Precision design, solution behavior and application of stimuli-responsive *N*-vinylamides containing copolymers.

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Introduction

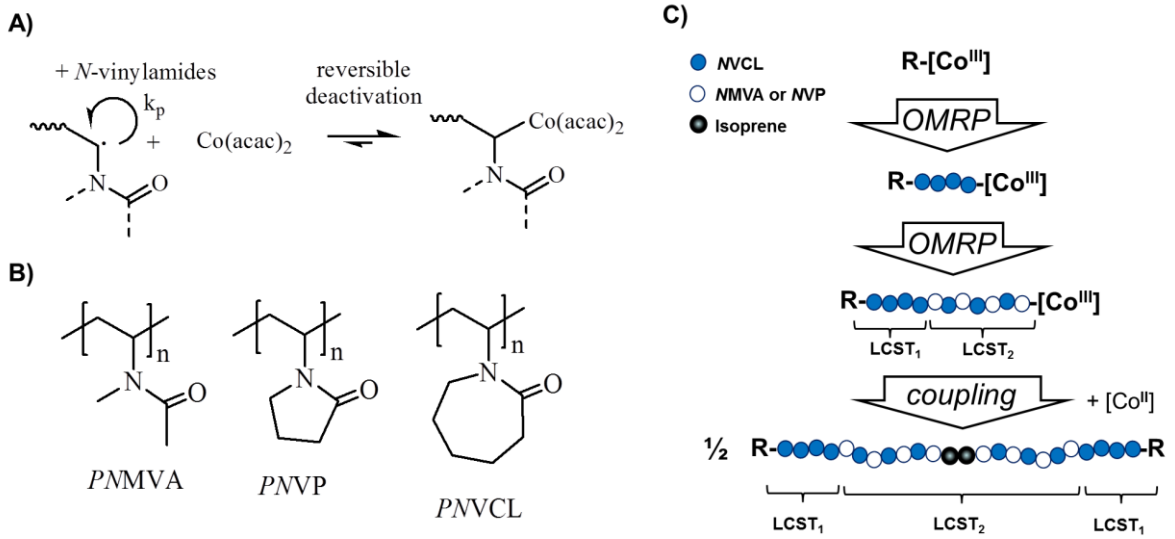
Recent years have witnessed an increasing development of "smart" or "stimuli-responsive" polymers.[1-3] The behavior and properties of such materials can drastically change when small modifications occur in their environment. Numerous stimuli have been investigated including temperature, light, pH, redox, etc. For example, the water solubility of polymers like poly(acid acrylic) (PAA) or poly(vinyl pyridine) (PVP) can be modulated by pH adjustment.[4] Other polymers exhibit a phase transition at a certain temperature leading to a sharp modification of their solubility. Poly(N-isopropylacrylamide) (PNIPAM)[5] and poly(oligo(ethylene glycol)methacrylate) (POEGMA)[6, 7] are typical examples of such thermo-responsive polymers. Interestingly, the stimuli responsive polymer sequences can be integrated in more complex macromolecular architectures like block copolymers. In this case, a change in the temperature or pH can trigger the reversible self-assembly of the copolymer into micelles or vesicles. At high copolymer concentration in water, reversible gelation phenomena can also occur. These materials can be considered as real "adaptive systems" and are exploited in more and more applications, notably for the development of drug delivery systems (DDS).

In this work, we focused on the synthesis of novel thermo-responsive copolymers based on poly(N-vinylcaprolactam) (PNVCL).[8-11] The latter is considered as a biocompatible and exhibits a lower critical solution temperature (LCST) in water that is close to the physiological temperature, which is of particular interest for the development in the biomedical field. Although N-vinylamides, like NVCL, can easily be polymerized radically, their growing radicals are quite reactive which makes the control of their polymerization and the insertion of well-defined poly(N-vinylamide)s segments into complex architectures difficult. For this reason, we developed a controlled radical polymerization (CRP) technique, called Organometallic-Mediated Radical Polymerization (OMRP),[12,13] which is very efficient for non-conjugated monomers (see section A).[8, 14-16] This tool notably permitted us to prepare single- and double- thermo-responsive diblock and triblock copolymers that follow a multi-step assembly behavior in water upon temperature changes (see section B).[9-11] Based on this technology, we also designed thermo- and redox- responsive nanogels which are promising drug delivery carriers (see section C).[11]

(A) Synthesis of NVCL-based copolymers.

In the last twenty years, controlled radical polymerization has become an important synthetic tool in the polymer chemist's arsenal. It decreases the extent of irreversible termination reactions that occur between the growing radical chains and responsible for the formation of ill-defined polymers. Recently, we found that OMRP is particularly suitable for controlling the polymerization of NVCL and other N-vinylamides like N-vinylpyrrolidone

(NVP) or N-methyl vinylacetamide (NMVA) (Scheme 1A).[8,14] This system relies on the temporary deactivation of the growing chains by a metal species, i.e. *bis*-(acetylacetonato) cobalt(II) complex, which protects radical chains from premature deactivation.

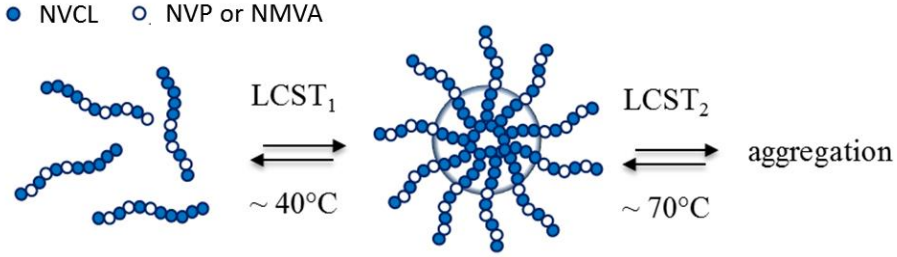


Scheme 1. OMRP mechanism for N-vinylamides (A), structures of common poly(N-vinylamide)s (B) and general strategy for the synthesis of double thermo-responsive block copolymers (C).

The OMRP technique made possible the production of poly(N-vinylamide)s with predictable molar masses (M_n) and low dispersity (Đ).[8] NVCL was also statistically copolymerized in a controlled fashion with hydrophilic and hydrophobic comonomers in order to tune up and down the LCST of the copolymer. [10] The sequential polymerization of two monomers by OMRP also gave access to well-defined block copolymers with a thermo-responsive block. Moreover, double thermo-responsive NVCL-based diblocks were prepared for the first time by homopolymerization of NVCL followed by the statistical copolymerization of the residual NVCL with a more hydrophilic N-vinylamide (Scheme 1C).[10] Finally, symmetrical double thermo-responsive triblock copolymers were obtained by Cobalt-Mediated Radical Coupling (CMRC)[17,18] of the corresponding diblock (Scheme 1C).

(B) Solution behavior of the thermo-responsive NVCL based copolymers.

The thermo-responsive properties and self-assembly behavior of these new NVCL-based copolymers were studied in dilute aqueous solutions by turbidimetry, dynamic light scattering and nuclear magnetic resonance.[9-11] For example, upon gradual heating of the double thermo-responsive copolymer solutions, we noticed a transition from free chains to micelles before full dehydration and collapse of the chains (Scheme 2).[10]

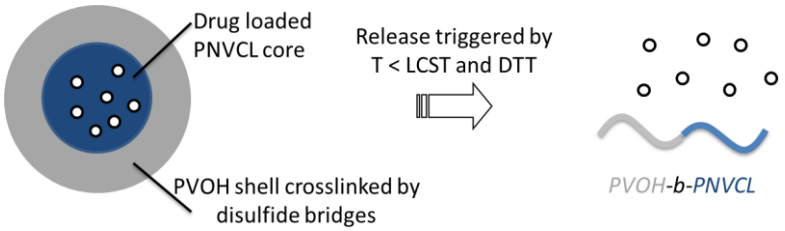


Scheme 2. Solution behavior of the double thermo-responsive NVCL-based diblock.

Rheological measurements also emphasized the ability of the above mentioned di- and tri-block copolymers to form reversible hydrogels at higher concentration in water. Temperature ramps were first performed to distinguish the different states, i.e. solubilized copolymers (below the two LCSTs), micelles (between the two LCSTs) and precipitated polymers (above the two LCSTs). Frequency and strain sweeps were realized in the different regimes highlighting the superiority of the triblock based hydrogels probably due to bridging of the micelles.

(C) Design of thermo- and redox-responsive nanogels for controlled drug release.

Well-defined poly(vinyl alcohol)-*b*-poly(N-vinylcaprolactam) (PVOH-*b*-PNVCL) prepared by OMRP were used to build thermo- and redox-responsive nanogels, which are interesting candidates for drug delivery application.[11] After self-assembly above the LCST of the PNVCL and loading the core of the micelles with a drug model, the PVOH shell was cross-linked with 3,3'-dithiodipropionic acid (DPA). Drug release was then evaluated below the LCST under reductive conditions by exposure to dithiothreitol (DTT), which mimics the intracellular glutathione and is able to cleave the disulfide bonds in the shell of the nanogel. The cytotoxicity of the nanogels against a mouse fibroblast-like L929 cell line was also assessed via the MTS assay.



Scheme 3. Thermo- and redox- responsive nanogels for drug delivery carrier.

Conclusion.

The OMRP of N-vinylamides described herein represents a significant step for the synthesis of new thermo-responsive copolymers with single or multi step assembly behaviors, which are of particular interest for future developments in the field of drug delivery systems.

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