibrilar network takes place through a highly hierarchicalised process to provide very well structure micro and nano-structures.[102]

Table 1
Synthesis of bis-urea pseudopeptidic compounds

	Product	Aaa	Yield[a]
1	**13a**	Phe	76
2	**13b**	Val	80
3	**14a**	Phe	81
4	**14b**	Val	83
5	*b*-**14a**	Phe	71
6	*b*-**14b**	Val	85
7	*d*-**14a**	Phe	60
8	*d*-**14b**	Val	88
9	*n*-**14b**	Val	95
10	**15a**	Phe	78
11	**15b**	Val	77
12	*d*-**15a**	Phe	66
13	*d*-**16a**	Phe	60
14	**17a**	Phe	40[b]
15	**17b**	Val	84
16	*b*-**17a**	Phe	80
17	*b*-**17b**	Val	86
18	*d*-**17a**	Phe	84
19	*d*-**17b**	Val	66
20	*n*-**17a**	Phe	92
21	**18a**	Phe	84
22	**18b**	Val	60
23	**19a**	Phe	68
24	**19b**	Val	70
25	**20a**	Phe	91
26	**20b**	Val	94

[a] Isolated yields (%) after purification.
[b] The yield was low, as this compound was the most soluble and it was difficult to purify.

In order to study the ability of the bis-urea compounds to self-assemble into supramolecular nano-structures in the solid state we performed Scanning Electron Microscopy (SEM) experiments on slowly evaporated samples (ca. 2 mg/mL) onto aluminum surfaces. The samples were grown from solvents of different polarities such as $CHCl_3$, acetonitrile, MeOH or solvent mixtures in order to study the effect of the environment in the aggregation behavior. In general, the most observed nano-structures from bis-urea compounds were fibers (Fig. 1 and Supplementary data).

Most of the derivatives prepared were only slightly soluble in the solvents assayed. The single exception to this trend was the behavior of **17a**, showing a good solubility in a variety of solvents. In this case, very different nano-structures (fibers, tapes or even spheres) were obtained depending on the solvent used for growing the samples. Evaporation from polar solvents always afforded the best defined nano-structures (Fig. 2 and Supplementary data).

In all cases, a general trend can be observed as is that upon increasing the polarity of the solvent, an increment of the presence of fibers is observed. Moreover, these fibers are also more organized in polar solvents as can be seen in Fig. 3 and Supplementary data.

In order to evaluate the driving forces behind the association process of bis-urea compounds under different conditions ATR FT-IR spectra were recorded. Upon association the vibration of the carbonyl bond of the urea group moves to lower wavenumbers, which can be used as an indicator of the strengths of the hydrogen-bond interactions involving this group. Thus, as can be seen in Fig. 4 those interactions increase when going from diluted solutions to the solid state. Only for concentrated solutions the sample start to become opaque.

In general, all compounds prepared show a low solubility, which can be associated to the strong tendency to be intermolecularly associated via hydrogen bonding. Fig. 5 shows the expected hydrogen-bonding pattern expected for those compounds. It is worth mentioning that the presence of the urea groups plays a key role in determining the self-assembling properties of those

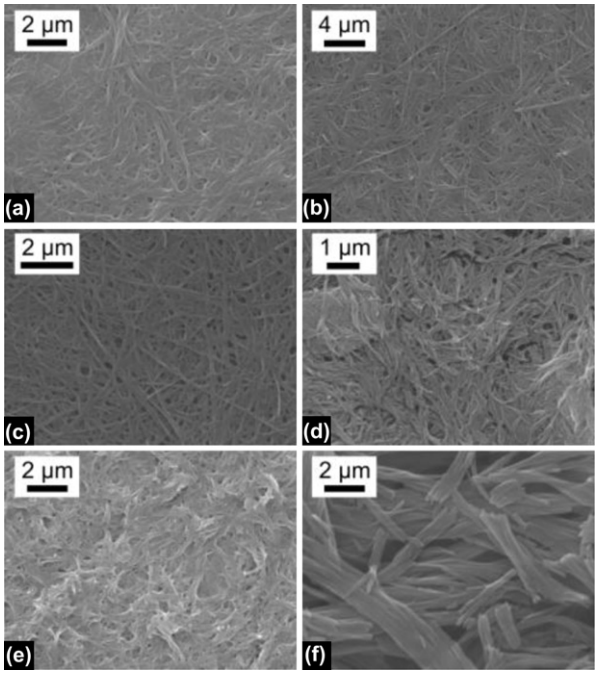


Fig. 1. SEM micrographs of: (a) *b*-**14a** and (b) *d*-**14a** grown from $CHCl_3$; (c) *b*-**14a** and (d) **14b** grown from acetonitrile; and (e) **14b** and (f) *d*-**14b** grown from MeOH.

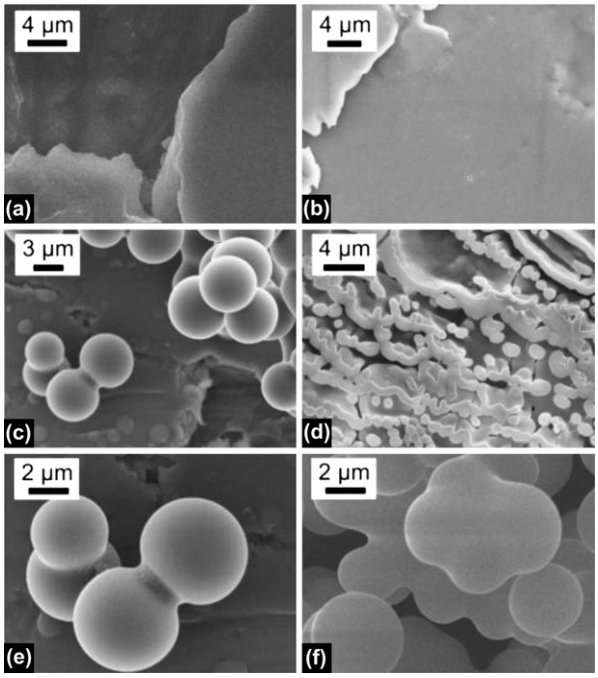


Fig. 2. SEM micrographs of **17a** grown from: (a) $CHCl_3$, (b) $CHCl_3$+20% MeOH, (c–e) MeOH+20% $CHCl_3$, and (f) MeOH.

compounds. Similar compounds without urea groups, prepared in our research group, are able to form different nano-structures, but they are not able to form gels.[89,90]

MMFF calculations are in a good agreement with this proposed model. This can be seen in Fig. 6 showing the most stable conformer calculated for an individual molecule of **14b** in the gas phase and the structure obtained though minimization of a set of four interacting molecules. For the sake of simplicity the model was built from a molecule containing a short chain bonded to the urea group.

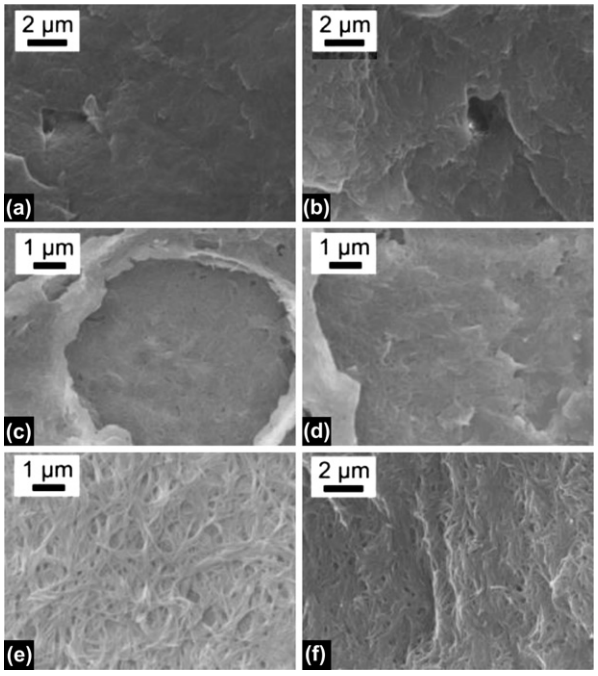


Fig. 3. SEM micrographs of **14b** grown from: (a) $CHCl_3$, (b) $CHCl_3$+5% MeOH, (c) $CHCl_3$+10% MeOH, (d) $CHCl_3$+20% MeOH, (e) MeOH+10% $CHCl_3$, and (f) MeOH.

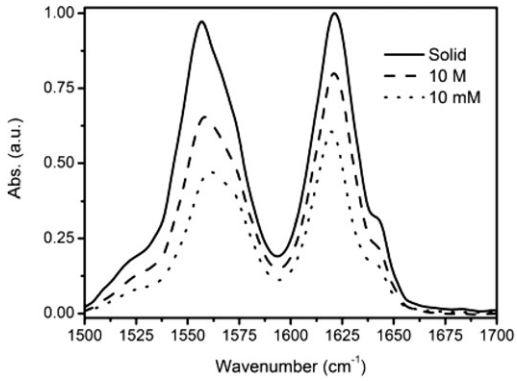


Fig. 4. ATR FT-IR spectra during the evaporation of a solution of compound *d*-**15a** in $CHCl_3$.

2.3. Supramolecular gels formation

Studies in solution using different solvents revealed the capacity of these bis-urea pseudopeptides to act as efficient organogelators. In order to get a clearer picture of this ability, a systematic study was carried out in different solvents. The main results of this study are gathered in Table 2 and some examples of the obtained gels are shown in Fig. 7.

Several general trends can be concluded from the data in Table 2. First of all, the tendency to gelation of different solvents by the bis-urea pseudopeptidic compounds is the following: ACN>toluene>MeOH>DMF>DMSO>CH_2Cl_2>$CHCl_3$. Only in the case of hexane, gelation could not be accomplished with any of the bis-urea derivatives studied. Secondly, structural changes in the central spacer show that compounds with aromatic spacers cannot form gels (entries 7, 8, 9 and 16, 17, 18 in Table 2). Some related compounds containing functionalized aromatic spacers have been reported to have organogelating properties,[52] but, in this case, the property seems to be associated to the presence of the specific functional groups present in the aromatic subunit. However,

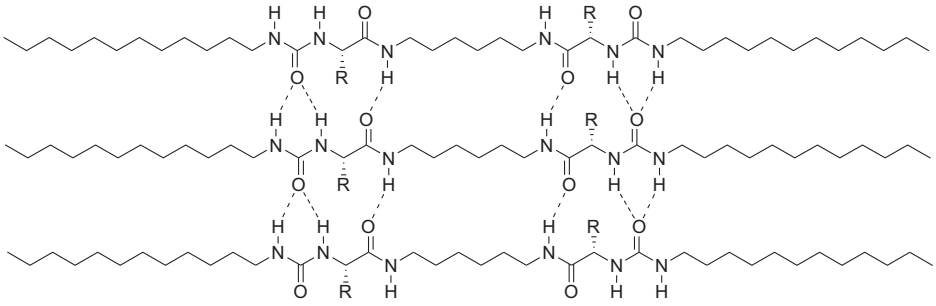


Fig. 5. General aggregation scheme for the aggregation of bis-urea pseudopeptidic compounds. Hydrogen bonds are devoted by dashed lines.

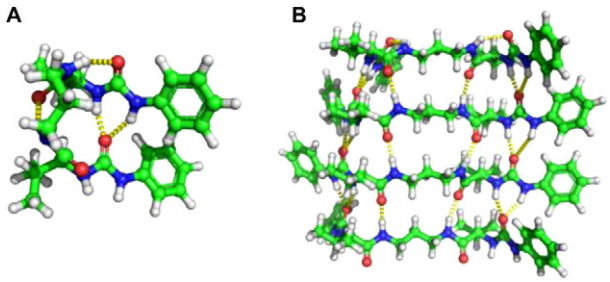


Fig. 6. MMFF molecular models: (a) most stable conformer **14b**, (b) proposed aggregation model of 4 molecules of compound **14b**.

Table 2
Gelation behavior of bis-urea pseudopeptidic compounds in different organic solvents[a]

	Compound	DMF	DMSO	CH_2Cl_2	MeOH	ACN	Toluene	$CHCl_3$	Hexane
1	**14b**	S	S	I	I	I	S	I	I
2	*b*-**14b**	G (3.5)	G (3.9)	I	G (3.2)	G (4.1)	G (4.5)	I	I
3	*d*-**14b**	G (5.4)	S	I	G (4.4)	G (4.4)	G (3.9)	I	I
4	**17b**	S	S	I	I	I	I	I	I
5	*b*-**17b**	G (4.3)	G (4.2)	I	G (3.9)	G (4.5)	G (3.9)	I	I
6	*d*-**17b**	G (3.1)	G (4.8)	G (4.7)	G (3.4)	G (3.4)	G (4.2)	G (3.5)	I
7	**18b**	S	S	I	I	I	I	I	I
8	**19b**	S	S	I	I	I	I	I	I
9	**20b**	S	S	I	I	I	I	I	I
10	**14a**	S	S	I	I	I	I	I	I
11	*b*-**14a**	S	S	G (5.8)	S	G (5.2)	G (4.9)	G (4.9)	I
12	*d*-**14a**	G (4.3)	G (6)	G (4.3)	G (3.9)	G (4.6)	G (3.7)	G (4.1)	I
13	**17a**	S	S	S	S	S	S	S	I
14	*b*-**17a**	S	S	G (4.9)	S	G (5.3)	S	S	I
15	*d*-**17a**	G (5.3)	G (6)	G (5.9)	G (5.7)	G (6.3)	G (5.3)	G (5.0)	I
16	**18a**	S	S	I	I	I	I	I	I
17	**19a**	S	S	I	I	I	I	I	I
18	**20a**	S	S	I	I	I	I	I	I

[a] G: gel (Minimum gelator concentration (g L^{-1})); S: soluble; I: insoluble.

compounds containing aliphatic spacers of variable lengths are able to gelate a wide variety of solvents. This trend is similar for compounds having both short and long aliphatic central spacers (entries 2 and 5 in Table 2).[39,40]

The third trend is the ability of compounds with long hydrophobic tails to form gels more efficiently than those bearing short tails (entries 14 and 15 in Table 2). On the contrary, compounds with aromatic tails are not able to form gels (entries 1, 7, and 10 in Table 2).

Finally, it can be observed how the amino acid side chain has a minor influence on the gelifying process. Similar gels in different solvents are obtained for Val and Phe bis-urea derivatives (entries 3 and 15 in Table 2).

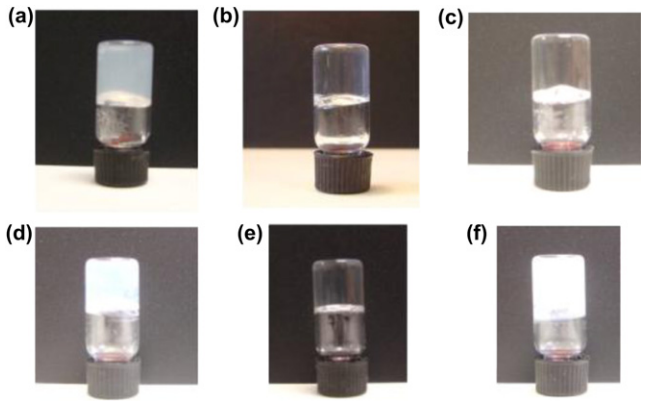


Fig. 7. Gels obtained using organic solvents and bis-urea pseudopeptidic compounds. (a) *b*-**17a** in CH_2Cl_2 (entry 14 in Table 2), (b) *d*-**17b** in $CHCl_3$ and (c) in toluene (entry 6 in Table 2), (d) *b*-**14a** in acetonitrile (entry 11 in Table 2), (e) *d*-**14a** in toluene (entry 12 in Table 2) and (f) *d*-**17a** in acetonitrile (entry 15 in Table 2).

2.4. Thermal stability of the gels

Finally, the thermal stability of the gels was measured using two different techniques: NMR (Fig. 8) and UV–vis (Fig. 9). Both techniques revealed that the gels show a remarkable thermal stability, maintaining the gel structure up to high temperatures. In many cases, the gel structure was kept even at temperatures close to 100 °C.

The NMR spectroscopy is a very useful technique for studying the melting of supramolecular gels, since the molecules in the gel state are unobservable by NMR due to relaxation produced line

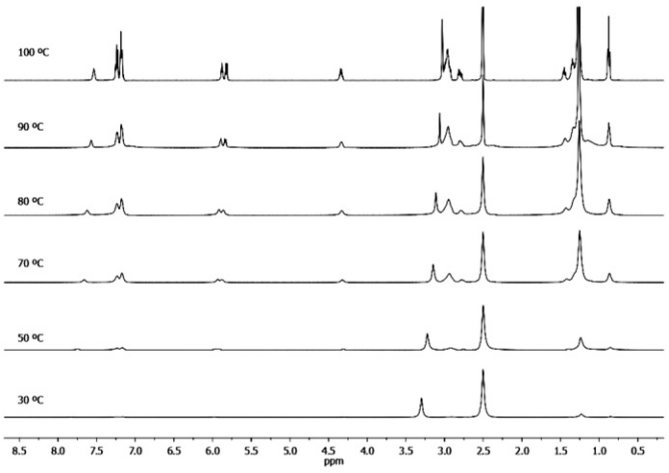


Fig. 8. ^1H NMR (500 MHz) spectra of *d*-**14a** in DMSO-d_6 at different temperatures.

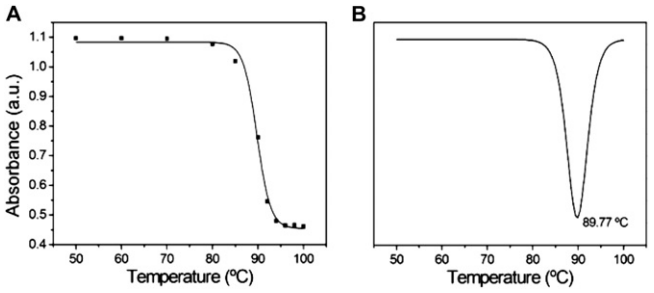


Fig. 9. A) Absorbance at 600 nm at different temperatures, B) derivative of the absorbance at 600 nm at different temperatures, for the gel obtained in DMSO with *b*-**14b**.

broadening. Actually, for the solution-state NMR observation, the molecules in the fibers of the gel behave as a solid matrix. Thus, when acquiring the ^{1}H NMR spectra in the gel state, the corresponding proton signals are essentially unobservable, as is illustrated in Fig. 8 for *d*-**14a** in DMSO-d_6 (lower trace). As the temperature of the sample is raised, the supramolecular interactions responsible for the formation of the gel begin to be broken, and the molecules of the pseudopeptidic bis-urea compounds start to equilibrate between the two possible states, fibers and solution. In this situation, molecules in solution can be observable by NMR. Accordingly, the corresponding proton signals grow when the temperature is raised (see middle traces in Fig. 8). Only when the fibers responsible of the formation of the gel are completely destroyed, a well defined and resolved ^{1}H NMR spectrum is observable (upper trace in Fig. 8). In the case shown in Fig. 8, this situation is achieved above 90 °C.

Similar melting/transition studies can be performed by UV–vis spectroscopy. The formation of a gel structure is, in general, accompanied by the appearance of some turbidity (absorbance at 600 nm), or at least by some changes in the observed absorption. This is eliminated when the gel is completely transformed in a clear solution. Therefore, the absorbance at 600 nm decreases when the temperature increases (Fig. 9A), which allows estimating the temperature for the sol–gel transition (Fig. 9B). Similar results are obtained by DSC analysis.

Compound *d*-**17b** was able to form gels with sunflower oil (that contains mainly triglycerides derived from the linoleic acid and oleic acid). The thermal stability was measured by the inversion of tube (Fig. 10) and by DSC (Fig. 11), being in both cases greater than 150 °C. The presence of hydrogen-bonding moieties in the chemical structure of the oil has a direct effect on the selfassembly of the gelator molecules and plays key role in the formation of high temperature stable gels.

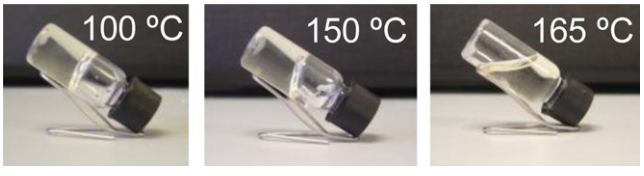


Fig. 10. Thermal stability of the gel sunflower oil with *d*-**17b** (4 g L^{-1}).

3. Conclusions

A large variety of bis-urea pseudopeptidic compounds can be easily prepared from previously developed bis(amino amide) pseudopeptidic structures with C_2 symmetry, using different commercial isocyanates. The process is highly modular and allows a simple sequential modification of the different structural

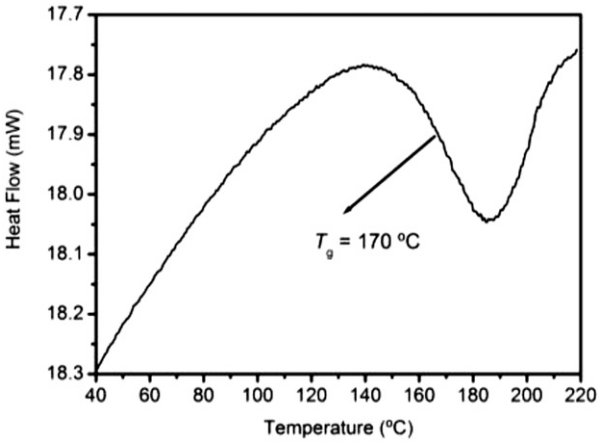


Fig. 11. Thermal stability of the gel sunflower oil with *d*-**17b** (4 g L^{-1}) measured by DSC.

elements in order to obtain compounds displaying the desired properties. The presence of the urea groups plays a key role in determining the self-assembling properties of those compounds, as long as similar compounds without urea groups are not able to form gels. The resulting amphiphilic compounds have a limited solubility in many solvents, but show interesting properties regarding their self-assembling behavior either in the solid state or in liquid matrices. The results obtained are clearly different from those obtained from related amphiphilic derivatives obtained from the same family of bis(amino amide) pseudopeptidic compounds but lacking the urea groups. Of particular relevance are the properties of these compounds as strong organogelators for a variety of organic solvents. Their use as organogelators provide access to two important properties that cannot be easily achieved in this field. First, some compounds of this family are able to efficiently gelate a large variety of solvents with very different properties. Even most important is the second property associated to this family of organogelators: once the gel is formed, its thermal stability is unusually high. Sol–gel transition temperatures for many of those gels, as measured by NMR or UV–vis techniques, can reach values close to 100 °C. Those two elements, combined with the latent biocompatibility of the molecules here developed, allows considering a high potential for their use in different technological applications in the areas of cosmetics, pharmaceutical compounds, etc.

4. Experimental section

4.1. General

Reagents and solvents were purchased from commercial suppliers (Aldrich, Fluka or Merck) and were used without further purification. The C_2 symmetrical bis(amidoamines) were prepared as previously described.[104,106]

4.2. Electron microscopy

Scanning Electron Microscopy was performed either in a LEO 440I or in a JEOL 7001F microscope with a digital camera. Samples were obtained by slow evaporation of a solution of the compounds (~1–2 mg mL^{-1}) directly onto the sample holder, and were conventionally coated previous to the measurement. Transmission Electron Microscopy was carried out in a JEOL 2100 microscope at 120 kV. The micrographs were obtained from ~1 mg mL^{-1} solutions onto a holey carbon copper grid. The samples were sonicated

for 10 min previous to the measurement, one drop added onto the grid and collected directly without staining.

4.3. NMR spectroscopy

The NMR experiments were carried out on a Varian INOVA 500 spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C) or on a Varian UNITY 300 (300 MHz for ^{1}H and 75 MHz for ^{13}C). Chemical shifts are reported in parts per milion using solvent residual peak as reference.

4.4. Gelation procedure

The studied compounds were dissolved in a series of organic solvents in a screw-capped cylindrical glass vial (diameter: 1 cm), heated to the boiling temperature of the solvent, and left to cool by standing at room temperature. A gel was considered to have formed when the soft material was stable upon turning the vial upside-down.

4.5. Infrared spectroscopy

ATR FT-IR spectra were acquired in a JASCO 6200 equipment having a MIRacle Single Reflection ATR Diamond/ZnSe accessory. Samples of the corresponding pseudopeptide at different concentration and in the solid state were prepared and seeded onto the ATR sample holder, and the FT-IR spectra were collected. The raw IR data were processed with the JASCO spectral manager software.

4.6. UV–vis spectroscopy

UV–vis absorption measurements were made using a Hewlett–Packard 8453 spectrophotometer, equipped with a control temperature system.

4.7. Differential scanning calorimetry

DSC measurements were performed in a Perkin Elmer DSC 6 Differential Scanning Calorimeter. Sample was weighed and sealed in the aluminum sample pan, and then heated at a rate of 5 °C min^{-1} in nitrogen atmosphere.

4.8. Molecular modeling

All the theoretical calculations were performed with Spartan '08 software,[107] using the MMFF level of theory for the geometry optimizations.

4.9. General procedure for the synthesis of bis-urea pseudopeptidic compounds

Synthesis of 13a. The corresponding pseudopeptidic bis(amino amide) precursor (217.6 mg, 0.614 mmol) was dissolved in anhydrous dichloromethane (20 mL). Triethylamine (189.13 μL, 1.35 mmol) and phenyl isocyanate (150.2 μL, 1.35 mmol) were added at 0 °C under stirring. After 15 min the mixture was left at room temperature overnight, under stirring. The reaction mixture was then evaporated to dryness. The residue obtained was recrystallised from 2-propanol to yield a white solid (276.6 mg, 0.467 mmol, 76% yield). Mp 267.6 °C; $[\alpha]_D^{25}$ +45.5 (*c* 0.01, DMSO); IR (ATR) 3288, 1644, 1540, 1441 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.78 (m, 2H), 3.02 (m, 6H), 4.38 (m, 2H), 6.30 (m, 2H), 6.86 (m, 2H), 7.17 (m, 12H), 7.24 (m, 4H), 7.30 (m, 4H), 8.07 (s, 2H), 8.62 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 38.6, 39.1, 54.6, 118.0, 121.7, 126.8, 128.5, 129.1, 129.7, 137.9, 140.6, 155.0, 172.1; HRMS (ESI-TOF)$^+$ calcd for $C_{34}H_{36}N_6O_4$ $(M+H)^+$: 593.2876; found 593.2876; Anal. Calcd for $C_{34}H_{36}N_6O_4\cdot H_2O$: C, 68.87; H, 6.27; N, 13.76; found: C, 68.45; H, 6.70; N, 13.53.

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Supplementary data

General experimental and synthetic procedures, ^{1}H and ^{13}C NMR spectra, and mass spectra for compounds, SEM micrographs of compounds from chloroform, acetonitrile, and methanol solutions. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.01.007.

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