Understanding the Expression of Molecular Chirality in the Self-Assembly of a Peptidomimetic Organogelator

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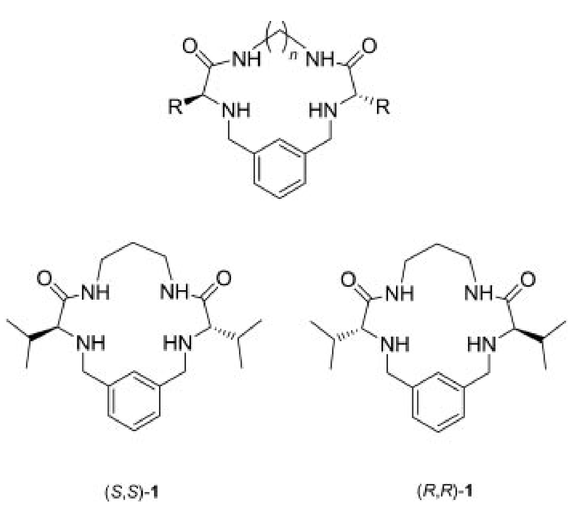
The expression of molecular chirality during the self-assembly of an amino-acid-based macrocyclic organogelator (**1**) has been studied. The gelation behaviour of enantiopure samples, as well as mixtures of both enantiomers, of this compound have been studied and important differences have been found between them. For example, the enantiopure samples form gels whereas the racemates does not. Electron microscopy reveals the formation of helicoidal fibers of opposite handedness in the gels formed by pure enantiomers, whereas only straight ribbons are found in the racemate and most of the nonenantiopure mixtures. X-ray powder diffraction shows an enantiospecific self-assembly in the mixtures that indicates the formation of enantiopure aggregates in all cases. These results are rationalized by considering the influence of the aggregates size on the gelation ability as well as the chirality expression at the supramolecular level.

Introduction

The expression of molecular chirality at the supramolecular level is present in nature and has been one of the major issues in supramolecular chemistry.[1,2] There are many examples of synthetic systems (e.g. surfactants and amphiphilic systems among others) where a fine tuning of the molecular structure leads to a controlled macroscopic chirality.[3] In this field, spontaneous, enantioselective self-assembly is nowadays a major goal that was set more than 100 years ago with the spontaneous resolution of crystals discovered by Pasteur.[4] Although most of the examples reported since then deal with solid-state structures, some examples of spontaneous self-association in solution have been reported recently, such as the formation of homochiral cyclic dimers and double-rosette assemblies or even large homochiral supramolecular assemblies.[5]

Organogels, which are formed by the entanglement of a network of polycrystalline fibers, can be considered as an intermediate state between the solution and crystal states. Several studies have reported the influence of the chirality of the organogelator on the gelation ability,[6,7] and some of these compounds have been widely used to transfer their chiral information into nanostructured inorganic materials such as silica in order to obtain valuable, new materials such as chiral stationary-phases or enantiospecific catalytic media.[8] However, spontaneous resolution of racemic organogelators has only been reported in a very few cases.[9]

Recently, we have studied the self-assembly features of a family of small peptidomimetic cyclophanes, derived from natural L-amino acids, such as those depicted in Scheme 1.[10] We have shown that some of them are able to form one-dimensional arrays of H-bonds in aromatic organic solvents, which give rise to the formation of columns that further assemble into either crystalline materials or physical gels. We observed by SEM that some of the gels formed by compound (*S*,*S*)-**1** in organic solvents contain right-handed helicoidal supramolecular aggregates.



Scheme 1

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In this paper we study the relationship between the chirality of the organogelator and that of the supramolecular aggregates formed. For this purpose we have prepared the enantiomer of the former compound [(*R*,*R*)-**1**] and we have compared its gelation behavior with that reported for (*S*,*S*)-**1** as well as that of different mixtures of both.

Results and Discussion

Compound (*R*,*R*)-**1** forms gels in the same solvents and conditions as those previously reported for its antipode (*S*,*S*)-**1**. Thus, these compounds are able to form gels in aromatic organic solvents as well as in ethyl acetate at concentrations of about 0.5 wt.-%. However, when we studied the racemic mixture of **1** in such solvents no gels were formed in any case; fibrilar precipitates were obtained instead. Intrigued by this fact, we decided to investigate the aggregation behavior of different mixtures of both enantiomers in benzene. First, a racemic mixture with a global concentration of 0.5 wt.-% in benzene was studied. Gelation was not accomplished either by spontaneous cooling to room temperature or by faster cooling (putting the sample in an ice bath). The next step was to increase the enantiomeric excess of (*S*,*S*)-**1** in the mixture whilst keeping the overall concentration constant. In these cases, we did not observe gel formation until the enantiomeric ratio was higher than 85:15. A racemate with an overall concentration of 1 wt.-%, which ensures that both enantiomers are present at their critical gel concentration, was also studied; even under these conditions no gel was obtained. However, in this case, the formation of an incipient weak gel could be observed upon fast cooling of the hot solution to –80 °C.

Electron Microscopy

Scanning electron microscopy was used to investigate the transcription of the molecular chirality at the nanoscopic level. Since (*S*,*S*)-**1** has been shown to form right-handed helices in benzene, it was not surprising that its antipode (*R*,*R*)-**1** contains helicoidal fibers of opposite handedness in its benzene gel (Figure 1). However, the electron micrographs of the viscous precipitate found for the racemate revealed the presence of straight, shorter fibers and the com-

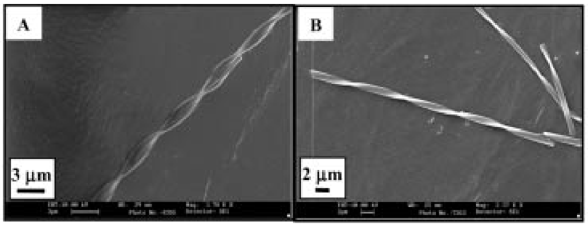

Figure 1. Scanning electron micrographs showing the detail of the helicoidal fibers found in the benzene gels of compounds (*S*,*S*)-**1** (A) and (*R*,*R*)-**1** (B)

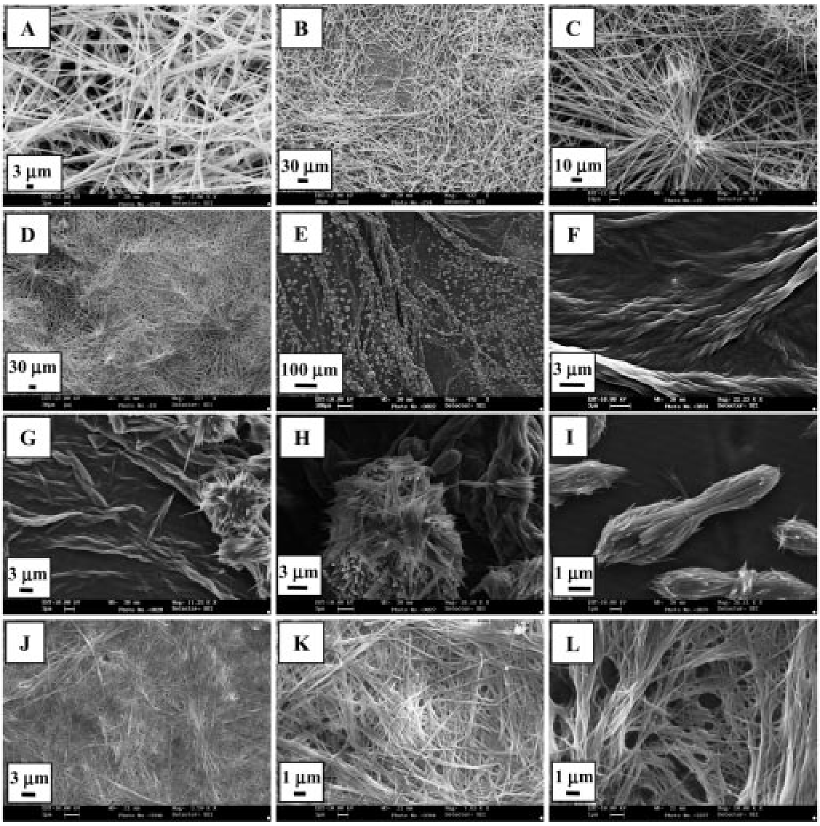

Figure 2. Scanning electron micrographs for the xerogels of mixtures of (*S*,*S*)-**1** and (*R*,*R*)-**1** in benzene: (A, B) 50:50, (C, D) 80:20 and (E–I) 95:5 at room temperature; (J–L) 50:50 at –80 °C

plete absence of helicoidal aggregates (see A and B in Figure 2).[11] The nonracemic mixtures show an increase in the length of the fibers together with a higher degree of physical crosslinking of them, as can be seen by the appearance of the fiber junction points (C,D in Figure 2). In the case of the 95:5 mixture, the presence of two clearly different domains of aggregates can be observed (E in Figure 2). The main component of the sample contains bundles of fibers hundreds of micrometers long, which are formed by the coiling of smaller-sized twisted fibrils (F,G in Figure 2). The minor component appears spread over the first and is made up of flat ribbons less than 10 µm long that are stuck together to form nest-like aggregates (H,I in Figure 2). The electron micrographs of the xerogel made from the weak gel obtained at –80 °C reveal the presence of a fibrilar entangled network typical of a gel (J–L in Figure 2).

Wide-Angle X-ray Powder Diffraction

Powder diffraction studies were undertaken in order to gain further information on the crystalline nature of the gels as well as the nonjellified mixtures. As described before, the benzene gel of compound (*S*,*S*)-**1** shows a hexagonal packing of the columnar assemblies.[10b] Remarkably, the wide-angle diffraction pattern of the racemic precipitate is similar to that of the xerogel of pure (*S*,*S*)-**1** in benzene; namely, a similar molecular arrangement is present in both crystalline materials (Figure 3).

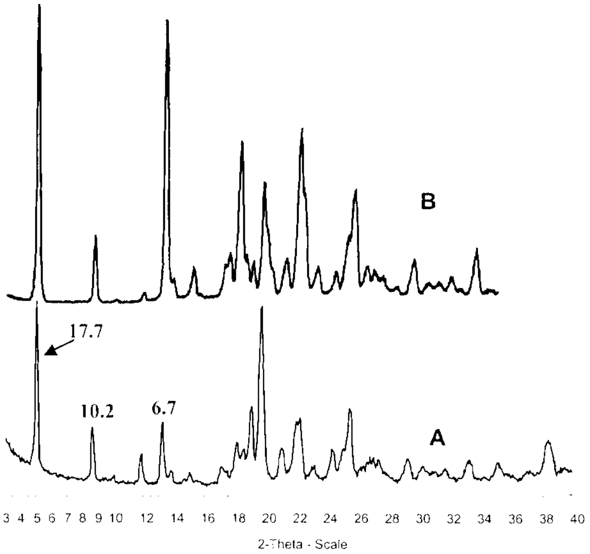

Figure 3. X-ray powder diffractograms of the xerogels obtained for (A) (*S*,*S*)-**1** and (B) a racemate of **1**; spacing distances in angstroms

Discussion

The lack of gelation by racemate gelators has been previously reported by other authors, and has been explained by the so-called "chiral bilayer effect", which was introduced by Fuhrhop to rationalize why pure enantiomers form gels whereas racemates of amphiphilic gelators tend to crystallize instead.[12] The general validity of this effect in organic solvents has been questioned,[13] and amphiphilic racemates showing better gelling properties than the pure enantiomer have also been reported.[6c,6e] However, the present case does not fit with the examples reported of this effect, since it does not deal with facially amphiphilic molecules that tend to organize into bilayers. Thus, the macroscopic changes observed for the racemate should be due to a different reason.

A systematic study of the self-assembly features of compound (*S*,*S*)-**1** and other related compound has been reported recently.[10] There, we showed that these compounds self-assemble in a hierarchical manner that involves several steps starting from the initial intermolecular H-bonding. We found a strong dependence between the molecular structure and the ultimate self-assembly properties. Thus, some of them formed gels, whereas in other cases crystalline precipitates were formed instead. In the case of (*S*,*S*)-**1**, the assembly process can be rationalized as depicted in Figure 4. In the first step of the process intermolecular H-bonding leads to the formation of incipient columnar aggregates that further pack into fibrils and at a higher assembly level into fibers several micrometers long. Those fibers were revealed to be formed by right-handed twisted ribbons. A similar assembly process can be envisaged for the enantiomer (*R*,*R*)-**1**, with the result that fibers of opposite handedness are formed, as shown in part B of Figure 1.

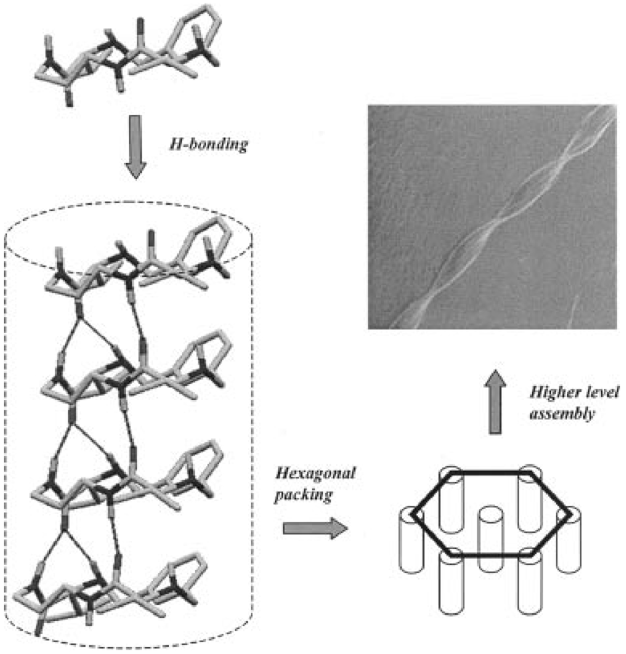

Figure 4. Scheme of the hierarchical self-assembly of compound (*S*,*S*)-**1** in benzene

However, a more complex situation can be found in the study of mixtures of both. In principle, three different situations can be proposed for the mixture of two enantiomers. First, one could consider a completely enantiospecific self-assembly process in which one enantiomer does not interact at all with the other. In such a case, a mixture of aggregates of opposite handedness would be found, thus revealing a spontaneous enantiomer resolution at the molecular as well as at the supramolecular level. In this case, the gelation properties of the mixtures would be related to the partial concentration of each component. Thus, for the racemate with a global concentration of 1 wt.-%, the formation of a strong gel in the same conditions as for the enantiopure compounds would be expected.

A second possibility is the cooperative interaction between both enantiomers. In this case, gels would be expected to be formed by co-assembly of both for all the mixtures with a global concentration of at least 0.5 wt.-%, and the dried gel would present a diffraction pattern different to those of the enantiopure xerogels (crystalline for the regular co-assembly or amorphous for a random one).

An intermediate situation could be proposed in which a nonspecific competitive interaction would arise between the enantiomers, leading to a disruption in the growth of the enantiopure fibers. This will result in a reduction of the size of the aggregates, with the prevention of gelation as the ultimate consequence.

The experimental results described above seem to agree with the latter situation. We have already shown that, at least for this family of compounds, the size of the initial aggregates is critical for the formation of gels. Thus, when aggregates not large enough to form the gel network exist in solution for a period of time they tend to crystallize instead of forming a gel.[10b] The critical factor could be either the cooling rate, as reported previously, or the presence of a weak competitor, as could be the case for the mixtures of enantiomers. The reduction of the size of the aggregates will be greatest for a racemate due to the cross-competition between the enantiomers. On the other hand, the increase of the ratio of one of the enantiomers will be accompanied by an increase in the length of the fibers it forms. At some point near the minimum gel concentration, their size becomes enough to entrap the solvent and form a gel. As mentioned above, this is the case we have found in the study of mixtures going from 50:50 to 95:5 enantiomer ratios. The same consideration can explain the changes in the microstructures observed by SEM. Another fact supporting this line of reasoning is the incipient gelation observed for the racemate at 1 wt.-% when the hot sample is quickly cooled to –80 °C. In this case, the fast lowering of temperature favors the formation of longer fibers.

Although helices could not be directly observed by SEM for either the 95:5 mixture or the weak gel formed at –80 °C, partially twisted long fibers are present in both cases, which shows that a transfer of the chiral information from the molecular to the supramolecular level occurs to some extent. In contrast, the crystalline precipitates made by racemates at room temperature and other mixtures present only straight ribbons, thus revealing an intriguing relationship between the length of the elongated aggregates and their shape.

Conclusions

In conclusion, we have presented an example of the importance of the transcription of molecular chiral information in all the successive levels of organization in hierarchically assembled materials such as organogels. Scanning electron microscopy experiments reveal the expression of molecular chirality at the supramolecular level by the presence of helicoidal aggregates of opposite handedness for pure samples of both enantiomers of compound **1**. This effect disappears upon the addition of small amounts of the opposite enantiomer. X-ray powder diffraction shows that gels as well as precipitates of the mixtures are polycrystalline and reveals a similar structural arrangement independently of the composition. Zinic et al. have recently shown an example where a pure enantiomer and a racemate assemble in closely related packing modes that can be explained either by the formation of enantiopure or *meso* bilayers.[6c] Our results could suggest that, in nonenantiopure mixtures, compound **1** self-assembles into enantiopure crystalline conglomerates disrupted by the nonspecific competition between the enantiomers. However, we cannot discard the alternative packing made of layers of opposite enantiomers stacking on top of each other to form a *meso* aggregate instead of a conglomerate. In both possibilities, the presence of the opposite enantiomer has an important effect on the length of the initial aggregates, and it is critical for macroscopically detectable properties such as the gelation ability and the expression of their chirality into helical nanostructures.

Experimental Section

General Remarks: Compound (*R*,*R*)-**1** was prepared as described previously for (*S*,*S*)-**1** (included as Supporting Information).[14]

Gelation Test: The studied compounds were dissolved in hot benzene in a screw-capped cylindrical glass vial (diameter: 2 cm) and the mixture was left at room temperature. A gel was considered to have formed when the soft material was stable upon turning the vial upside-down.

Scanning Electron Microscopy: Scanning electron micrographs were taken with a LEO 440I microscope equipped with a digital camera. Samples of the xerogels were prepared by placing the gel on top of a tin plate and, after drying of the solvent, they were sputtered with Au/Pd in a Polaron SC7610 Sputter Coater from Fisons Instruments.

Wide-Angle X-ray Powder Diffraction: X-ray powder diffraction was performed at room temperature on a Siemens D5000 diffractometer using Cu-K_α radiation. The powdered xerogels were placed in a quartz sample holder and data were collected for 2θ values between 3° and 35–40° with a step size of 0.05° and a time step of 20 s.

Acknowledgments

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