Supporting information for:

Poly(2-isopropyl-2-oxazoline)-b-Poly(lactide) (PiPOx-b-PLA) nanoparticles in water: interblock van der Waals attraction opposes amphiphilic phase separation

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S1: Equations for light and neutron scattering experiments

*Light scattering:*

The hydrodynamic radius $R_h$ was calculated according to Stokes-Einstein equation:

$$R_h = \frac{kT}{6\pi\eta D} \quad \text{(Equation 1)}$$

where $k$ is the Boltzmann constant, $T$ the absolute temperature, $\eta$ the viscosity of the solvent, and $D$ the mutual diffusion coefficient obtained by a linear fit of the decay rate $\Gamma$ vs. the squared scattering vector $q^2$, with:

$$\Gamma = Dq^2 \quad \text{(Equation 2)}$$

$$q = \frac{4n_0}{\lambda} \sin \frac{\theta}{2} \quad \text{(Equation 3)}$$

where $n_0$ is the refractive index of the solvent, $\lambda$ the wavelength of the laser, and $\theta$ the scattering angle. $\Gamma$ is obtained from a second order cumulant expansion of the first-order electric field correlation function of the scattered electric field $g_1(t)$. Particle size and dispersity were analyzed also by the CONTIN algorithm (see SI4).

The averaged intensity of scattered light $I_{\text{sample}}$ at $\theta$ was measured by SLS over 3 min, the accumulation time in the DLS experiment, and used to calculate the Rayleigh ratio of the sample $R_{\theta}^{\text{sample}}$.

$$R_{\theta}^{\text{sample}} = \left( I_{\text{sample}} - I_{\text{solvent}} \right) \frac{R_{\text{tot}}}{T_{\text{tot}}} \quad \text{(Equation 4)}$$
where $I_{\text{solvent}}$ and $I_{\text{tol}}$ are the scattered light intensities of the pure solvent and toluene at 90°, respectively, and $R_{\text{tol}}$ the Rayleigh ratio of toluene. For a precise extrapolation of $R_{\Theta}^{\text{sample}}$ to $\Theta = 0°$, measurements were conducted at 11 angles between 50° and 150°. The resulting form factor $P(\Theta)$ was fitted to a Guinier model to obtain the radius of gyration $R_g$.

$$ P(\Theta) = \frac{R_{\Theta}}{R_{\Theta=0}} = \exp \left( -\frac{q^2}{3}(R_g^2) \right) $$  

(Equation 5)

**Small angle neutron scattering:**

The absolute value of the wave-vector, is given by:

$$ q = \frac{4\pi}{\lambda} \sin (\Theta) $$  

(Equation 6)

where $\Theta$ is the scattering angle. The samples were kept in 2 mm quartz cuvettes, equipped with stoppers. The measuring cells were placed onto a copper base for good thermal contact before mounting in the sample chamber. Samples were kept at a temperature of 25 °C. The transmission was measured separately. The absolute scattering cross section (cm$^{-1}$) was calculated by taking into account the contribution from the empty cell and the general background. The samples were prepared in D$_2$O instead of H$_2$O to enhance contrast and reduce incoherent background.

The size of non-interacting moieties was determined in terms of the radius of gyration ($R_g$) at small q-values through the Guinier expression for the scattered intensity ($I(q)$):

$$ \ln I(q) = \ln I(0) - \frac{1}{3}q^2R_g^2 $$  

(Equation 7)

This approximation is valid only for $qR_g < 1$. Since the Guinier approximation yielded quite coarse fits of the data, we also made full model fits of the scattering curve:
\[ I(q) = \frac{N}{V} P(q) S(q) \]  

(Equation 8)

where \( N \) is the number of particles inside a sample volume \( V \), \( P(q) \) the particle form factor, and \( S(q) \) the particle structure factor. Since the particle dispersions used here are quite dilute we can assume non-interacting particles and for this case \( S(q)=1 \). The form factor of homogenous spherical objects with a radius \( R \) can be written as:

\[ P(q) = (\Delta \rho)^2 V_p^2 \frac{3}{(qR)^3} \left( \sin(qR) - qR \cos(qR) \right)^2 \]  

(Equation 9)

where \( \Delta \rho = \rho_p - \rho_0 \) is the difference in scattering length density (SLD) between particle and solvent (scattering contrast) and \( V_p \) is the particle volume. In the fitting of the SANS data, we generally found this model adequate for the samples measured before heating. However, in one case it was necessary to employ the spherical core-shell model given by

\[ P(q) = \frac{scale}{V_s} \left[ \frac{3V_c(\rho_c - \rho_0)j_1(qR_c)}{qR_c} + \frac{3V_s(\rho_s - \rho_0)j_1(qR_s)}{qR_s} \right]^2 \]  

(Equation 10)

where \( V_s \) is the total particle volume (including the shell), \( V_c \) is the volume of the core, \( R_s \) is the radius of the shell, and \( R_c \) is the radius of the core, thus \( R_s = R_c + d \), where \( d \) is the thickness of the shell. The parameter \( \rho_c \) is the scattering length density of the core and \( \rho_s \) is the scattering length density of the shell. \( j_1(x) = (\sin x - x \cos x)/ x^2 \), and \( scale \) is a scale factor proportional to the sample concentration.

Some of the samples were best described by a cylinder model after heating. The core-shell cylinder model for overall random particle orientation has a form factor \( P(q) \) described by:
\[ P(q) = \frac{\text{scale}}{V_s} \int_0^\pi f^2(q, \alpha) \sin \alpha \ d\alpha \]  \hspace{1cm} \text{(Equation 11)}

with

\[ f(q, \alpha) = 2(\rho_c - \rho_s) V_c j_0(qH \cos \alpha) \frac{J_1(qR_c \sin \alpha)}{q R_c \sin \alpha} + 2(\rho_s - \rho_{\text{solv}}) V_s j_0[q(H + t) \cos \alpha] \frac{J_1(qR_s \sin \alpha)}{q R_s \sin \alpha} \]  \hspace{1cm} \text{(Equation 12)}

Here, \( \alpha \) is the angle between the axis of the cylinder and the \( q \)-vector, \( V_c \) and \( V_s \) are the core volume and total volume, as before. Thus, for the cylinder \( V_c = \pi R_c^2 L \) and \( V_s = \pi R_s^2 L \), where \( L \) is the length of the core, \( R_c \) is the radius of the core, and \( t \) is the thickness of the shell (\( R_s = R_c + t \)). The total length of the outer shell is given by \( L + 2t \). \( J_1 \) is the first order Bessel function, and \( j_0(x) = \sin x / x \).

The scattering length densities employed in this study are 1.73e-06 Å\(^{-2}\) for PLA\(^{33}\) and 0.7e-06 Å\(^{-2}\) for PiPOx. The model fitting was implemented via the SasView analysis package (http://www.sasview.org/).

**S2: Solubility of PLA in H\(_2\)O/THF mixtures**

In a series of vials, PLA homopolymers were dissolved in THF (1 wt\%, 1 mL) and different amounts of water were added under stirring. The onset of turbidity was detected visually (Table S2-1).
Two criteria define the hydrophobicity of each PLA. The first is the minimal water volume fraction at which each PLA instantaneously turns turbid (marked red). According to this PLLA3 is the most and PDLLA1 the least hydrophobic polymer of the selection. The second criterion is the duration until precipitation occurs at a constant water volume fraction. For example, at 20 vol% water, all PDLLA homopolymers remain soluble for 40 days but all PLLA homopolymers precipitate in finite time. Both criteria taken together, the hydrophobicity increases in the order: PDLLA1 < PDLLA2 < PDLLA3 < PLLA1 < PLLA2 < PLLA3.

Table S2-1  Duration until the onset of turbidity after the addition of different amounts of water to PLA solutions (1 wt% in THF). Solutions reported as “clear” remained clear for at least 40 days.

| polymer | water volume fraction / vol% |
|---------|-----------------------------|
| PLLA1   | - 24 h - 3 h 16 min 3 min 2 min instant - - |
| PLLA2   | 24 h 2.5 h - 14 min 1 min instant instant instant - - |
| PLLA3   | 24 h 15 min 5 min 5 min instant instant - - - |
| PDLLA1  | clear clear clear clear clear clear clear 20 min instant instant |
| PDLLA2  | clear clear clear clear clear + 10 d instant - - - |
| PDLLA3  | clear clear clear clear clear instant instant - - - |
S3: Particle stability at room temperature

The particle stability at room temperature ($c_{BCP}$: 0.5 g/L) was investigated by light scattering. The samples (0.5 g/L) were placed in cuvettes and not agitated for the duration of the stability test. Figure S2-1 shows size information (z-average) and derived count rate normalized to the respective quantity at day one. Particles of 2L3 were stable for 20 days, neither size nor count rate changed considerably. Particles of 3DL3 started to aggregate and sediment after 10 days causing the count rate to drop significantly. After 20 days a bimodal distribution had developed that was unsuitable to analysis by light scattering. The stability test demonstrates that the more compact 2L3 particles ($R_h$: 28 nm) are stable compared to the larger 3DL3 particles ($R_h$: 60 nm). Both BCPs have a similar PiPOx mol fraction (~38%).

![Figure S3-1](image)

**Figure S3-1** Stability of 2L3 and 3DL3 particles in aqueous solution (0.5 g/L) at room temperature. Size and derived count rate were normalized to the value at day one.
S4: Light scattering results

**Figure S4-1** Decay rates $\Gamma$ from the second order cumulant analysis vs squared scattering vector $q$ for (A) PiPOx2-b-PLA dispersions and (B) PiPOx3-b-PLA dispersions. The dashed lines are linear fits according to $\Gamma = Dq^2$. 
Figure S4-2  2L1, at 20 °C, before annealing. Selected normalized autocorrelation function of scattered light intensity $|g_2(t)|$ vs time $t$, ln$[g_1(t)]$ vs tq$^2$, and CONTIN distributions at scattering angles of 60 ° (squares, black line), 90 ° (circles, red line), and 120 ° (triangles, blue line). Natural logarithm of the form factor P(q) vs q$^2$ and linear fit.
Figure S4-3  2L2, at 20 °C, before annealing. Selected normalized autocorrelation function of scattered light intensity $|g_2(t)|$ vs time $t$, $\ln[g_1(t)]$ vs $tq^2$, and CONTIN distributions at scattering angles of 60 ° (squares, black line), 90 ° (circles, red line), and 120 ° (triangles, blue line). Natural logarithm of the form factor $P(q)$ vs $q^2$ and linear fit.
Figure S4-4  2L2, at 20 °C, after annealing at 50 °C for 2 h. Selected normalized autocorrelation function of scattered light intensity $|g_2(t)|$ vs time $t$, $\ln[g_1(t)]$ vs $tq^2$, and CONTIN distributions at scattering angles of 60 ° (squares, black line), 90 ° (circles, red line), and 120 ° (triangles, blue line). Natural logarithm of the form factor $P(q)$ vs $q^2$ and linear fit.
Figure S4-5  2L3, at 20 °C, before annealing. Selected normalized autocorrelation function of scattered light intensity |g₂(t)| vs time t, ln|g₁(t)| vs tq², and CONTIN distributions at scattering angles of 60 ° (squares, black line), 90 ° (circles, red line), and 120 ° (triangles, blue line). Natural logarithm of the form factor P(q) vs q² and linear fit.
Figure S4-6  2DL1, at 20 °C, before annealing. Selected normalized autocorrelation function of scattered light intensity $|g_2(t)|$ vs time $t$, $\ln[g_1(t)]$ vs $tq^2$, and CONTIN distributions at scattering angles of 60 ° (squares, black line), 90 ° (circles, red line), and 120 ° (triangles, blue line). Natural logarithm of the form factor $P(q)$ vs $q^2$ and linear fit.
Figure S4-7  2DL1, at 20 °C, after annealing at 50 °C for 2 h. Selected normalized autocorrelation function of scattered light intensity $|g_2(t)|$ vs time $t$, $\ln[g_1(t)]$ vs $tq^2$, and CONTIN distributions at scattering angles of 60 ° (squares, black line), 90 ° (circles, red line), and 120 ° (triangles, blue line). Natural logarithm of the form factor $P(q)$ vs $q^2$. Guinier fit inappropriate due to bimodality.
Figure S4-8 2DL2, at 20 °C, before annealing. Selected normalized autocorrelation function of scattered light intensity $|g_2(t)|$ vs time $t$, ln[$g_1(t)$] vs tq$^2$, and CONTIN distributions at scattering angles of 60 ° (squares, black line), 90 ° (circles, red line), and 120 ° (triangles, blue line). Natural logarithm of the form factor P(q) vs q$^2$ and linear fit.
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Figure S4-10 3L1, at 20 °C, before annealing. Selected normalized autocorrelation function of scattered light intensity \(|g_2(t)|\) vs time \(t\), \(\ln[g_1(t)]\) vs \(tq^2\), and CONTIN distributions at scattering angles of 60 ° (squares, black line), 90 ° (circles, red line), and 120 ° (triangles, blue line). Natural logarithm of the form factor \(P(q)\) vs \(q^2\) and linear fit.
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Figure S4-12 3L3, at 20 °C, after annealing at 50 °C for 2 h. Selected normalized autocorrelation function of scattered light intensity $|g_2(t)|$ vs time t, $\ln[g_1(t)]$ vs tq^2, and CONTIN distributions at scattering angles of 60 ° (squares, black line), 90 ° (circles, red line), and 120 ° (triangles, blue line). Natural logarithm of the form factor P(q) vs q^2 and second order fit.
Figure S4-13 3DL1, at 20 °C, before annealing. Selected normalized autocorrelation function of scattered light intensity $|g_2(t)|$ vs time $t$, $\ln[g_1(t)]$ vs $tq^2$, and CONTIN distributions at scattering angles of 60 ° (squares, black line), 90 ° (circles, red line), and 120 ° (triangles, blue line). Natural logarithm of the form factor $P(q)$ vs $q^2$ and linear fit.
Figure S4-14 3DL3, at 20 °C, before annealing. Selected normalized autocorrelation function of scattered light intensity |g₂(t)| vs time t, ln|g₁(t)| vs tq², and CONTIN distributions of 3DL3 at scattering angles of 60 ° (squares, black line), 90 ° (circles, red line), and 120 ° (triangles, blue line). Natural logarithm of the form factor P(q) vs q² and second order fit.
Figure S4-15 3DL3, at 20 °C, after annealing 50 °C for 2 h. Selected normalized autocorrelation function of scattered light intensity $|g_2(t)|$ vs time t, $\ln[g_1(t)]$ vs $tq^2$, and CONTIN distributions at scattering angles of 60 ° (squares, black line), 90 ° (circles, red line), and 120 ° (triangles, blue line). Natural logarithm of the form factor $P(q)$ vs $q^2$. Guinier fit not appropriate due to bimodality.
S5: TEM of 3L3 after annealing

Figure S5-1  TEM image of 3L3 particles after annealing
S6: WAXS of 3L3 particles

**Figure S6-1**  WAXS patterns of 3L3 before (blue) and after annealing at 50 °C for 2 hours (green).