Tetrahedron Letters 51 (2010) 5861–5867

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Gemini amphiphilic pseudopeptides: synthesis and preliminary study of their self-assembling properties

Jenifer Rubio [a], Ignacio Alfonso [b,*], Miriam Bru [a], M. Isabel Burguete [a], Santiago V. Luis [a,*]

[a] Departamento de Química Inorgánica y Orgánica, Universidad Jaume I, Avd. Sos Baynat s/n, Castellón, Spain
[b] Departamento de Química Biológica y Modelización Molecular, Instituto de Química Avanzada de Cataluña, CSIC, Jordi Girona 18-26, Barcelona, Spain

ARTICLE INFO

Article history:
Received 9 June 2010
Revised 21 July 2010
Accepted 26 July 2010
Available online 6 September 2010

Dedicated to the memory of Professor J. M. Concellón

Keywords:
Supramolecular chemistry
Amphiphiles
Self-assembly
Pseudopeptides
Nanostructures

ABSTRACT

The synthesis of a family of Gemini Amphiphilic Pseudopeptide (GAP) molecules by a reductive amination reaction has been carried out. The process is highly modular and can be efficiently performed with different pseudopeptidic diamines as well as aliphatic and aromatic aldehydes. Preliminary studies showed the abilities of the GAPs to self-assemble into supramolecular nanostructures.

The study of self-assembled organic nanostructures is an emerging field in supramolecular chemistry and can be considered as a bottom-up approach to nanoscience.[1] Among all the possible building blocks, those based on peptide-like structures are especially attractive due to their modular synthesis, good biocompatibility and large variety of possible non-covalent interactions.[2] However, understanding and controlling the final nanostructures is still a challenging work. Regarding that, some elegant examples have been recently reported, using different stimuli to modulate the size and shape of the supramolecular nanostructures.[3] Following our work in the field of supramolecular nanostructures based on pseudopeptidic compounds,[4] we envisioned to prepare simple molecules able to display differential self-assembling properties in different environments. Within this field, simple Gemini Amphiphilic Pseudopeptide (GAP) molecules are good candidates due to their structural properties, which can modulate their self-assembling behaviour in different media. We designed a family of C_2 symmetrical gemini bis(amidoamines) (**1**) formed by two amino acid units connected by an aliphatic flexible spacer and bearing two hydrophobic tails (Fig. 1). With this design, the final systems would have two hydrophobic tails, as well as a polar pseudopeptidic core bearing H-bonding donors and acceptors. This would allow the modulation of their self-assembling properties in environments of different polarity.

Considering the basic design of the GAPs, we proposed a retrosynthetic analysis using simple bis(amidoamines) **2** and **3** previously synthesized by our research group (Fig. 1).[5] Our initial approach was based on the alkylation of the precursor diamines (**2**–**3**) with alkyl halides ($R'CH_2X$) in the presence of a base.[5,6] We tried different reaction conditions, varying the leaving group, solvent, base and temperature. In all the cases we obtained a complicated mixture of compounds, showing polyalkylation of the amino nitrogens. Moreover, the isolation of the desired products was additionally complicated by the formation of foamy crudes of reaction during the work-up procedures. Considering these results we envisioned to use a reductive amination reaction (Scheme 1) as a

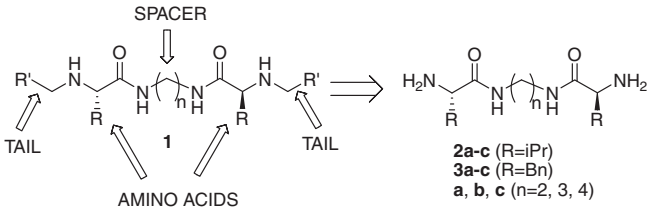
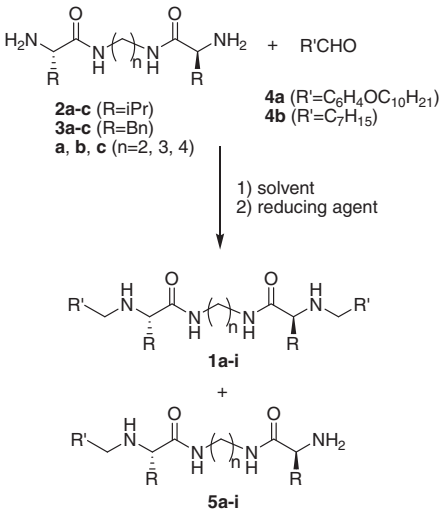


Figure 1. Design of the GAP molecules.

* Corresponding authors. Tel.: +34 934006100x1381; fax: +34 932045904 (I.A.); tel.: +34 964728239; fax: +34 964728214 (S.V.L.).
E-mail addresses: ignacio.alfonso@iqac.csic.es (I. Alfonso), luiss@qio.uji.es (S.V. Luis).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.07.146



Scheme 1.

Table 2
Self-assembled nanostructures observed in the SEM micrographs of samples grown from different solvents

Entry	Compound	$CHCl_3$ (width in μm)	MeOH (width in μm)
1	**1a**	'Worm' fibrils (~0.2)	Not homogeneous[a]
2	**1b**	Not observed	Not observed
3	**1c**	Not observed	Fibres (~0.10–0.2)
4	**1d**	Not observed	Not observed
5	**1e**	Not observed	'Worm' fibrils (~0.1)
6	**1f**	Not observed	Not observed
7	**1g**	Tubes (~0.2–0.4)	Fibres (~1–2)
8	**1h**	Tapes (~10)	Tapes (~5)
9	**1i**	Not observed	Fibres (~1–3)

[a] The SEM micrographs showed the formation of some fibres, although they do not appear uniformly on the whole surface.

selective method for the monoalkylation of the two primary amine nitrogens.[6,7] First, we used bis(amidoamine) **2a** and aldehyde **4a** as a model system (Table 1, entries 1–5). Surprisingly, the conventional reaction conditions for this process (formation of the imine

Table 1
Syntheses of GAPs by reductive amination reaction

Entry	Diamine (*n*, R)	Aldehyde (R′)	Solvent	Reducing agent	Yield **1**[a] (%)	Yield **5**[a] (%)
1	**2a** (2, *i*Pr)	**4a** ($C_6H_4OC_{10}H_{21}$)	MeOH	$NaBH_4$	8 (**1a**)	17 (**5a**)
2	**2a** (2, *i*Pr)	**4a** ($C_6H_4OC_{10}H_{21}$)	CH_2Cl_2	$NaBH_4$	22 (**1a**)	33 (**5a**)
3	**2a** (2, *i*Pr)	**4a** ($C_6H_4OC_{10}H_{21}$)	CH_3CN	$NaBH_4$	45 (**1a**)	33 (**5a**)
4	**2a** (2, *i*Pr)	**4a** ($C_6H_4OC_{10}H_{21}$)	CH_3CN	BH_3·Py	27 (**1a**)	12 (**5a**)
5	**2a** (2, *i*Pr)	**4a** ($C_6H_4OC_{10}H_{21}$)	$CHCl_3$	BH_3·Py	63 (**1a**)	5 (**5a**)
6	**2b** (3, *i*Pr)	**4a** ($C_6H_4OC_{10}H_{21}$)	$CHCl_3$	BH_3·Py	68 (**1b**)	15 (**5b**)
7	**2c** (4, *i*Pr)	**4a** ($C_6H_4OC_{10}H_{21}$)	$CHCl_3$	BH_3·Py	66 (**1c**)	19 (**5c**)
8	**3a** (2, Bn)	**4a** ($C_6H_4OC_{10}H_{21}$)	$CHCl_3$	BH_3·Py	66 (**1d**)	21 (**5d**)
9	**3b** (3, Bn)	**4a** ($C_6H_4OC_{10}H_{21}$)	$CHCl_3$	BH_3·Py	61 (**1e**)	19 (**5e**)
10	**3c** (4, Bn)	**4a** ($C_6H_4OC_{10}H_{21}$)	$CHCl_3$	BH_3·Py	74 (**1f**)	23 (**5f**)
11	**2a** (2, *i*Pr)	**4b** (C_7H_{15})	$CHCl_3$	BH_3·Py	26 (**1g**)	—[b]
12	**2b** (3, *i*Pr)	**4b** (C_7H_{15})	$CHCl_3$	BH_3·Py	21 (**1h**)	—[b]
13	**2c** (4, *i*Pr)	**4b** (C_7H_{15})	$CHCl_3$	BH_3·Py	32 (**1i**)	—[b]

[a] Isolated yields.
[b] Not observed.

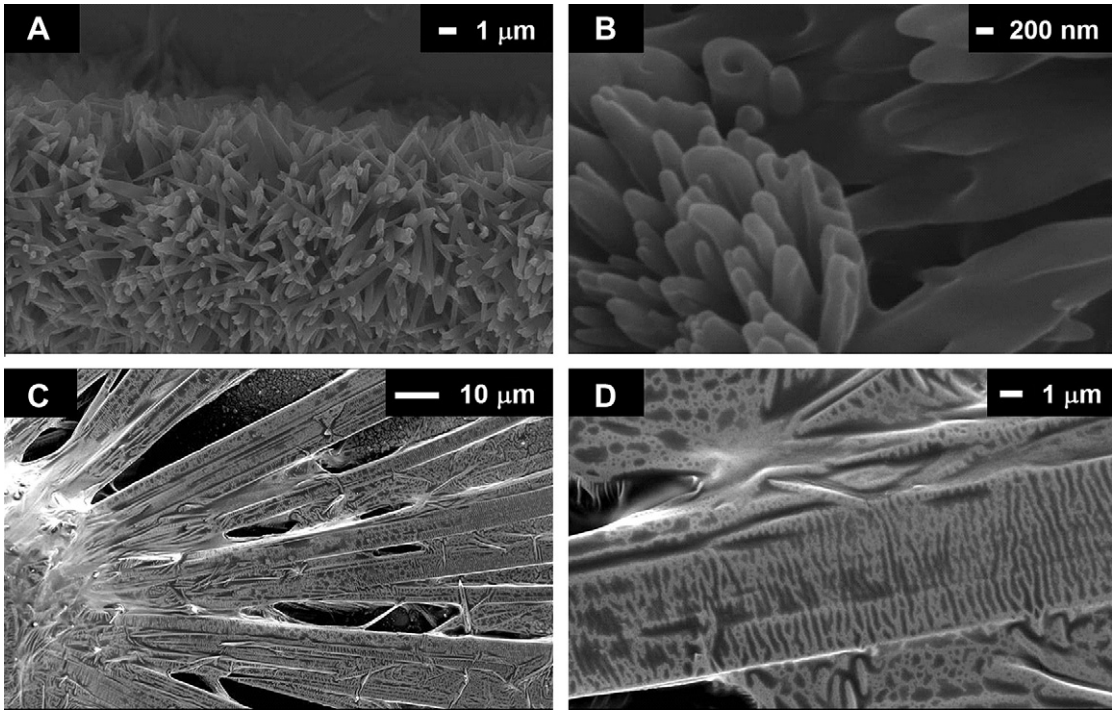


Figure 2. SEM micrographs of (A and B) **1g** and (C and D) **1h** compounds grown from chloroform solutions. Two different magnifications are shown with the corresponding scale bars for every picture.

in methanol and subsequent reduction with $NaBH_4$) rendered poor yield, and a mixture of the intended dialkylated (**1**) and the undesired monoalkylated (**5**) products (Table 1, entry 1). The use of less polar (entry 2) or non-protic polar solvents (entry 3) slightly increased the overall yield but still with low selectivity towards the dialkylated product. The observed low yields were not due to the low solubility of $NaBH_4$ in non-protic solvents as confirmed by the results obtained with borane pyridine complex (BH_3·Py) as the reducing agent (entry 4).[8]

Since the reaction comprises a one-pot two-steps process, we decided to study the formation of the imine intermediate in different solvents by NMR. The ^{1}H NMR spectra (500 MHz, 303 K) of **2a** with a slight excess of **4a** after equilibration (24 h) rendered a proportion of the corresponding mono- and diimine of 50:50 (in CD_3OD) or 20:80 (in CD_3CN). However, when performing the same condensation in a less polar solvent like chloroform, the mixture showed a quantitative conversion to the diimine. Thus, the formation of the desired intermediate seems to be favoured by non-polar solvents. We decided to use these conditions for the reaction, by shifting to BH_3·Py as reducing agent, due to the very poor solubility of $NaBH_4$ in $CHCl_3$. Satisfyingly, using this combination of solvent and reductant (entry 5), we obtained very good yield and selectivity, after the work-up and the chromatographic purification processes.[9] The reaction can be carried out from bis(amidoamines) having spacers with different lengths (entries 6 and 7), and both aliphatic (entries 5–7) and aromatic side chains (entries 8–10) with good yields and reasonable selectivity. However, when doing the reaction with aliphatic aldehydes (entries 11–13) the yields were lower. Since we did not observe starting materials or the corresponding monoalkylated derivatives, we ascribed the lower yields to problems in the purification process, because compounds **1g–i** showed a high trend to self-aggregate (see below) and thus,

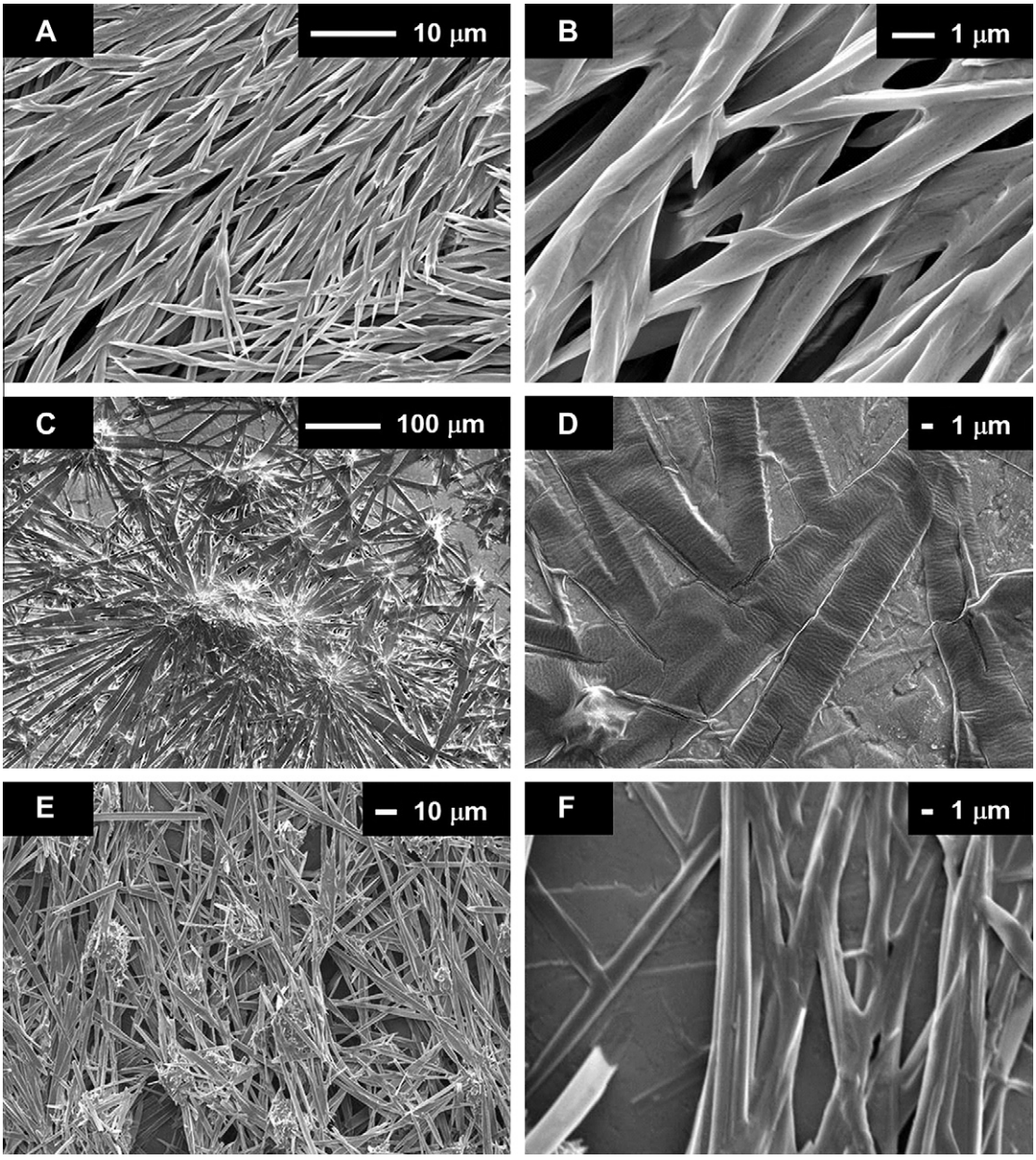


Figure 3. SEM micrographs of (A and B) **1g**, (C and D) **1h** and (E and F) **1i** compounds grown from methanol solutions. Two different magnifications are shown with the corresponding scale bars for every picture.

lower solubility in organic solvents (both polar and non-polar). Despite the moderate isolated yields observed with these compounds, the complete selectivity towards the dialkylated products made the reaction a useful synthetic applicability.

Preliminary study of the self-assembling behaviour of the synthesized GAPs has also been carried out. The morphology of the obtained self-assembled nanostructures was initially studied by scanning electron microscopy (SEM). Since the compounds are amphiphilic, we assayed different environments from non-polar (chloroform) to polar (MeOH) medium. Samples for SEM were prepared by dissolving the corresponding compound in a given solvent (~1–3 mg/mL), placing the solution directly onto the sample holder and slowly evaporating at room temperature. A summary of the results obtained for the compounds **1a**–**i** is shown in Table 2. Different nanostructures were observed, such as worm-like fibrils (entries 1 and 5), hollow tubes (entry 7), fibres (entries 3, 7 and 9) or tapes (entry 8). As a general trend, the self-assembling is more effective in MeOH than in chloroform. Besides, the Val derivatives are more efficient that the Phe derivatives, which can be explained by the shielding effect of intermolecular interactions with aromatic side chains, previously observed for structurally related compounds.[10] With regards to the length of the spacer, no obvious trends were observed.

As previously commented, the GAPs bearing exclusive aliphatic tails showed a higher tendency to aggregate (entries 7–9). Ultrastructure analysis from chloroform solutions showed that **1g** self-assembled in hollow tubes (Fig. 2a and b) while **1h** aggregated in large straight tapes (Fig. 2c and d). Since **1g** and **1h** only differ in one methylene of the aliphatic spacer, the observed differences can be ascribed to distinct relative disposition of the H-bonding groups in both compounds, which could dictate the geometry of the established intermolecular interactions.

Studies performed from a polar medium (MeOH) with the same compounds (Fig. 3) showed the formation of fibres for **1g** and **1i**, while tapes for **1h**. These data suggest that, in the case of the GAPs with exclusive aliphatic tails, the self-aggregation process is

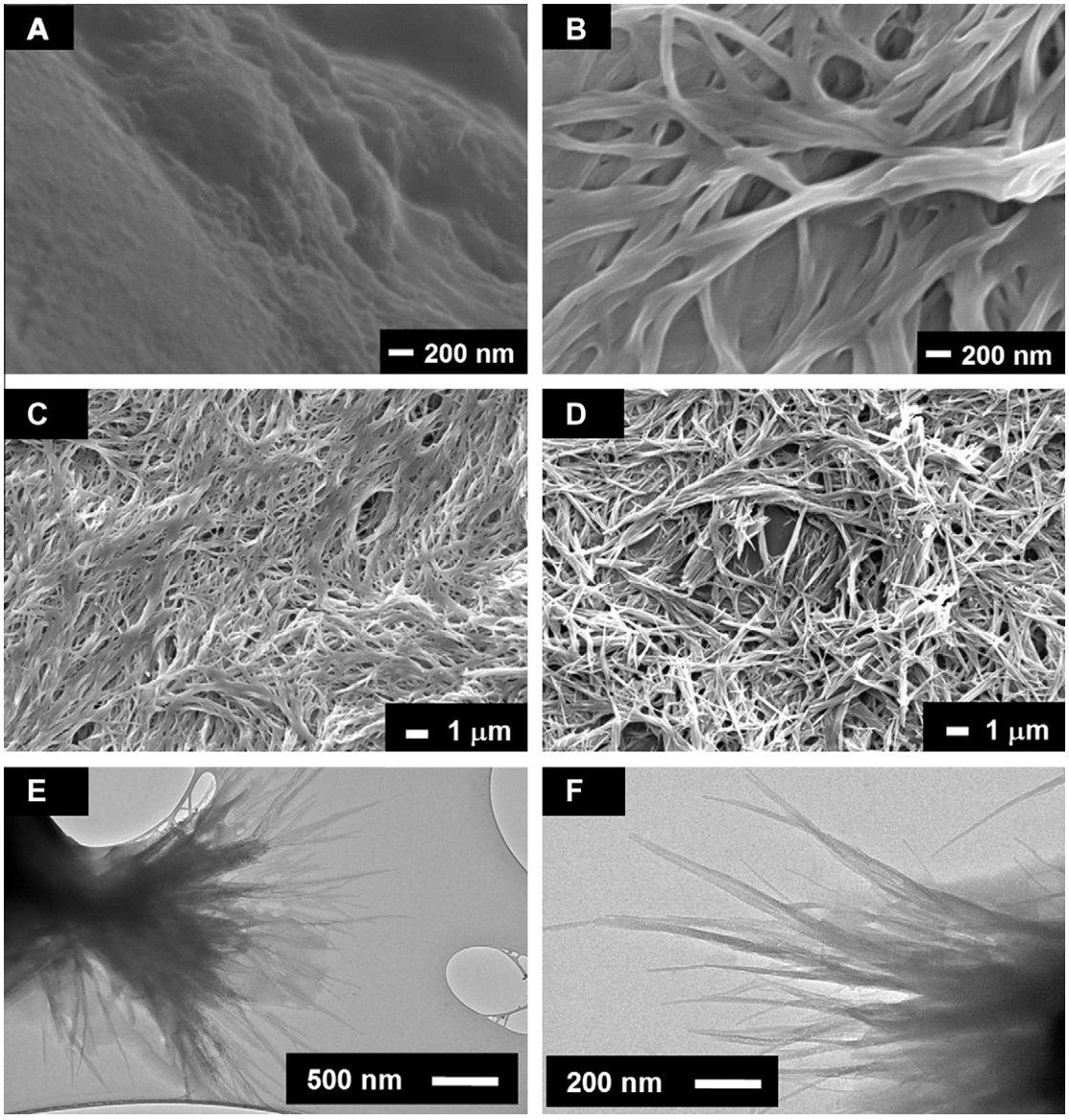


Figure 4. SEM micrographs of **1c** grown from (A) chloroform and (B and C) methanol and (D) 2:1 methanol/water solutions. (E and F) Unstained TEM micrographs of samples like in (B). Scale bars are shown for every picture.

efficient in different environments. Besides, the shape of the nanostructures suggested the establishment of the intermolecular interactions along a preferred direction.

Interestingly, the Val derivatives with the butylenic spacer showed differential self-aggregation abilities in solvents of different polarity (see entries 3 and 9 in Table 2). Thus, for instance, the SEM study of samples of **1c** grown from chloroform showed the lack of self-assembled nanostructures (Fig. 4a), while the same compound from methanol showed nanometre-sized fibres (Fig. 4b). The width of the fibres were in the range of 100–200 nm and they were grouped in bunches of several micrometres (Fig. 4c). The morphology and size of the fibres of **1c** did not substantially change by using 2:1 methanol/water as the solvent (Fig. 4d), although we observed a more efficient and homogenous coverage of the surface. These results suggest that the hydrophobic interactions between the tails in **1c** were playing an important role in the self-assembling process. Additionally, TEM analysis of unstained samples (Fig. 4e–f) confirmed the formation of fibrous nanostructures. The different behaviour of some of these GAPs in solvents of different polarity is especially interesting for the future preparation of a second generation of self-assembling pseudopeptides able to respond to external stimuli.

In order to get deeper structural information of **1c** in solution, we studied its ^{1}H NMR spectra both in polar and in non-polar solvent, below the critical concentration for the aggregation (Fig. 5). The chemical shift (>7.00 ppm) and temperature dependence ($\Delta\delta$NH/ΔT = −3.5 ppb/K) of amide NH protons signal in $CDCl_3$ suggested the presence of partially H-bonded amide groups. The high chemical shift values of protons at α and β positions are also in line with this proposal. Besides, the methylene vicinal to the amide group (A in Fig. 5) showed chemical non-equivalence [$\Delta\delta$ ($H_{A/A'}$) = 0.052 ppm at 294 K] which was decreased upon heating [$\Delta\delta$ ($H_{A/A'}$) = 0.038 ppm at 323 K]. All these observations supported that the pseudopeptidic moiety is intramolecularly H-bonded in a relatively rigid conformation in chloroform. However, when acquiring the ^{1}H NMR spectrum in methanol, the signals corresponding to the protons from the pseudopeptidic moiety (α, β, γ and A) moved up-field, while those from the hydrophobic tails did not significantly change. More importantly, the methylenes in A position lost their chemical non-equivalence, appearing as a broad triplet. These observations were consistent with the breaking of the intramolecularly H-bonded pseudopeptidic structure, leading to an unfolded conformation in solution. Thus, in non-polar medium, the molecule tends to fold into a turn/hairpin conformation while in MeOH, the interactions with the solvent would produce an unfolding of the pseudopeptidic moiety to an extended flexible conformation. With the aim of connecting this soluble structure with the self-assembling process, the formation of the nano-fibres of **1c** was studied by ATR FT-IR spectroscopy. Thus, we followed the evolution of representative bands during the concentration of the sample by slow evaporation of the solvent directly on the ATR sample holder (Fig. 6). Accordingly, we monitored the amide A (N–H stretching at 3100–3500 cm^{-1}), the amide I (C=O stretching at 1600–1700 cm^{-1}) and the aliphatic region (CH stretching at 2800–3000 cm^{-1}). In methanolic solution, all the bands were relatively broad, suggesting the presence of a mixture of different conformations in solution. The slow evaporation of the solvent produced a gradual sharpening of the bands, which implies a conformational ordering of the molecules. The final values in the dried fibres were 3300 cm^{-1} (amide A), 1636 cm^{-1} (amide I), 2921 cm^{-1} (ν_{ass} C–H) and 2853 cm^{-1} (ν_{sym} C–H), showing the formation of strongly H-bound β-stacks[11] of the pseudopeptidic core and a crystal-liquid phase[12] for the aliphatic tails. These spectroscopic evidences highlighted the importance of both polar (H-bonding) and non-polar interactions in the self-assembling process.

In summary, herein we report on the synthesis of new GAPs by a reductive amination reaction. Preliminary studies suggest that

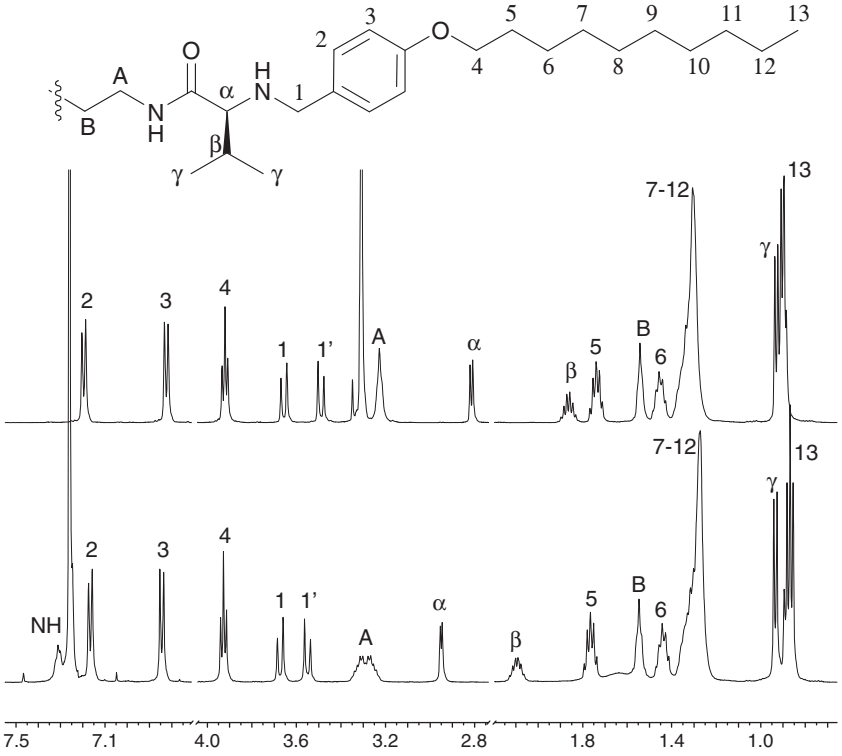


Figure 5. ^{1}H NMR spectra of **1c** (500 MHz, 303 K) in $CDCl_3$ (lower trace) and CD_3OD (upper trace).

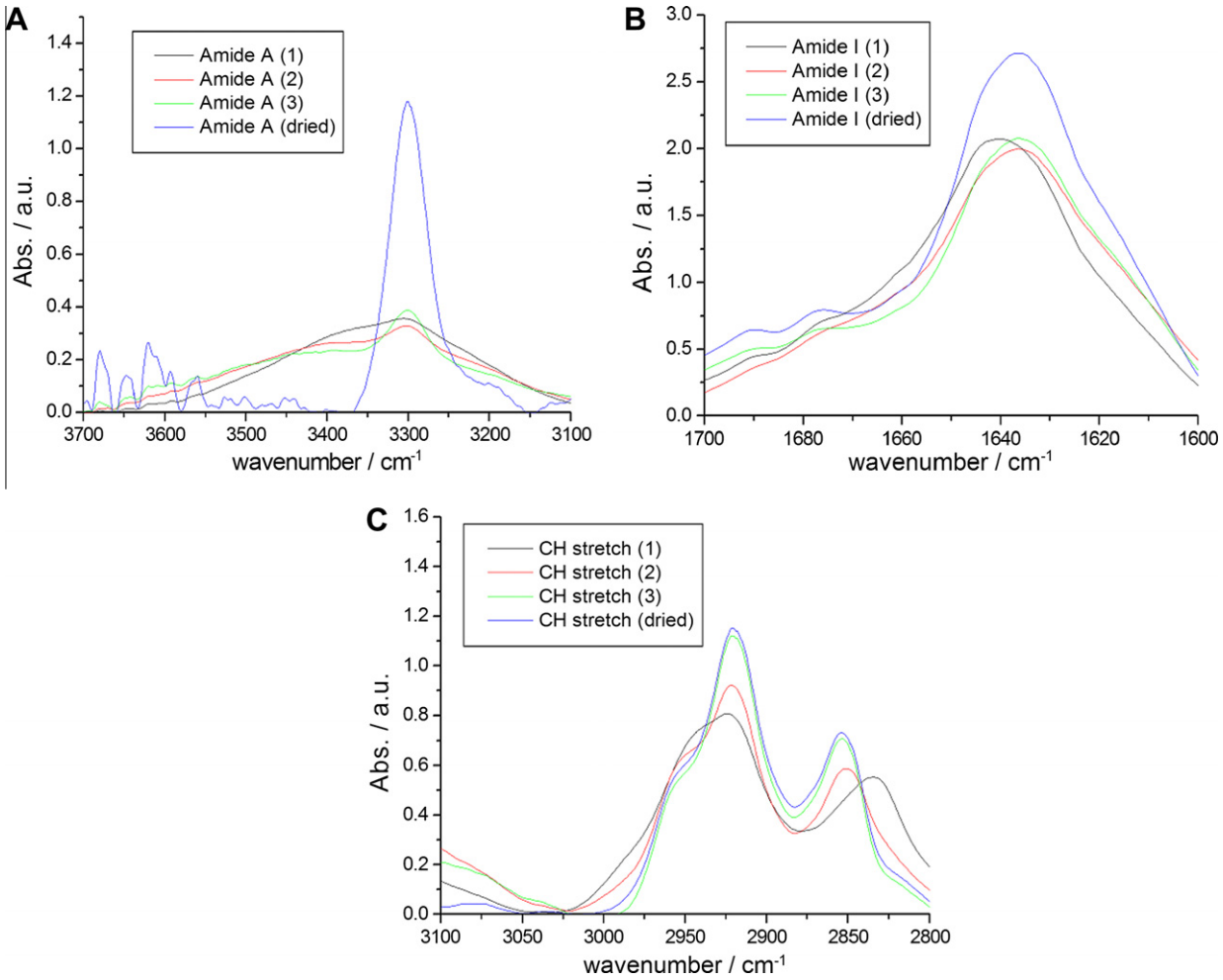


Figure 6. Evolution (1–3) of the ATR FT-IR spectra of **1c** form MeOH solutions to dried fibres obtained upon slow evaporation. Selected bands are shown for (A) amide A, (B) amide I and (C) C–H stretching regions.

the formation of self-assembled nanostructures can be accomplished by a delicate tune of the polar and non-polar intermolecular interactions, in some cases allowing the control of the process by changing the polarity of the medium. Besides, we have found that some structural features are needed for the modulation of the self-assembling properties. The Val derivative with a relatively flexible spacer and bearing two hydrophobic tails does not self-assemble in non-polar solvent but self-assemble in fibres from a polar medium. This fact pointed these systems as good candidates for further development of stimulus responsive self-assembling nanostructures. Studies on the effect of these and other structural variables are undergoing in our laboratories.

Acknowledgements

This work was supported by the Spanish Ministry of Science and Innovation (CTQ2009-14366-C02). J.R. thanks MICINN for personal financial support (FPU fellowship). We also thank Bogdan Duma for his helpful assistance.

Supplementary data

Supplementary data (experimental and synthetic procedures, full spectroscopic characterization of **1a–i** and **5a–f**, as well as additional SEM micrographs) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.146.

References and notes

1. (a) Pramod, P.; Thomas, K. G.; George, M. V. *Chem. Asian J.* **2009**, *4*, 806–832; (b) Lehn, J. M. *Science* **2002**, *295*, 2400–2403; (c) Schneider, H.-J.; Yatsimirsky, A. *Principles and Methods in Supramolecular Chemistry*; Wiley: Chichester, 2000; (d) Steed, J. W.; Atwood, J. L. *Supramolecular Chemistry*; Wiley: Chichester, 2000; (e) Lehn, J.-M. *Supramolecular Chemistry*; VCH: Weinheim, 1995.
2. For some recent reviews, see: (a) Cavalli, S.; Albericio, F.; Kros, A. *Chem. Soc. Rev.* **2010**, *39*, 241–263; (b) Cui, H.; Webber, M. J.; Stupp, S. I. *Pept. Sci.* **2010**, *94*, 1–18; (c) Cherny, I.; Gazit, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 4062–4069; (d) Ulijn, R. V.; Smith, A. M. *Chem. Soc. Rev.* **2008**, *37*, 664–675; (e) Gazit, E. *Chem. Soc. Rev.* **2007**, *36*, 1263–1269; (f) Zhaoa, X.; Zhang, S. *Chem. Soc. Rev.* **2006**, *35*, 1105–1110.
3. (a) Cui, H.; Pashuck, E. T.; Velichko, Y. S.; Weigand, S. J.; Cheetham, A. G.; Newcomb, C. J.; Stupp, S. I. *Science* **2010**, *327*, 555–559; (b) Williams, R. J.; Smith, A. M.; Collins, R.; Hodson, N.; Das, A. K.; Ulijn, R. V. *Nat. Nanotech.* **2009**, *9*, 19–24; (c) Muraoka, T.; Koh, C.-Y.; Cui, H.; Stupp, S. I. *Angew. Chem., Int. Ed.* **2009**, *48*, 5946–5949; (d) Naskar, J.; Banerjee, A. *Chem. Asian J.* **2009**, *4*, 1817–1823; (e) Shera, J. N.; Sun, X. S. *Biomacromolecules* **2009**, *10*, 2446–2450; (f) Ghosh, S.; Verma, S. *Tetrahedron* **2008**, *64*, 6202–6208; (g) Lu, K.; Guo, L.; Mehta, A. K.; Childers, W. S.; Dublin, S. N.; Skanthakumar, S.; Conticello, V. P.; Thiyagarajan, P.; Apkarianc, R. P.; Lynn, D. G. *Chem. Commun.* **2007**, 2729–2731; (i) Ghosh, S.; Singh, S. K.; Verma, S. *Chem. Commun.* **2007**, 2296–2298.
4. (a) Alfonso, I.; Bru, M.; Burguete, M. I.; García-Verdugo, E.; Luis, S. V. *Chem. Eur. J.* **2010**, *16*, 1246–1255; (b) Alfonso, I.; Bolte, M.; Bru, M.; Burguete, M. I.; Luis, S. V. *CrystEngCommun* **2009**, *11*, 735–738; (c) Becerril, J.; Burguete, M. I.; Escuder, B.; Galindo, F.; Gavara, R.; Miravet, J. F.; Luis, S. V.; Peris, G. *Chem. Eur. J.* **2004**, *10*, 3879–3890.
5. Becerril, J.; Bolte, M.; Burguete, M. I.; Galindo, F.; García-España, E.; Luis, S. V.; Miravet, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 6677–6686.
6. Salvatore, R. N.; Yoon, C. H.; Jung, K. W. *Tetrahedron* **2001**, *57*, 7785–7811.
7. (a) Alfonso, I.; Bolte, M.; Bru, M.; Burguete, M. I.; Luis, S. V. *Chem. Eur. J.* **2008**, *14*, 8879–8891; (b) Alfonso, I.; Bolte, M.; Bru, M.; Burguete, M. I.; Luis, S. V.; Rubio, J. *J. Am. Chem. Soc.* **2008**, *130*, 6137–6144.

8. Campbell, F.; Kilner, C. A.; Wilson, A. J. *Tetrahedron Lett.* **2010**, *51*, 1361–1362.
9. *General procedure for the reductive amination reaction, exemplified for the preparation of* **1a**: Pseudopeptidic bis(amidoamine) **2a** (96.5 mg, 0.374 mmol) was dissolved in 4 mL of $CHCl_3$ and the solution was placed inside a flask under nitrogen atmosphere. 4-Decyloxybenzaldehyde **4a** (213.0 μL, 202.3 mg, 0.748 mmol) was dissolved in 3 mL of $CHCl_3$, this solution was added over the solution of **2a** and then, 1 mL of $CHCl_3$ were added until a final volume of 8 mL (0.05 M final concentration each). The mixture was stirred overnight, then a large excess of Py·BH_3 complex, 95% (395.6 μL, 363.9 mg, 4.01 mmol) was carefully added at 35 °C, and the mixture was allowed to react for 24 h before being hydrolyzed (concd HCl, to acidity) and evaporated to dryness. The residue obtained was dissolved in water, basified with 1 N NaOH, and extracted with $CHCl_3$. The combined organic layers were dried ($MgSO_4$) and evaporated in vacuum. The product was purified by flash chromatography on silica gel using CH_2Cl_2 as eluent, increasing slowly the polarity with MeOH and several drops of aqueous ammonia yielding **1a** (firstly eluted) and **5a** (secondly eluted). Compound **1a**: 63% yield; mp 95–104 °C; $[\alpha]_D^{25}$ −27.0 (*c* 0.01, $CHCl_3$); IR (ATR) 3303, 2921, 2851, 1641, 1555, 1513 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.79 (m, 18H), 0.86 (m, 24H), 1.23 (m, 4H), 1.38 (s, 2H), 1.48 (m, 4H), 1.7 (m, 2H), 2.01 (m, 2H), 2.87 (m, 4H), 3.35 (dd, 2H, *J* = 5.2, 8.1 Hz), 3.45 (dd, 2H, *J* = 5.4, 8.2 Hz), 3.61 (t, 4H, *J* = 6.6 Hz), 6.77 (d, 4H, *J* = 6.7 Hz), 7.10 (d, 4H, *J* = 7.1 Hz), 7.53 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.3, 18.0, 19.8, 22.9, 26.3, 29.5, 29.8, 29.9, 31.5, 32.1, 39.6, 53.1, 68.0, 68.3, 114.8, 129.5, 131.7, 158.7, 174.7; HRMS (ESI-TOF)$^+$ calcd for $C_{46}H_{78}N_4O_4$ $(M+H)^+$: 751.6101; found 751.6102. Anal. calcd for $C_{46}H_{78}N_4O_4{\cdot}H_2O$: C, 71.93; H, 11.17; N, 6.70. Found: C, 71.83; H, 10.98; N, 6.90. Compound **5a**: 5% yield; mp 78–82 °C; $[\alpha]_D^{25}$ −2.5 (*c* 0.01, $CHCl_3$); IR (ATR) 3299, 2958, 2852, 1631, 1553, 1513, 1467, 1244 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.81 (d, 6H, *J* = 6.7 Hz), 0.87 (m, 3H), 0.95 (d, 6H, *J* = 6.0 Hz), 1.30 (m, 12H), 1.43 (m, 2H), 1.65 (m, 2H), 1.76 (td, 1H, *J* = 6.6, 13.0 Hz), 2.08 (m, 1H), 2.25 (m, 1H), 2.96 (s, 1H), 3.19 (s, 1H), 3.40 (t, 4H, *J* = 12.5 Hz), 3.55 (d, 1H, *J* = 12.8 Hz), 3.69 (d, 1H, *J* = 11.4 Hz), 3.93 (t, 2H, *J* = 6.5 Hz), 6.84 (m, 2H), 7.19 (m, 2H), 7.61 (s, 2H), 7.69 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 16.4, 18.1, 19.7, 22.9, 26.3, 29.5, 29.6, 29.8, 31.0, 31.4, 32.1, 39.3, 39.8, 52.9, 60.4, 67.9, 68.3, 114.8, 129.6, 131.4, 158.8, 174.7, 175.1; HRMS (ESI-TOF)$^+$ calcd for $C_{29}H_{52}N_4O_3$ $(M+H)^+$: 505.4118; found 505.4114. Anal. calcd for $C_{29}H_{52}N_4O_3$: C, 69.01; H, 10.38; N, 11.10. Found: C, 68.85; H, 10.70; N, 11.43.
10. (a) Alfonso, I.; Bolte, M.; Bru, M.; Burguete, M. I.; Luis, S. V.; Vicent, C. *Org. Biomol. Chem.* **2010**, *8*, 1329–1339; (b) Alfonso, I.; Burguete, M. I.; Galindo, F.; Luis, S. V.; Vigara, L. *J. Org. Chem.* **2007**, *72*, 7947–7956; (c) Alfonso, I.; Burguete, M. I.; Luis, S. V. *J. Org. Chem.* **2006**, *71*, 2242–2250.
11. Kim, S. H.; Hartgerink, D.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1998**, *120*, 4417–4424.
12. Hull, M. C.; Cambrea, L. R.; Hovis, J. S. *Anal. Chem.* **2005**, *77*, 6096–6099.