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- Title: Beating Brine. Supramolecular Crosslinker gives Salt Resistant PIC Micelles and Improved MRI Contrast Agents.
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# Beating Brine. Supramolecular Crosslinker gives Salt Resistant PIC Micelles and Improved MRI Contrast Agents.

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Abstract: A versatile way to prepare nanoparticles in a wide range of compositions is by spontaneous multi-component assembly. Any chosen composition can be realized by simply mixing ingredients, and the available choices for each component determine the accessible variations. We explore here threecomponent mixtures (diblock copolymer/metal ion/oligoligand) which assemble into micellar particles due to a combination of supramolecular polymerization and electrostatic complex formation. Such particles indeed allow covering a large range of compositions, but it turns out that the electrostatic forces keeping them together make them rather susceptible to disintegration by added salt. In this report we show how we can tune the salt stability in a continuous way by employing both a bis-ligand and a tris-ligand, and varying the ratio of these in the mixture. Moreover, we find that for magnetic ions like Mn(II) and Fe(III) the choice of the multiligand also affects the ion/water interaction and, hence, the magnetic relaxivity, so that we can also tune that property. The approach presented here is generally applicable. As an example, we discuss Mn(II)-based nanoparticles with a very high longitudinal relaxivity (10.8 mM<sup>-1</sup>s<sup>-1</sup>) that are not only biocompatible, but also feature strong contrast enhancement in target organs (liver, kidney) as shown by T1-weighted in vivo magnetic resonance imaging (MRI).

It is well known that upon mixing oppositely charged polymers in aqueous solution, complex coacervation takes place, leading to macroscopic phase separation with a polyelectrolyte-rich bottom phase (coacervate) and a dilute top phase.<sup>[1]</sup> Obviously, this charge-driven coacervation is tunable by means of many parameters, such as type of chemical groups, pH, ionic strength and charge mixing ratio.<sup>[2]</sup> Among these, the ionic strength is a crucial factor that generally controls the phase separation, structure, dynamics and mechanical properties of coacervate complexes.<sup>[3]</sup> As is the case with all amphiphiles, the macroscopic

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phase separation can be exploited in the colloidal domain: by attaching a neutral block to one or both of the charged polymers, two-component, nanosized core-shell polymer micelles are formed, known either as complex coacervate core micelles (C3Ms), as polyion complex micelles (PIC micelles), or as block ionomer complex micelles (BICs).<sup>[4]</sup> This type of micelles has attracted increasing attention in recent years because of their perceived potential as carriers for drugs, enzymes, or DNA.<sup>[5]</sup> However, the fact that charge provides the driving force makes polyelectrolyte micelles very sensitive to ionic strength: salt screens the electrostatic interaction between charged blocks and significantly weakens the coacervation and the stability of the coacervate complexes that constitute the micellar core.[6] Typically, PIC micelles hardly tolerate physiological salt concentration, which seriously limits their application in biomedical contexts. To address this problem, various strategies have been developed, such as covalent cross-linking and introduction of more hydrophobic or dendritic components.<sup>[7]</sup> These approaches indeed solve stability problems, but in order to meet various requirements associated with application, what one really looks for is a kind of coacervate micelles with a tunable response to salt (stability) and tunable functional properties, rather than just enhanced salt stability. This is still a challenge to date.



Scheme 1. a) Structure of P2MVP<sub>41</sub>-*b*-PEO<sub>205</sub>. b) Structure of bis-ligand  $L_2$ . c) Illustration of the formation of M-L<sub>2</sub>-L<sub>3</sub> micelles. d) Structure of tris-ligand L<sub>3</sub>.

Some time ago, we have reported a novel type of threecomponent PIC micelles prepared from a polycationic-neutral diblock copolymer and an anionic supramolecular, reversible coordination polyelectrolyte.<sup>[8]</sup> The latter had been obtained by

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coordination between various metal ions and a bis-ligand (L<sub>2</sub>) containing two dipicolinic acid (DPA) groups connected by a tetraethylene oxide spacer (4EO). Unlike micelles formed by common synthetic polyelectrolytes only, such coordination polyelectrolytes bring hundreds of metal ions in the micellar core, resulting in novel functional properties, e.g., magnetic and fluorescent properties.<sup>[9]</sup> Moreover, control of the coordination structures allows to manipulate the strength of the magnetic response or the fluorescence of the micelles, which gives them great potential as imaging probes.<sup>[10]</sup> Regrettably, it was the poor stability against salt that hampered their practical application, particularly for firstrow transition metals.<sup>[11]</sup> The reason for this may be that the combination of bis-ligand (L<sub>2</sub>) with these ions can only form linear coordination polymers, producing highly mobile, liquid-like coacervates.

In the present study, we therefore introduce, as an alternative for L<sub>2</sub>, a *triple* ligand with three DPA groups grafted on a benzene ring (L<sub>3</sub>). When L<sub>3</sub> is added, it creates cross-links between the linear metal-L<sub>2</sub> coordination structures, and then produces reversible network coordination polymers that, as we demonstrate, lead to coacervates that are less easily destroyed by salt. The cross-link density can be simply controlled by varying the L<sub>3</sub>/L<sub>2</sub> ratio, so that we have a method to prepare micelles with adjustable composition, tunable and enhanced salt stability, and hopefully other improved properties. The presented strategy is generally applicable with different metal ions. In particular, we find that Mn-L<sub>3</sub> micelles feature both high stability and high magnetic relaxivity, and exhibit good biocompatibility and strong contrast in T<sub>1</sub>-weighted *in vivo* magnetic resonance imaging, thereby showing excellent performance as MRI contrast agent.

The chemical structures of the bis-ligand 1,11-bis(2,6dicarboxypyridin-4-yloxy)-3,6,9-trioxaundecane (L<sub>2</sub>), and the newly designed tris-ligand 1,3,5-tris(2,6-dicarboxypyridin-4yloxymethyl) benzene (L<sub>3</sub>, see Supporting Information, SI) are shown in Scheme 1. The diblock copolymer poly(N-methyl-2vinyl-pyridinium iodide)-b-poly(ethylene oxide) (P2MVP41-b-PEO<sub>205</sub>) has a linear structure and a fixed number of charges independent of the pH, due to the guaternized pyridinium groups. To discuss the effect of the tris-ligand we select manganese, Mn(II) which has potential as contrast agent in MRI. [12] Other metals (e.g., Zn, Ni) form very similar structures (seel) so that the method is generic. The metal/DPA (from both L<sub>2</sub> and L<sub>3</sub>) ratio is fixed at 1/2, in order to keep the metal ion fully coordinated; under these conditions one creates a supramolecular, anionic coordination polymer with two negative charges on each coordination unit (4COO<sup>-</sup> + Mn<sup>2+</sup>). These polymers reversibly assemble with the cationic/neutral P2MVP<sub>41</sub>-b-PEO<sub>205</sub> block copolymers into micellar particles. In the following, we vary the L<sub>3</sub>/L<sub>2</sub> ratio and measure response in terms of micellar size, salt stability, and magnetic properties.

Figure 1a shows size and size distribution of  $Mn-L_2-L_3$ micelles as a function of the percentage of  $L_3$  in the ligand (defined as DPA groups from  $L_3$  divided by the total DPA amount). The hydrodynamic radius is around 24 nm with a narrow distribution independent of  $L_3$  fraction. Angular dependent light scattering results indicate that both  $Mn-L_2$  and  $Mn-L_3$  micelles are spherical nanoparticles. (Figure S3) This is confirmed by cryo-TEM images (Figure 1c, 1d) which feature small and fairly uniform spherical particles for both  $Mn-L_2$  (corresponding to 0%  $L_3$ , Fig. 1c) and Mn $L_3$  (corresponding to 100%  $L_3$ , Fig. 1d) micelles. Note that the images here highlight the micellar core part due to the enhanced electron density from  $Mn^{2+}$ . The core radius is about 9 nm, which implies that the shell (corona) thickness is around 15 nm (using hydrodynamic radius from light scattering as the total radius).



Figure 1. Effect of L<sub>3</sub> on Mn-based micelles (metal concentration equals 0.3 mM in all cases). a) Hydrodynamic radius and size distribution of Mn-L<sub>2</sub>-L<sub>3</sub> micelles as a function of L<sub>3</sub> ligand percentage; b) Scattering intensity (normalized by the original value I<sub>0</sub>, where no salt is added yet) for Mn-L<sub>2</sub>-L<sub>3</sub> micelles at different L<sub>3</sub>% with increasing salt concentration; c, d) cyro-TEM images of Mn-L<sub>2</sub> (c) and Mn-L<sub>3</sub> micelles (d).

As noticed above, many C3Ms are very sensitive to ionic strength and dissociate completely above a critical salt concentration. Figure 1b shows such a typical salt response of Mn-L<sub>2</sub> micelles (for 0% L<sub>3</sub>): the samples' light scattering intensity goes down with increasing salt concentration and levels off around 180 mM NaNO<sub>3</sub>, where the micelles fall apart completely, as evidenced by the low intensity and the disappearance of a reliable correlation function. (Figure SI 4) Equivalently, one can say that the CMC of the micelles increases due to added salt so that, at fixed total concentration, the concentration of unassociated components increases at the expense of the micelles. Introducing no more than 20% of L<sub>3</sub> already appears to strongly suppress the salt response, thereby considerably lowering the CMC, and shifting the appearance of the intensity plateau to significantly higher salt concentration. The absolute intensity at the plateau is also higher for mixed L<sub>2</sub>-L<sub>3</sub> micelles than for pure L<sub>2</sub> micelles. This may come from two contributions: 1) The CMC has been lowered so much that micelles largely survive. Indeed, for all mixed systems, the intensity correlation curve appears clearly, even at very high salt concentration, and CONTIN analysis confirms that there is a well-defined size peak which must be assigned to (micellar) nanoparticles (Figure SI 5-SI 8). 2) In addition, some metal- $L_2$ - $L_3$  complex released during micellar dissociation presumably forms 'naked' coordination aggregates, which are insensitive to added salt, and have a size different from that of the micelles, as indicated by the new peaks corresponding to a bigger size and a broad size distribution. With

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increasing L<sub>3</sub> fraction, the dissociation of the Mn-L<sub>2</sub>-L<sub>3</sub> micelles is increasingly suppressed, finally leading to very minor decrease of light scattering intensity. Pure L<sub>3</sub> micelles hardly dissociate at all and the CONTIN size distribution remains narrow with increasing salt concentration, in contrast to micelles formed from mixed L<sub>2</sub>-L<sub>3</sub> ligands (Figure S9). Hence, we may conclude that replacing bis-ligand by tris-ligand strongly and tunably enhances the salt stability of the micelles, up to salt concentrations well beyond physiological conditions.



Figure 2. a) The relaxivity  $r_1$  of Mn-L<sub>2</sub>-L<sub>3</sub> micelles at different L<sub>3</sub> fractions.  $r_1$  is the longitudinal relaxivity of water protons in the presence of Mn-L<sub>2</sub>-L<sub>3</sub> micelles. b) UV-vis spectra of Fe-L<sub>2</sub>-L<sub>3</sub> micelles at different L<sub>3</sub>%.

From light scattering and cyro-TEM, we conclude that by varying L<sub>3</sub>/L<sub>2</sub> ratios we can get mixed Mn-L<sub>2</sub>-L<sub>3</sub> micelles with constant size but tunable cross-link density and salt response. We now consider the magnetic properties and detailed coordination structures. The paramagnetic manganese(II) ion carries five unpaired 3d electrons and is one of the metal ions that can effectively enhance positive contrast in magnetic resonance imaging (MRI).<sup>[13]</sup> However, free Mn<sup>2+</sup> is neurotoxic <sup>[18]</sup> and cannot be used as such; some sort of sequestering inside inert particles is needed. Mn-based MRI contrast agents have recently been receiving more attention as an alternative for gadolinium-based contrast agents, which are associated with a nephrogenic systemic fibrosis (NSF) problem and increased safety concerns.<sup>[14]</sup> As a measure of contrast strength, we use the longitudinal relaxivity, defined as r<sub>1</sub>=[(1/T<sub>1</sub>)-(1/T<sub>1,0</sub>)]/C<sub>Mn</sub>, (here,  $C_{\text{Mn}}$  is the manganese concentration, and  $T_1$  and  $T_{1,0}$  are the longitudinal relaxation times of the micellar solution and pure water, respectively). For our Mn-containing micelles, the longitudinal relaxivity is shown in Figure 2. We found that it is around 5.6 mM<sup>-1</sup>s<sup>-1</sup> for Mn-L<sub>2</sub>, and increases with increasing  $L_3$ fraction, initially in a linear fashion but eventually levelling off around 60% of L<sub>3</sub>. Pure Mn-L<sub>3</sub> micelles display the highest relaxivity of 10.8 mM<sup>-1</sup>s<sup>-1</sup>, which is higher than any of the Mnbased contrast agents reported so far, including free Mn<sup>2+</sup>.<sup>[15]</sup> The non-linear dependence of relaxivity on L<sub>2</sub>/L<sub>3</sub> implies that in these mixed micelles the environment of the manganese ion varies with L<sub>3</sub> fraction. Even though the coordinating DPA moieties are the same, L<sub>3</sub> is clearly less flexible than L<sub>2</sub> which may lead to strain and distortion of the local coordination structure. [16] In order to further investigate detailed coordination structures, we also investigated Fe-L<sub>2</sub>-L<sub>3</sub> micelles which show similar size and salt response behavior as Mn-L<sub>2</sub>-L<sub>3</sub> micelles (Figure SI 11). Fully coordinated Fe-(DPA)<sub>2</sub> features a typical UV-vis absorption around 370 nm.<sup>[9a]</sup> As shown in Figure 2b, Fe-based micelles show differences in UV absorption in the range 320-370 nm, between the typical spectrum of pure L<sub>2</sub> systems (identical to that of fully coordinated Fe-(DPA)<sub>2</sub>) and that of mixed systems: the absorption at 350 nm decreases with increasing L<sub>3</sub>/L<sub>2</sub> ratio and levels off at around 60% of L<sub>3</sub>. The relaxivity of Fe-L<sub>2</sub>-L<sub>3</sub> micelles was measured as well, (Figure SI 12) and we find that, as for Mn, it again increases with increasing percentage L<sub>3</sub>, reaching a plateau around 60% of L<sub>3</sub>, just like what we found with UV-vis. Apparently, rigid L<sub>3</sub> causes distortion with respect to the ideal M-(DPA)<sub>2</sub> coordination, leading to a better access for water (inner sphere H<sub>2</sub>O) to the metal ion, which is favorable for magnetic relaxation.<sup>[17]</sup> In other words, the increased number of inner sphere water molecules in the distorted M-(DPA)<sub>2</sub> coordination sphere enhances the magnetic relaxivity. We also note that the non-linear dependence on  $L_2/L_3$  implies that the ligands really mix inside the micelles rather than forming a mixture of pure L<sub>2</sub> and L<sub>3</sub> micelles.

As the free Mn<sup>2+</sup> is neurotoxic <sup>[18]</sup>, it cannot be used *in vivo*. Therefore, the high stability and relaxivity of the Mn-L<sub>3</sub> micelles make them very interesting candidates as in vivo MRI contrast agent. We first investigated their cytotoxic effect, by means of the standard 3-(4.5-dimethylthiazol-2-yl)-2.5-diphenyltetrazolium bromide (MTT) assay (Figure 3a). Our results indicate that Mn-L<sub>3</sub> micelles do not show any obvious toxic effects to cells after incubation for 24h, up to the largest concentration of 60 µM, demonstrating good biocompatibility. Finally, in vivo MRI is performed on 6-week-old male mice through tail vein injection at a dose of 30 µmol/kg. The first diagrams (0 seconds) serve here as control. As shown in figure 3b, the contrast enhancement develops gradually over time, and reaches a maximum about 2h after injection. The brightening effects are found mainly in liver and kidney, which is consistent with literature reports that particles are mainly taken up and accumulated by these two organs.<sup>[19]</sup>

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**Figure 3.** a) Relative viabilities of SMCC-7721 cells incubated with Mn-L<sub>3</sub> micelles at different Mn<sup>2+</sup> concentration for 24h. b) In vivo T<sub>1</sub>-weighted MR images (0.47T) and color-mapped images of a mouse at different time post-injection of a Mn-L<sub>3</sub> micelles solution at a dose of 30 µmol /kg based on Mn<sup>2+</sup>. Arrows indicate the kidney and liver.

In conclusion, we have synthesized and employed a new trisligand with three DPA groups grafted on a benzene ring, to create branched coordination polymers. Combining mixtures of this trisligand (L<sub>3</sub>) and a DPA-based bis-ligand (L<sub>2</sub>) with a polycationicneutral diblock copolymer we obtain mixed PIC micelles with a number of cross-links in the micellar core regulated simply by varying the L<sub>3</sub>/L<sub>2</sub> ratio. These mixed Mn-L<sub>2</sub>-L<sub>3</sub> micelles feature enhanced, tunable salt stability and magnetic relaxivity.

The presented strategy is generally applicable to other metal ions. For example, both Zn-L<sub>2</sub>-L<sub>3</sub> and Ni-L<sub>2</sub>-L<sub>3</sub> micelles show tunable response and enhanced stability against salt (Figures S12, S13). Hence, by simple variation of composition (in terms of metals and ligands) we can make many kinds of polyelectrolyte complex micelles (PIC micelles) with adjusted properties which will most likely see more applications in different fields. As an example of a biomedical application, we prepared Mn-L<sub>3</sub> micelles and find that these micelles feature high stability against salt, high relaxivity, good biocompatibility and strong contrast enhancement in a T<sub>1</sub>-weighted *in vivo* MRI test, demonstrating their excellent performance as MRI contrast agent.

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**Keywords:** polyelectrolytes micelles, coordination polymer, tunable stability and properties, MRI contrast agent

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Using two different DPA-based oligo-ligands, namely a bisligand (L<sub>2</sub>) and tris-ligand (L<sub>3</sub>), and metal ions we produce a supramolecular polyelectrolyte system with cross-links, the number of which can be varied by varying the  $L_3/L_2$  ratio. Combining this with a chargedneutral diblock copolymer we obtain M-L<sub>2</sub>-L<sub>3</sub> micelles with tuneable and enhanced salt stability and magnetic relaxivity, that perform very well as MRI contrast agent.



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