Formation of Nanoparticles of Polylactide-Containing Diblock Copolymers: Is Stereocomplexation the Driving Force?

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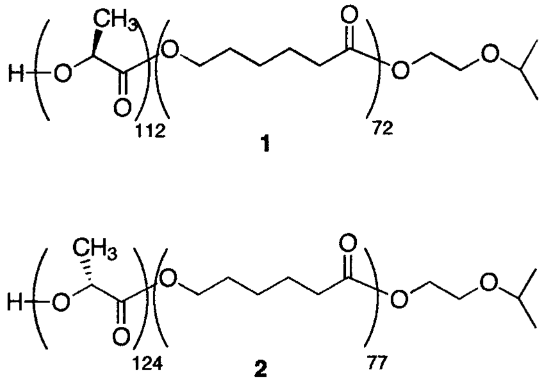
Introduction. Self-assembly of AB block copolymers in a selective solvent of one of the blocks is often used to obtain well-defined nanoparticles that may have interesting properties for electronic or biomedical applications. In dilute solutions, when the insoluble A block forms amorphous aggregates, spherical micelles are usually obtained. On the other hand, when the insoluble A block self-organizes within the aggregates, particles with a variety of shapes can result. This has been nicely demonstrated in the case of rod−coil block copolymers where the organization is driven by the packing of the rigid A blocks.[1] Organization within the core can also occur with flexible A blocks, if they crystallize. Such systems have been studied theoretically[2] and experimentally in the case of poly(ethylene oxide)−polystyrene[3−5] and polyethylene−poly(ethylpropylene)[6] diblock copolymers in hydrocarbon solvents. It was shown that these copolymers form thin platelet structures consisting of chain-folded crystalline domains of the insoluble block, surrounded by a solvated layer of the second block. The size of the particles can potentially be tuned by changing the length of each block, the solvent, or the temperature, but it is difficult to obtain stable dispersions of flat monodisperse nanoparticles of given lateral dimensions.

Here, our aim is to study the structure of nanoparticles obtained in solution by cocrystallization of an AB and an A′B diblock copolymer, such that the A and A′ blocks can cocrystallize. The main advantage of such a system is that the molar ratio between the two diblocks can be used to potentially adjust the size of the nanoparticles. A second advantage is that particles can simply be obtained by mixing the solutions of each diblock. This preparative technique is soft and should make it possible to reach an equilibrium, which is not always granted with the usual techniques of cooling a warm solution or dialysis.

Poly(L-lactide) (polyLLA) and poly(D-lactide) (polyDLA) are semicrystalline polymers which form a racemic crystal (stereocomplex).[7] The stereocomplex is much more stable than the crystals of each polyenantiomer, because the chains are packed as pairs of helices of opposite configurations.[8] Because of strong van der Waals interactions, the melting point of the stereocomplex is 50 °C higher than the melting point of both polyenantiomers. Thus, we have synthesized poly(L-lactide)−poly(ϵ-caprolactone) and poly(D-lactide)−poly(ϵ-caprolactone) diblock copolymers and studied their association in tetrahydrofuran, a good solvent of the poly(ϵ-caprolactone) block. We report here the preliminary results showing that it is indeed possible to obtain nanoparticles in this way.



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2

Figure 1. Structure of diblock copolymers **1** and **2**.

Experimental Section. Block copolymer **1** (**2**) (Figure 1) was synthesized by addition of L-lactide (D-lactide) to a living poly(ϵ-caprolactone) (polyCL), which had been prepared with an yttrium alkoxide initiator ($Y(OCH_2CH_2OCH(CH_3)_2)_3$) as previously described.[9] The structure was confirmed by size exclusion chromatography (SEC) with tetrahydrofuran (THF) as eluent, ^1H NMR and ^{13}C NMR in $CDCl_3$, and polarimetry in THF. The degrees of polymerization reported in Figure 1 were determined by combination of SEC of the polyCL precursor[10] and integration of polylactide (polyLA) (5.28 ppm) and polyCL (4.14 ppm) signals on the ^1H NMR spectra of the copolymers. The polydispersity determined by SEC is 1.19 and 1.16 for **1** and **2**, respectively.

Dynamic light scattering measurements were performed with an experimental setup previously described,[11] at a wavelength (λ) of 514.5 nm. Samples were prepared by dissolving separately the same weight of each copolymer in THF (analytical reagent, Prolabo) at room temperature. Then, the solutions were filtered through Whatman Anotop filters (porosity 0.2 μm) and finally mixed together. The correlation functions were measured at 25 °C and at various angles of observation (θ) ranging from 30° to 130°. All correlation functions of the mixtures are characterized by a single peaked relaxation time distribution. The average relaxation times (τ) are q^2-dependent and are used to calculate an apparent diffusion coefficient $D = (q^2\tau)^{-1}$, where q is the scattering wave vector defined as $q = (4\pi n/\lambda \sin(\theta/2))$ with n the refractive index of the solvent. Finally, an apparent hydrodynamic radius has been estimated using the Stokes−Einstein relation: $R_{h,app} = kT/6\pi\eta D$, where k is the Boltzmann constant, T the absolute temperature, and η the viscosity of the solvent.

All NMR spectra were recorded on a Bruker AC 200 spectrometer equipped with a Bruker Aspect 3000 computer and a 5 mm dual probe (^1H, ^{13}C). The temperature of the probe was controlled with a BVT 1000 temperature unit (300 K). Typical conditions for recording spectra were as follows: spectral width 4000 Hz, data point 16K, nutation angle 30°, and pulse repetition 10 s. The Fourier transform was carried out with 32K data points after zero filling, so that the digital resolution was 0.24 Hz/point. The chemical shifts were

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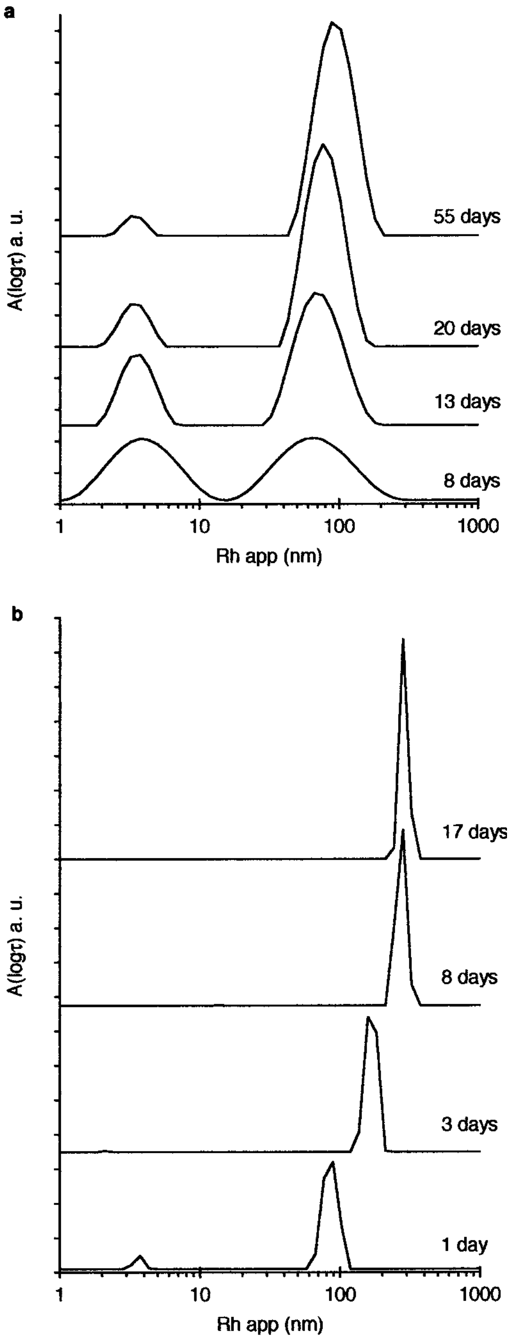

Figure 2. Distribution of hydrodynamic radii (measured at 90°) ($R_{\mathrm{h,app}}$) for a 10 g/L solution of **1** in THF (a) at different times after dissolution and for a solution of **1** and **2** in THF (b) at different times after mixing the same weight of freshly prepared solutions of **1** and **2**, at 10 g/L in THF.

referenced to the solvent peak at 3.7 ppm. Samples were prepared by dissolving separately the same weight of each copolymer in [D$_8$]THF (Euriso-top) at room temperature and mixing the two solutions.

Results and Discussion. In a first kind of experiment, diblock copolymers **1** and **2** were dissolved separately in THF, which is a good solvent of polyCL and a poor solvent for polyLLA and polyDLA. Diblock copolymers **1** and **2** dissolved in THF at room temperature within a few minutes to give clear solutions at a concentration of 10 g/L; however, dynamic light scattering shows that some aggregation occurred (Figure 2a). The distribution of the hydrodynamic radius was bimodal with a fast component ($R_{\mathrm{h,app}} = 3 \pm 0.5$ nm) corresponding to the individual diblock copolymer chain and a slow component corresponding to some aggregate. The proportion of these aggregates increased slowly with time, and an equilibrium seems to be reached after 2 months. This equilibrium is characterized by the presence of a significant amount of individual chains, showing that the strength of the aggregation is moderate.

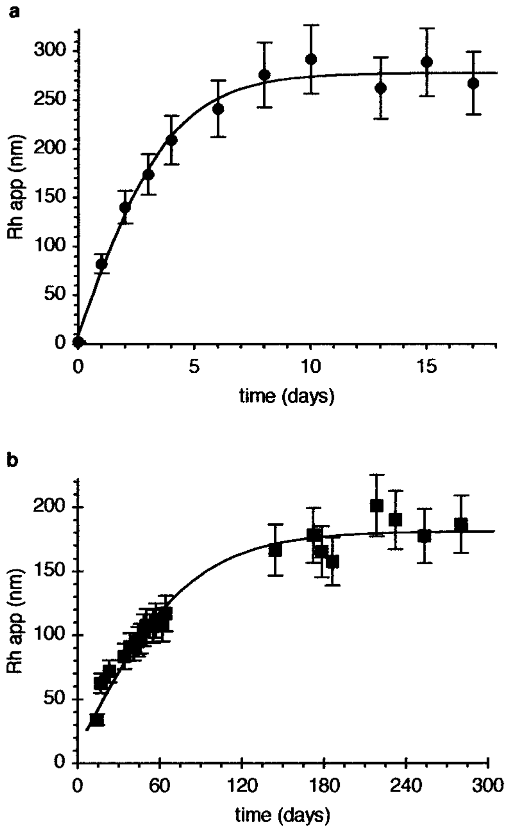

Figure 3. Apparent hydrodynamic radius ($R_{\mathrm{h,app}}$) of the aggregates vs time after mixing the same weight of solutions of **1** and **2**, at 10 g/L (a) and at 1 g/L (b) in THF. The curves are a guide for the eye only.

In a second kind of experiment, two mother solutions of **1** and **2** at 10 g/L in THF were prepared and immediately mixed together, and the resulting solution was characterized. After 8 days at room temperature, the solution became cloudy, and after 1 month, a thin white precipitate began to settle down, whereas the mother solutions containing only one copolymer at the same concentration remained clear for more than 1 year. The formation of particles in the case of the mixture of **1** and **2** was confirmed by dynamic light scattering (Figure 2b). In contrast to the mother solutions, the mixture shows a monomodal distribution of the hydrodynamic radius after 1 day. Moreover, the average apparent hydrodynamic radius increased continuously from a value of 2 ± 0.6 nm (corresponding to unaggregated copolymer chains) to more than 200 nm in 10 days (Figure 3a). Measurements after 17 days were not possible anymore due to the turbidity of the solutions. The same solutions were prepared in deuterated THF for ^{1}H NMR characterization. Just after preparing the samples, the NMR spectra of copolymer **1** and the mixture of **1** and **2** were identical. After 82 days, the spectrum of copolymer **1** in [D$_8$]THF had not changed, whereas Figure 4 shows that for the mixture of **1** and **2** in [D$_8$]THF the intensity of the signal at 5.28 ppm corresponding to the polyLA methine group had signifi-

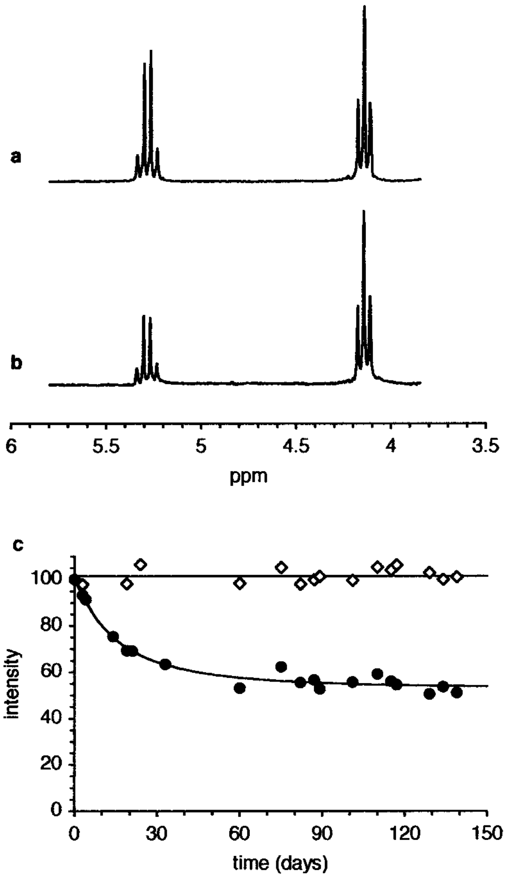

Figure 4. Part of ^{1}H NMR spectra of a sample prepared by mixing the same weight of solutions of **1** and **2**, at 10 g/L in [D$_8$]THF, just after preparation (a) and 82 days afterward (b). Normalized intensity (c) of the NMR signal at 5.28 ppm (polyLA) relative to the signal at 4.14 ppm (polyCL) vs time for a 10 g/L solution of **1** in [D$_8$]THF (◇) and for the sample described in (a) and (b) (●). The curves are a guide for the eye only.

cantly decreased. This phenomenon is due to a reduced mobility of the polyLA blocks, indicating that, in the aggregates, polyLA blocks form domains that are poorly solvated. The intensity of the polyLA methine signal was monitored over a period of 5 months and is plotted in Figure 4c. A constant value was reached after 2 months, showing that the self-assembly process responsible for the formation of the particles is slow.

Although these preliminary results do not inform us on the shape of the aggregates, both light scattering and NMR results point to a very different structure for the aggregates of the mother solutions and of the mixture of **1** and **2**. In the case of solutions of copolymer **1** alone, some kind of core–shell structure of undetermined shape is expected, due to the poor solubility of the polylactide block. In the case of solutions containing the mixture of **1** and **2**, Figure 4 shows that a polylactide core is also formed and that this core is much tighter than for copolymer **1** alone. The high strength of the interaction responsible for the coaggregation of **1** and **2** is also shown by the larger size of the particles formed and by the fact that the presence of individual chains is not detected.

Moreover, the size distribution of the aggregates is much narrower in the case of the mixture of **1** and **2**, which rules out the formation of ill-defined aggregates. In the case of the mixture of **1** and **2**, the formation of well-defined particles with a tight core can only be due to interactions between polyLLA and polyDLA blocks, because the presence of both polyenantiomers is the only compositional difference between the mixture of **1** and **2** and the reference solutions of **1** or **2**. It is not demonstrated yet that these interactions lead to the formation of a stereocomplex as in the solid state, but it is probable.

To see whether the formation of particles is concentration dependent, mother solutions of **1** and **2** were prepared at 1 g/L in THF and mixed together as before. Visual examination of the sample showed that the 1 g/L solution was still clear to the eye after more than 1 year. Although no aggregation in the mother solutions at 1 g/L was detected by light scattering, Figure 3b shows that aggregation did occur at this concentration for the mixture of **1** and **2**. The particles are formed more slowly than at 10 g/L and they are smaller, but the most important difference is that the dispersion is more stable: no sedimentation has occurred after more than 1 year.

Conclusions. We have shown that poly(L-lactide)–poly(ϵ-caprolactone) and poly(D-lactide)–poly(ϵ-caprolactone) diblock copolymers self-assemble in THF to form particles with a size roughly equal to 200 nm. The self-assembly process is driven by interactions between the poly(L-lactide) and poly(D-lactide) blocks, but the formation of a stereocomplex has not been demonstrated yet. The formation of the nanoparticles is extremely slow, which makes it possible to study the kinetics of the process and have a good control of the structure. Further work in this direction is under way.

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References and Notes

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