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# Reversible addition–fragmentation chain transfer synthesis and micellar characteristics of biocompatible amphiphilic poly(vinyl acetate)-*graft*-poly(*N*-vinyl-2-pyrrolidone) copolymers

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ABSTRACT

Poly(vinyl acetate)-*graft*-poly(*N*-vinyl-2-pyrrolidone) (PVAc-*graft*-PNVP) copolymers of low grafting density and with a constant PVAc backbone of $DP_n = 72$, were synthesized by reversible addition–fragmentation chain transfer (RAFT) polymerization. A poly(vinyl acetate-*co*-vinyl chloroacetate) P(VAc-*co*-VClAc) gradient copolymer, also prepared by RAFT, was used as a macromolecular chain transfer agent. For this purpose it was functionalized by substitution of chlorine groups by xanthate moieties. In the NVP "grafting-from" polymerization step, PVAc-*graft*-PNVP copolymers were obtained, with PNVP contents from 85 to 95 mol% and with, on the average, 2–3 grafts per backbone with $DP_n$ ranging from 196 to 530. Their self-aggregation in aqueous medium revealed the formation of star-like micelles, with, at 25 °C, a partially "frozen-in" PVAc core and a PNVP corona.



## 1. Introduction

Over the last two decades, reversible addition–fragmentation chain transfer (RAFT) polymerization became one of the most versatile synthesis techniques for conferring living characteristics to radical polymerizations. Access was thus provided to a large variety of well-defined vinylic and acrylic homopolymers and copolymers with predetermined molecular weights and controlled architectures [1–5]. With this approach, a broad range of copolymers are presently available for the system *N*-vinyl-2-pyrrolidone (NVP) and vinyl acetate (VAc). Poly(*N*-vinyl-2-pyrrolidone) (PNVP) is in fact an attractive water-soluble and biocompatible polymer, extensively used in biomedical and cosmetic formulations. According to the recent review of Nakabayashi and Mori [6] and as also outlined by Moad et al. [7], RAFT polymerization is one of the most preferred approaches to attain controlled character of NVP polymerization by using xanthate type chain transfer agents (CTA). Similar to NVP, VAc, classified by Benaglia et al. [8] in the category of less activated monomers (LAMs), is polymerizable by a RAFT process. Thus, successful control of VAc polymerization has been reported for dithiocarbamates [1,9] and xanthates [3,10,11] mediated RAFT mechanisms.

The combination of these two monomers in a biocompatible polymer structure, such as statistical-, gradient-, block- and graft copolymers, has furthermore opened interesting perspectives for the development of amphiphilic materials.

In this respect, PVAc–PNVP copolymers, synthesized by conventional free-radical polymerization are now well-known for several decades [12] and more recently gradient

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copolymers were obtained in a controlled manner by Kaneyoshi and Matyjaszewski [13]. This type of poly (VAc-co-NVP) copolymers have for instance found applications in drug delivery systems [14], polyelectrolyte membranes by complex formation with silver salts [15], pervaporation membranes [16] and as surfactant complexes [17].

Well-defined block structures, of low molar mass dispersity (Đ), were developed over these last years by reversible-deactivation radical polymerization (RDRP) techniques. A first approach was that of Nguyen et al. [18] who reported the preparation of PNVP-*block*-PVAc copolymers by a RAFT process followed by that of Debuigne et al. [19] who investigated the cobalt mediated radical polymerization of NVP using VAc macro-initiators of different chain length. Recently, Fandrich et al. [20,21] synthesized PNVP-*block*-PVAc copolymers via a xanthate-mediated polymerization system in dioxane. These authors have examined in detail the reaction mechanism involved in this type of copolymerization and concluded that the use of dioxane can be responsible for the irreversible chain transfers. The most recent publications concerning the synthesis of PNVP-*block*-PVAc copolymers are those of Bailly et al. [22,23]. These authors investigated the preparation and the micellar characteristics of PNVP-*block*-PVAc copolymers having a constant PNVP sequence of a polymerization degree ($DP_n$) = 90 and hydrophobic PVAc sequences in the $DP_n$ range of 210–290. These biocompatible copolymers, leading to vesicular structures, were reported as drug delivery vehicles for hydrophobic drugs. Mention has finally to be made of the synthesis of molecular bottlebrushes, a particular class of graft copolymers, with PNVP-*block*-PVAc as side chains [24].

Even if numerous examples of graft copolymers comprising either PVAc or PNVP are reported [25–31], however, to the best of our knowledge, no controlled synthesis was carried out up to now of graft copolymers containing simultaneously PVAc as backbone and PNVP as grafts. It was therefore of interest to examine the synthesis by controlled polymerization procedures of well-defined graft copolymers having a PVAc backbone and PNVP grafts. In addition to PVAc-*block*-PNVP block copolymers, these graft structures could provide original amphiphilic and colloidal properties.

Among the possible synthesis strategies, a "grafting-from" technique was selected in order to take advantage of the RAFT polymerization to generate as well the functionalized PVAc backbone as the PNVP grafts. More precisely, the first objective of the study was to prepare a PVAc backbone, as a macromolecular chain transfer agent (macroCTA), with a fixed amount of vinyl chloroacetate grafting sites that can easily be transformed in xanthate moieties as RAFT initiators sites for the NVP polymerization. In contrast to macromonomer and "grafting on" techniques, this "grafting-from" type of approach allows the preparation of the PNVP grafts with high molecular weight. A further advantage is that the PNVP grafts will be linked by a hydrolytically cleavable ester group to the PVAc backbone, which could be of practical interest for the design of biodegradable materials.

The second aim of the study was to obtain, by dynamic light scattering (DLS) and nuclear magnetic resonance (NMR), a valuable insight into the self-aggregation of these graft copolymers with a constant PVAc backbone and PNVP side chains of low grafting density as well as of variable chain lengths. The association of these graft copolymers, of higher $DP_n$ of PNVP than that of the PVAc backbone, may lead to so-called star-like micelles.

## 2. Materials and methods

### 2.1. Materials

Vinyl acetate (Acros Organics; 99%) and vinyl chloroacetate (Alfa Aesar; 99%) were dried over calcium hydride, distilled *in vacuo* and degassed with nitrogen. *N*-vinyl-2-pyrrolidone (Aldrich; 99%) was purified by passing through a column of aluminum oxide. 2,2′-Azobis(isobutyronitrile) was recrystallized from methanol prior to use. Rhodixan A1 (*O*-ethyl *S*-(1-methoxycarbonyl) ethyl xanthate) was a gift from Rhodia. Lauroyl peroxide (Degussa), potassium ethyl xanthogenate (Alfa Aesar; 98%), 1,1′-Azobis(cyclohexane-carbonitrile) (V-40) (Aldrich; 98%) were used as received.

### 2.2. Characterization

Molecular weight ($M_n$) and molar mass dispersity $M_w/M_n$, also designated by Đ, of the PVAc backbone were determined using size exclusion chromatography (SEC) analyses performed on a Shimadzu LC-20AD liquid chromatograph equipped with two Varian PL gel 5 μm MIXED-C columns (column, injection and refractometer temperature: 30 °C; injection volume: 100 μL) and a refractive index detector (Shimadzu RID-10A). THF was used as the eluent at a flow rate of 1.0 mL/min. The molecular characteristics were determined relative to linear polystyrene calibration standards.

The graft copolymers were analyzed at 60 °C on a Shimadzu LC20AD chromatograph equipped with three PLgel mixte B columns and having as eluent a mixture of 0.2 M LiBr and DMF, a common solvent for both PVAc and PNVP sequences, at a flow rate of 1 mL/min. These analyses were performed in order to gain qualitative information, especially on the grafting efficiency, as the absolute values of the molecular weights are not directly accessible for graft copolymers.

The analyses of the PNVP grafts, obtained after the hydrolysis step, were performed on a Dionex Ultimate 3000 chromatograph equipped with four columns Shodex OH, a UV spectrophotometer Dionex, a refractometer Optilab rex (Wyatt Techn.) and a multi-angles light detector Dawn Heleos II (Wyatt Techn.). A mixture of Millipore water, 0.1 M $NaNO_3$ and acetonitrile (40%) was used as eluent at a flow rate of 0.5 mL/min. Acetonitrile was added to the water phase in the SEC determinations to limit the hydrophobic interactions between the PNVP and the columns [32]. The differential index of refraction (dn/dc) was 0.181.