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The behavior of thermoresponsive star-shaped poly-2-isopropyl-2-oxazoline in saline media

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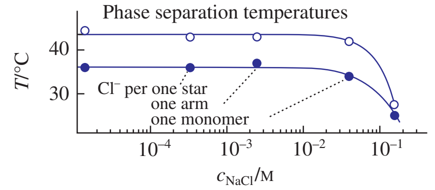
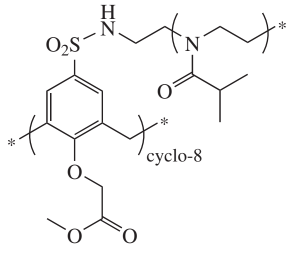
In aqueous and saline solutions, one or more chloride ions per monomer unit are necessary for evident changes in the self-organization of poly-2-isopropyl-2-oxazoline and solution behavior on heating.



Thermoresponsive polymers, including polyoxazolines, have a great potential in numerous applications, in particular, polymer-based drug delivery systems.[1] Polyoxazoline properties depend on the length of alkyl group in the monomer, molecular weight, and environmental conditions such as temperature,[2] ionic strength,[3] and pH.[4] For medical applications of polyoxazolines, reliable data on the behavior of polyoxazoline in aqueous NaCl solutions of different concentrations are necessary. Thus, the aim of this work was to study thermoresponsive star-shaped poly-2-isopropyl-2-oxazoline (PiPrOx) in salt solutions at different polymer concentrations using a physiological solution as a simple model system.[5]

The synthesis and characterization of eight-arm PiPrOx with a calix[8]arene core (weight-average molecular weight $M_w = 16300$; molar-mass dispersity index, 1.37; degree of polymerization of arm, 16) were described previously.[6] The sample behavior was studied within the concentration range $c = 0.00019$–0.0050 g ml^{-1} in 0.154 M NaCl and pure water. The effect of chloride ion concentration was analyzed in 0.3×10^{-3} M PiPrOx solutions (0.0050 g ml^{-1}) at NaCl concentrations c_{NaCl} of 0.33×10^{-3}, 2.47×10^{-3} and 39.3×10^{-3} M, which correspond to one Cl$^-$ per one macromolecule, one arm and one monomer unit of PiPrOx, respectively (for concentration calculations, see Online Supplementary Materials). A Photocor Complex instrument equipped with a diode laser (659.1 nm) and a detector for measuring transmitted light intensity I^* was used in static and dynamic light scattering and turbidimetry experiments. Temperature T was varied from 15 to 72 °C. Scattering intensity I, hydrodynamic dimensions $R_{\text{h-i}}$ of the scattering objects and the contribution S_{i} of each particle type to the total scattering intensity (as the square under the curved line of the corresponding peak of the distribution of I on R_{h}, Figure 1) were measured in equilibrium states at each particular T according to a procedure described previously.[7] The temperature boundaries T_1 and T_2 of phase separation were determined from the function $I(T)$ (Figure 1S, in Online Supplementary Materials).



Star-shaped poly-2-isopropyl-2-oxazoline

In PiPrOx solutions at $c = 0.0050$ g ml^{-1} and different c_{NaCl}, the measured values of $R_{\text{h-i}}$ and S_{i} did not differ from the data in pure water up to $c_{\text{NaCl}} = 2.47\times10^{-3}$ M. A trimodal distribution of light scattering intensity on hydrodynamic radii was observed for PiPrOx at room temperature. It was confirmed at scattering angles from 45° to 135° and justified the presence of three species of different hydrodynamic radii. The molecular species with the smallest hydrodynamic radius are single macromolecules, based on the similar hydrodynamic radii of fast mode in aqueous salt solutions and the radius of single star macromolecule in nitromethane.[6] Consequently, particles responsible for middle and slow modes are aggregates, which were not detected in organic solutions.[6] The same aggregates were observed in different thermoresponsive polymers,[8] including polyoxazoline stars;[9,10] they were formed due to interactions between hydrophobic calixarene or carbosilane cores in aqueous solutions. The hydrodynamic radii of fast $R_{\text{h-f}}$ and middle $R_{\text{h-m}}$ modes are the same in water and saline media (Figure 2), but the values of $R_{\text{h-s}}$ of large aggregates are higher in the presence of NaCl. The latter causes the growth

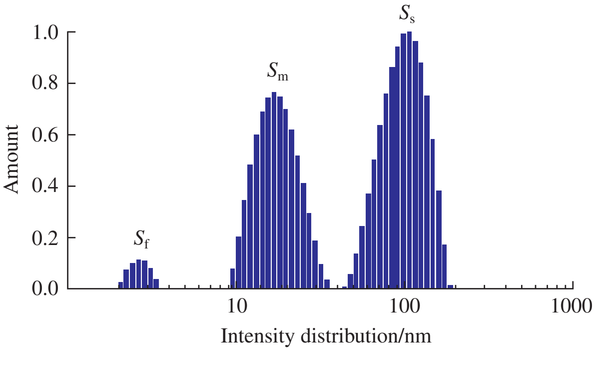


Figure 1 Distribution of light scattering intensity I on hydrodynamic radii $R_{\text{h-i}}$ of scattering species in 0.154 M NaCl solution of PiPrOx at concentration $c = 0.0050$ g ml^{-1} and $T = 21$ °C. The contributions of fast, middle and slow modes are marked as S_{f}, S_{m}, and S_{s}, respectively.

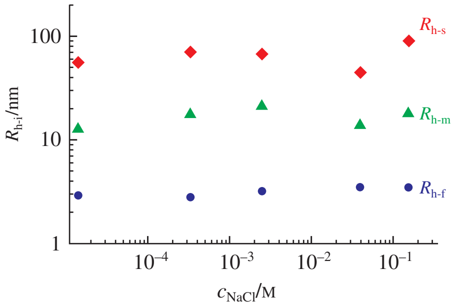


Figure 2 Hydrodynamic radii of fast $R_{\text{h-f}}$, middle $R_{\text{h-m}}$ and slow $R_{\text{h-s}}$ modes in solutions with polymer concentration $c = 0.0050$ g ml^{-1} *vs.* c_{NaCl} at $T = 21$ °C.

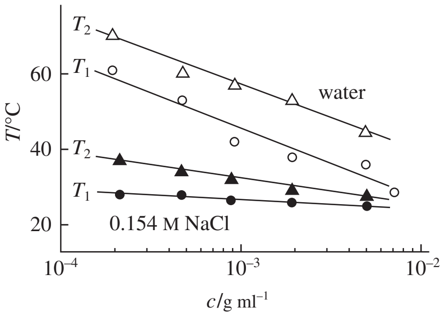


Figure 4 Phase transition temperatures *vs.* polymer concentration for polymer solutions in water and saline media.

of the contribution S_s of slow mode to scattering intensity as compared to the data in pure water. However, as estimated using a hard sphere model, single macromolecules dominate in solutions at a negligible concentration of large aggregates, which contain about 13000 and 53000 macromolecules in water and 0.154 M NaCl solution, respectively. The similarity of particle distributions in water and saline solutions of PiPrOx at $c_{\text{NaCl}} \leqslant 2.47 \times 10^{-3}$ M leads to constant phase separation temperatures, which are almost the same as those for PiPrOx in pure water (Figure 3).

High NaCl content causes a rearrangement of scattering objects in solutions. In spite of the data spread, the trend of the $R_{\text{h-s}}$ value to increase at $c_{\text{NaCl}} = 0.154$ M can be noted (see Figure 2). According to published data,[11,12] the salting-out effect of Cl$^-$ on poly-*N*-isopropyl acrylamide, a structural isomer of PiPrOx, and poly-2-ethyl-2-oxazoline is determined by (i) polymer dehydration by the polarization of water molecules involved in hydrogen bonding with amide group and (ii) an increase in surface tension at the hydrophobic/aqueous interface. Taking into account the NaCl concentration in physiological solution (about four NaCl molecules per oxazoline monomer unit), the formation of bigger aggregates is not surprising. For the same reasons, the phase transition temperatures decreased at high NaCl concentrations (Figure 3). This tendency was reported for other polyoxazolines;[13,14] however, the decrease of the cloud point temperature at comparable polymer concentrations in 0.15 M NaCl solutions was not as drastic as in our research.

At the next step, we analyzed the polymer concentration effect on the behavior of PiPrOx on heating in pure water and 0.154 M NaCl solution, where the most evident changes were detected. At room temperature, the same set of scattering particles was observed (Figure 2S, see Online Supplementary Materials), and the measured hydrodynamic dimensions did not depend on polymer concentration but some quantitative changes were found (Figure 3S). The polymer solubility worsened due to the above salting-out effect of Cl$^-$ and, as at a polymer concentration of 0.0050 g ml^{-1}, the hydrodynamic dimensions of aggregates were 20–40% higher than those in water within the entire concentration range (see Figure 2S). Probably, a similar size growth also occurred for fast and middle mode particles; however, a smaller increase cannot be measured reliably by dynamic light scattering. According to Kirila *et al.*,[10] changes in the dimensions of species in solution under various conditions strongly increase with the density. The salting-out effect is manifested in a more intense aggregation process, which results in a higher aggregate contribution to the total light scattering in saline media. Consequently, the accuracy in $R_{\text{h-f}}$ and $R_{\text{h-m}}$ values is reduced.

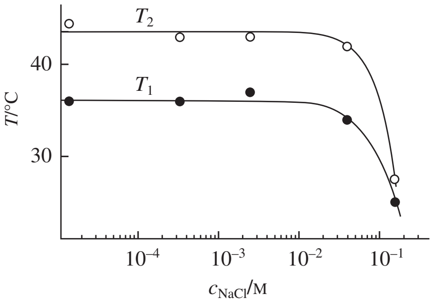


Figure 3 Phase transition temperatures *vs.* NaCl concentration for polymer solutions with concentration $c = 0.0050$ g ml^{-1}.

PiPrOx exhibited unusual concentration dependence of the phase transition temperatures T_1 and T_2. As a rule, for thermoresponsive polymers, the values of T_1 and T_2 grow with dilution, and the phase separation interval widens. However, the test star-shaped PiPrOx is characterized by an almost constant width of the separation interval within the selected concentration range in pure water. Figure 4 shows the salting-out effect of NaCl, which shifts phase transition boundaries to the low-temperature region. This correlates with a larger size of aggregates at room temperature (see Figure 2S) and within phase separation in 0.154 M NaCl, when aggregate dimensions are as high as 3000 nm in comparison with about 1000 nm in water (a similar effect was reported for PiPrOx-grafted nanoparticles of iron oxide[14]). The difference between T_1 and T_2 in aqueous and saline solutions increases with dilution and results in weaker concentration dependence of these temperatures in the presence of NaCl.

In conclusion, a similarity of star-shaped PiPrOx behaviors in aqueous and saline solutions was revealed. The minimal concentration of NaCl at which the salt effect on a polymer behavior manifested itself was determined. Changes in self-organization caused a decrease in the phase separation temperatures by about 2 °C at high concentrations of NaCl. A more pronounced drop in the phase separation temperatures (30 °C) occurred in a physiological solution and depended on polymer concentration. This should be taken into account in the development of polyoxazoline for medicine applications.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.07.040.

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