Synthesis and Characterisation of Dimeric Bolaamphiphilic Dehydrodipeptides for Biomedical Applications

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Introduction

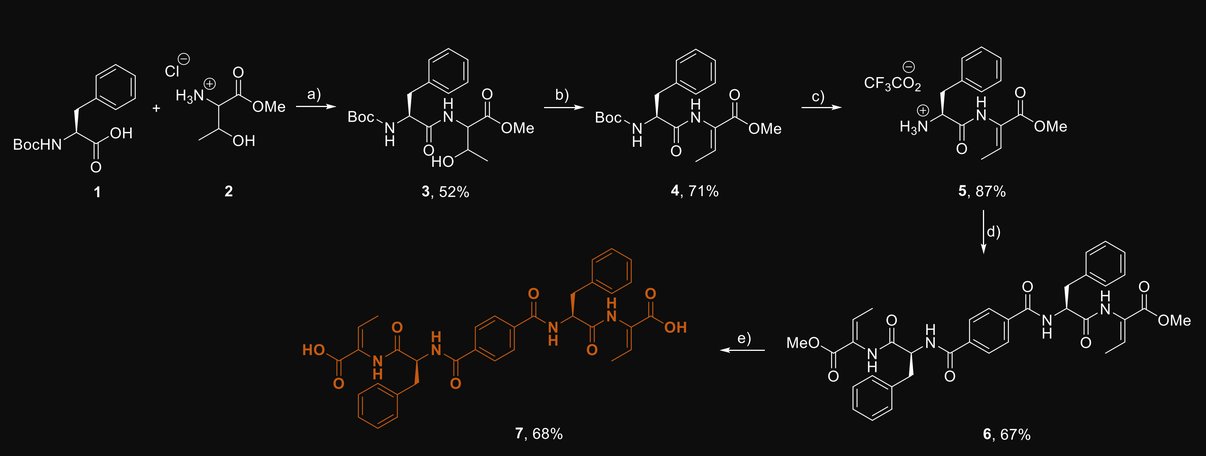
In this work we synthesized new dimeric bolaamphiphilic dehydrodipeptides, containing phenylalanine connected to a dehydroamino acid residue at the C-terminus. The *N*-terminus of the dipeptide was connected to both ends of a bifunctional central aromatic moiety, namely 1,4-benzenedicarboxylic acid and 1,3-benzenedicarboxylic acid, giving the compounds **7** and **12**, respectively.

The potential use of these new compounds as hydrogelators was evaluated. The results showed that these compounds synthesised behave as efficient molecular hydrogelators. The use of dehydroamino acids confers proteolytic stability to these hydrogels [1].

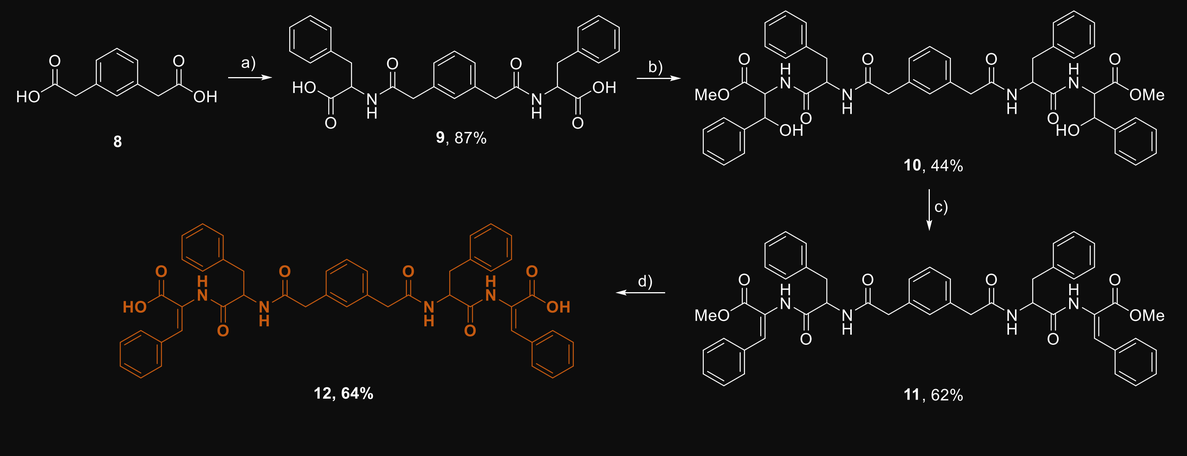
Supramolecular peptide-based hydrogels have potential applications in areas like tissue engineering, controlled release and drug delivery, nanofabrication and sensing, which are fundamental in biomedical research [2].

Results and discussion

Synthesis



Scheme 1: Synthesis of compound **7**. **a)** MeCN, Et_3N, HBTU; **b)** 1. Boc_2O, DMAP, dry MeCN, 2. TMG; **c)** TFA, rt; **d)** Terephtaloyl chloride, ET_3N, dry THF, N_2 atm, reflux, 80ºC; **e)** 1. NaOH, 1,4-dioxane, 2. $KHSO_4$.



Scheme 2: Synthesis of compound **12**. **a)** 1. DCC, NHS, DCM, 2. L-Phe-OH, $NaHCO_3$; **b)** DCC, HBOt, ET_3N, MeCN, H-DL-Phe-(β-OH)-OH; **c)** 1. Boc_2O, DMAP, dry MeCN, 2. TMG; **d)** 1. NaOH, 1,4-dioxane, 2. $KHSO_4$.

Hydrogels

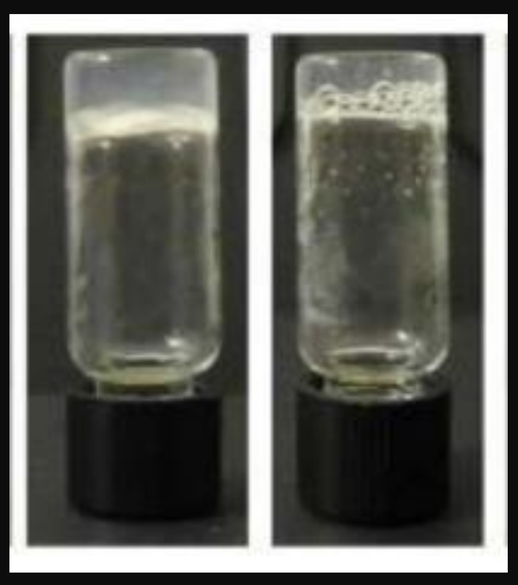


Figure 1: Optical images of hydrogels formed by hydrogelators **7** (left) and 12 (right).

Table 1: Optimized conditions for gelation of peptide **7** and **12**.

Compound	wt%	pH
7	0,8	6,0
12	0,3	6,2

Compound 12 is the most effective hydrogelator.

Scanning transmission electron microcopy (STEM)

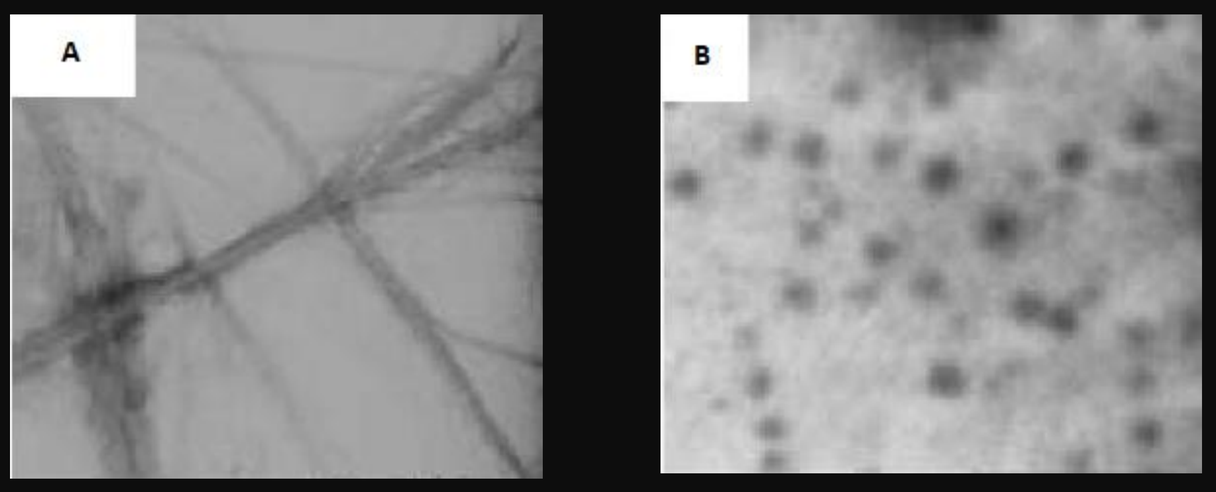


Figure 2: STEM images of the hydrogels formed by compounds 7 (A) and 12 (B).

Circular Dichroism Analysis

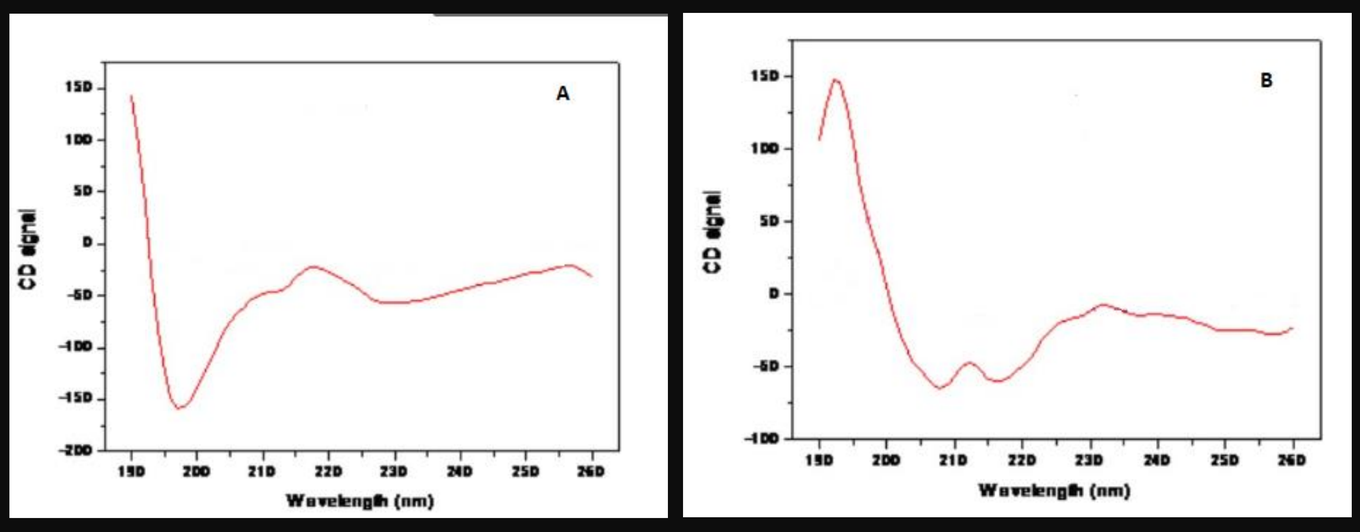


Figure 3: CD sprectra of hydrogelator **7** (A) and **12** (B).

Conclusions

- The results suggest that a space between the organic modifier and the dipeptide moiety could lead to lower critical gelation concentration (cgc), which happen with compound **12**.
- The hydrogel of compound **12** resulted in spherical aggregation patterns under the experimental conditions used for gel formation (Fig. 2-B).
- The CD spectrum for hydrogelator **12** (lower cgc – 0,3%) showed strong evidence of aggregation into a α-helical pattern (Fig. 3-B).

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References

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