

## Minimalist peptidomimetic cyclophanes as strong organogelators

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**L-Valine containing cyclophanes have been shown to gelate organic solvents leading to soft materials with a clear expression of their chirality at the supramolecular level.**

The design of systems capable of self-assembly into well-defined organized architectures is a topic of intense research. Among them, low molecular weight organic molecules have been shown to be capable of trapping large amounts of solvent resulting in the formation of strong gels constituted by fibrillar supramolecular networks reversibly assembled exclusively *via* non covalent interactions.<sup>1</sup>

Here we report how the minimalist peptidomimetic cyclophanes shown in Scheme 1 are able to gelate several organic solvents leading to soft materials made of reversible fibrillar structures, and how in some cases their molecular chirality is further expressed at the supramolecular level. Several examples of amino acid based organogelators, either linear or cyclic, have been reported in the literature.<sup>2,3</sup> However, to our knowledge, compounds **3a–c** are unique because of the ensemble of structural simplicity and preorganization that makes them good candidates for participating in self-assembling processes. One of the key features of macrocyclic compounds in regard to their participation in such processes is the increased preorganization of their interaction sites with respect to the acyclic analogues. This leads to more specific Van der Waals and H-bonding interactions that in the case reported here most likely contribute to the gelation process.

The preparation of compounds **3a–c** was carried out using well known peptide synthetic methodology. Thus, the benzyl-

oxycarbonyl protected L-valine was activated as the *N*-hydroxysuccinimidyl ester and coupled with the corresponding diamine. Deprotection of the amino groups led to compounds **2a–c** that were converted into macrocycles **3a–c** by coupling with 1,3-bis(bromomethyl)benzene in CH<sub>3</sub>CN using K<sub>2</sub>CO<sub>3</sub> as a base.<sup>4</sup>

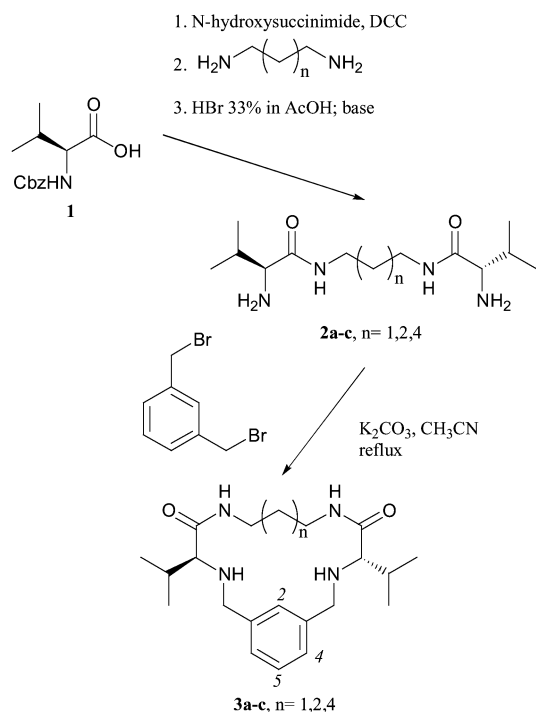
The gelation<sup>†</sup> behaviour of these small peptidomimetics was studied in a variety of solvents and some results are gathered in Table 1. As can be seen, these compounds are good organogelators, specially for aromatic solvents, forming transparent gels either by slow or fast cooling of their hot solutions (Fig. 1).

Scanning electron microscopy was used to study the microscopic structure of the gels. In most cases, an extended fibrillar network was observed (Fig. 2, top) but in some of them helical architectures could also be detected. The electron micrographs of the gel formed by compound **3a** in benzene revealed the presence of a mixture of isolated right-handed twisted ribbons of several micrometers of length and pitch, as well as cylindrical objects together with longer fibers (Fig. 2, bottom). When the gel was formed by fast cooling of the hot solution an increase in the number of helices was found together with a decrease in their size. It is known that twisted ribbons are often precursors in the growth of tubules.<sup>5</sup> According to this, the fast cooling could freeze the primitive helical states whereas slow cooling lead to the formation of long rod-like fibers

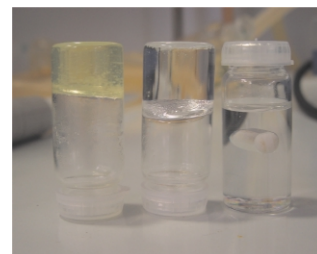
**Table 1** Gelation behaviour of **3a–c** in various solvents<sup>a</sup>

Solvent	<b>3a</b>	<b>3b</b>	<b>3c</b>
Benzene	0.3	0.5	0.3
Toluene	0.5	P	0.4
Xylene	0.5	P	1
Styrene	0.5	—	0.5
Anisole	0.5	0.5	0.3
Nitrobenzene	0.5	0.5	0.5
Acetone	P	P	P
THF	S	S	0.5
Isopropanol	S	S	S
n-Butanol	S	S	S
CH <sub>2</sub> Cl <sub>2</sub>	S	S	S
CHCl <sub>3</sub>	S	S	S
EtOAc	1	P	0.1
n-Hexane	NS	NS	NS

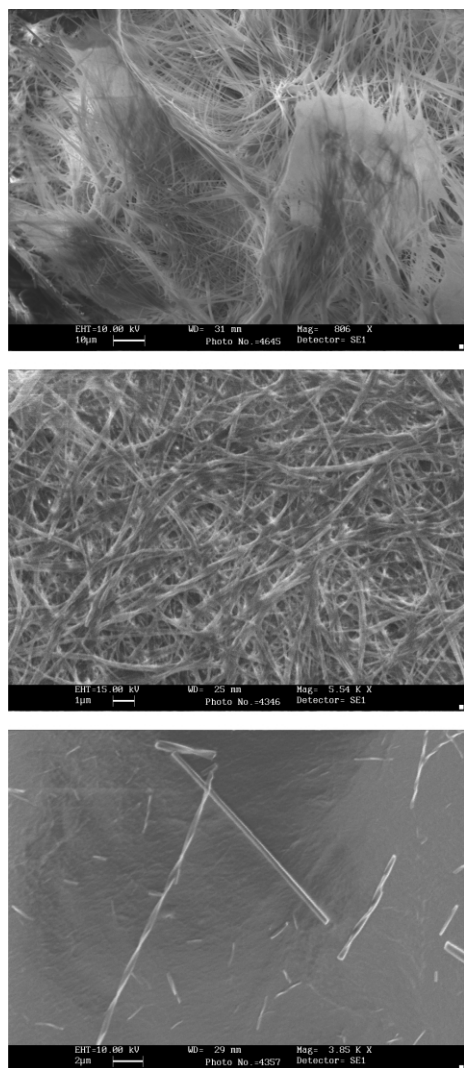
<sup>a</sup> Minimum gelator concentration, % wt; S: soluble; P: precipitated; NS: not soluble.



**Scheme 1**



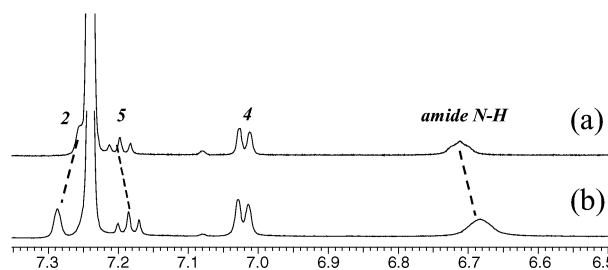
**Fig. 1** Gels formed by compound **3a** in nitrobenzene (left), EtOAc (middle) and benzene (right, the magnetic stirrer stands over the gel surface).



**Fig. 2** SEM pictures of the dried gels of **3c** in EtOAc (top), and in nitrobenzene (middle). Helices formed by **3a** in benzene (bottom).

together with a decrease in the number of helical aggregates seen.

$^1\text{H}$  NMR studies were carried out for solutions of 0.5–0.3% wt of compound **3a** in benzene- $\text{d}_6$  at different temperatures between 50 °C and 15 °C. The formation of transparent gels below *ca.* 22 °C was accompanied with the shift of the resonances for the aromatic protons in positions 2 and 5 as well as that of the amide signal (Fig. 3). When the spectra were recorded in the presence of 1  $\mu\text{L}$  of  $\text{CH}_2\text{Cl}_2$  as internal standard a decrease of *ca.* 25% of the relative intensity of the signals of compound **3a** was observed upon gel formation. This behaviour could be explained, as reported before for other organogelators,<sup>3</sup> as a consequence of the lowering in the concentration of the free gelator in the solution entrapped by the gel. The signals of the gelator molecules assembled in the gel network most likely broaden to the point of non-observability as a result of



**Fig. 3**  $^1\text{H}$  NMR of compound **3a** in benzene- $\text{d}_6$  (0.5% wt) as a gel at 20 °C (a), and in solution at 30 °C (b).

their long correlation times. Indeed, the molecules in the mobile part of the gel showed an increase in the  $^1\text{H}$  NMR longitudinal relaxation time ( $T_1$ ) when compared to solution, in agreement with the slower motion within the gel. The gelation process was also followed by IR spectroscopy which revealed an increase of the associated N–H band together with a shift in the C=O confirming the importance of H-bonding in the formation of the gel. Thus, the gel fibers could be formed by an infinite network of intermolecular H-bonds between the N–H and the carbonyl groups.

In conclusion, we have shown how small molecules with the required functional groups are able to organize themselves and the bulk solvent into reversible supramolecular architectures with a precise transcription of the molecular chirality at the supramolecular level. Currently we are investigating in detail the macroscopic and microscopic features of this family of organogelating chiral cyclophanes and related compounds, and envisaging future applications in the fields of molecular recognition and catalysis.

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## Notes and references

† Gelation procedure: the required amount of organogelator (3–10 mg) was dissolved in hot solvent (1 mL) and the gel was formed by cooling in an ice bath (fast cooling) or by standing at rt (slow cooling). Samples for SEM were prepared by slow drying of the gel followed by gold–palladium sputtering in a Polaron SC7610 Sputter Coater from Fisons Instruments. Scanning electron micrographs were taken using a LEO 440I spectrometer equipped with a digital camera.

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