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# Trithiocarbonate-Mediated RAFT Polymerization Enables the Synthesis of Homotelechelic *N*-Vinylpyrrolidone Oligomers with Surfactant Properties

Adèle Gapin and Frederik R. Wurm\*

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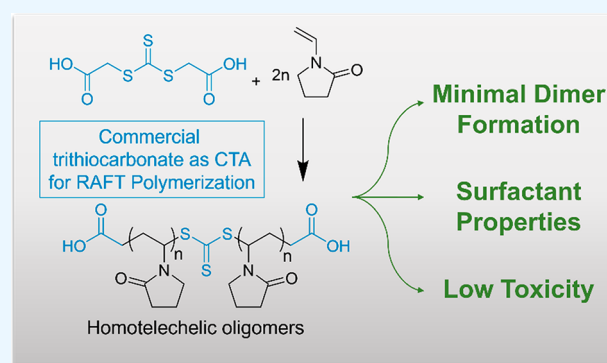
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**ABSTRACT:** Poly(*N*-vinylpyrrolidone) (PVP) is a well-known biocompatible polymer widely used in cosmetics, pharmaceuticals, and many other applications and is usually synthesized via radical polymerization. High molar mass PVP lacks biodegradability according to the OECD 301 F standard and can lead to permanent accumulation within the body or in the environment. Nowadays, lower molar mass PVP is produced via xanthate-mediated reversible addition–fragmentation chain-transfer (RAFT) polymerization. However, this type of polymerization also leads to a large amount of undesired dimer formation. Herein, various homotelechelic PVP oligomers were prepared via a trithiocarbonate-mediated RAFT polymerization with the production of a minimal amount of unsaturated dimer. These PVP oligomers showed similar surfactant properties as the well-known Lutensol AT50 surfactant, and they were used as a nonionic surfactant in a typical radical aqueous miniemulsion polymerization of methyl methacrylate (MMA) to produce well-defined PMMA nanoparticles. Additionally, PVP oligomers showed no toxicity to the bacterial strain *Escherichia coli* and to the water fleas *Daphnia pulex*, which is promising for safe release in wastewater systems.

**KEYWORDS:** Poly(*N*-vinylpyrrolidone), Oligomer, Homotelechelic, Trithiocarbonate, Surfactant



## INTRODUCTION

Surfactants are widely used in detergents, industrial processes, household products, and pesticide formulations. Nonionic surfactants are specifically found in many commercial products thanks to their high stabilization of dispersions.<sup>1</sup> Common nonionic surfactants include amphiphilic copolymers with poly(ethylene glycol) (PEG) as the hydrophilic segment such as Lutensol and copolymers of propylene oxide and ethylene oxide such as Pluronics.<sup>2</sup> *N*-Alkylpyrrolidones are also considered as nonionic surfactants, and poly(*N*-vinylpyrrolidone) (PVP) is used as a complexing agent due to the presence of its pyrrolidone ring capable of forming hydrogen bonds with organic compounds.<sup>3–5</sup>

PVP has numerous applications in medical, cosmetic, and food industries regarding its unique chemical and biological properties: it is nontoxic for humans, biocompatible, and water-soluble.<sup>6</sup> Poly(*N*-vinylpyrrolidone) is commonly associated with iodine to form a complex called povidone-iodine and used as an iodophor for hand disinfection, skin preparation, and antiseptic irrigation.<sup>7</sup> Generally, radical polymerization is the method of choice to produce high molar mass PVP; however, it remains resistant to biodegradation and its accumulation in the human body or in the environment could be a potential threat.<sup>8,9</sup> Trace concentration of high molar mass PVP is frequently found in

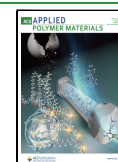
community wastewaters with a possible impact on the aquatic environment.<sup>10</sup> One solution to tackle this problem is to replace them by low molar mass PVP (i.e., oligomers). Chain transfer agents, such as hydrogen peroxide or mercaptoethanol, can be used to control their molar mass during radical polymerization.<sup>11–16</sup> For instance, Kratz et al. synthesized amino-terminated PVP oligomers ( $M_n = 5400$  g/mol) by using cysteamine as a chain-transfer agent.<sup>17</sup> Other methods can be used to obtain low molar mass PVP such as fractionation techniques used by Ranucci et al. for oligomeric drug carrier application or ultrafiltration techniques reported by Baldoli et al.<sup>18,19</sup> Nonetheless, these methods limit the range of end-groups accessible and give no access to well-defined PVP with low molar mass dispersity.

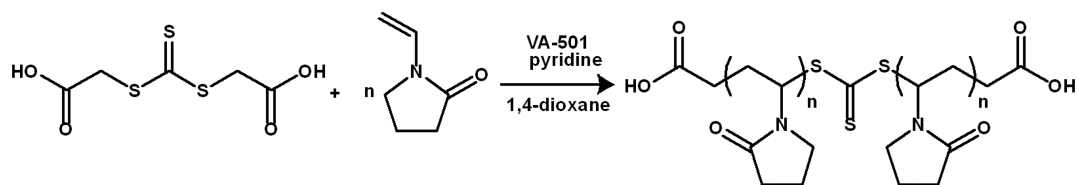
Reversible deactivation radical polymerization (RDRP) were investigated such as atom transfer radical polymerization (ATRP) to produce low to medium high molar mass PVP.<sup>20</sup>

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Scheme 1. Trithiocarbonate-Mediated RAFT Polymerization of *N*-VinylpyrrolidoneTable 1. RAFT Polymerizations of *N*-Vinylpyrrolidone

Entry	Polymer composition <sup>a</sup>	Polymer composition <sup>b</sup>	Conversion <sup>a</sup> %	$M_n^a$ g/mol	$M_n^b$ g/mol	$\bar{D}^b$	purity <sup>a</sup> %
1	PVP <sub>15</sub>	PVP <sub>6</sub>	46	1400	(550) <sup>c</sup>	(1.01) <sup>c</sup>	95
2	PVP <sub>18</sub>	PVP <sub>16</sub>	55	1800	1800	1.32	97
3	PVP <sub>27</sub>	PVP <sub>22</sub>	52	2300	2450	1.43	97
4	PVP <sub>28</sub>	PVP <sub>24</sub>	51	2300	2700	1.47	95
5	PVP <sub>37</sub>	PVP <sub>30</sub>	44	3400	5800	1.48	97

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopy. <sup>b</sup>Determined by SEC in DMF (vs PEG standards). <sup>c</sup>Limits of the calibration

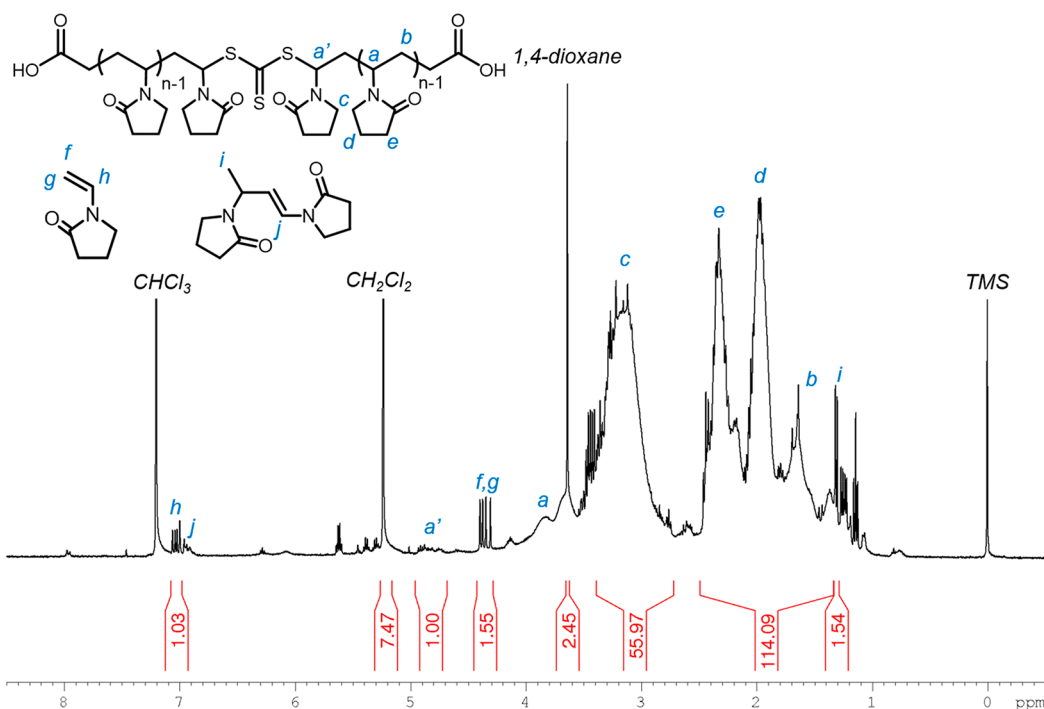
Recently, Mishra et al. synthesized alkynyl-terminated PVP oligomers ( $M_n = 3300$  g/mol) using propargyl-2-bromoisobutyrate as an ATRP initiator.<sup>21</sup> Chain-extension of a polyester via ATRP was performed by Huang et al. and led to amphiphilic polymer bottlebrushes containing short PVP segments.<sup>22</sup> However, they also reported an acid-catalyzed dimerization of *N*-vinylpyrrolidone (NVP), which occurred through a substitution reaction between bromides and the monomer.<sup>23</sup> Such dimerization is undesirable, because it prevents the formation of well-defined PVP homopolymer, and the olefinic moiety conjugated to the carbonyl group in the dimer structure is expected to be toxic toward microorganisms in an aquatic environment.<sup>24</sup> Thus, ATRP was replaced by xanthate-mediated reversible addition–fragmentation chain-transfer (RAFT) polymerization to synthesize well-defined PVP.<sup>25–28</sup> RAFT polymerization allows the synthesis of polymer with controlled molar masses and low dispersities, and usually xanthates are used as RAFT agents for the polymerization of less activated monomers (LAMs) such as *N*-vinylpyrrolidone.<sup>29–34</sup> For instance, Wan et al. reported the synthesis of low molar mass PVP up to  $M_n = 3700$  g/mol by using xanthates in fluoroalcohols, while Fandrich et al. used *O*-ethyl xanthate as a RAFT agent to yield PVP oligomers of  $M_n = 5000$  g/mol.<sup>35,36</sup> Nevertheless, it has been reported by Pound et al. that *N*-vinylpyrrolidone undergoes side reactions in the presence of specific xanthates and impurities.<sup>37</sup> A high number of byproducts can be produced such as hydration products and unsaturated dimers catalyzed by xanthates. Side reactions could be avoided by using different types of RAFT agents such as a trithiocarbonate chain-transfer agent, usually employed for the polymerization of more activated monomers (MAMs) such as methacrylic and acrylic monomers.<sup>38</sup> Recently, Liu et al. used a trithiocarbonate agent to synthesize relatively high molar mass PVP (i.e.,  $M_n = 15\,000$ – $21\,000$  g/mol,  $\bar{D} = 2.13$ – $2.16$ )<sup>39</sup> and Nandy et al. performed the chain extension polymerization of a macro-trithiocarbonate agent with *N*-vinylpyrrolidone obtaining a PVP block with relatively low molar mass (i.e.,  $M_n = 8000$  g/mol).<sup>40</sup> However, to our knowledge, a low molar mass homopolymer of *N*-vinylpyrrolidone has not been synthesized with trithiocarbonate RAFT agents. In addition, trithiocarbonate RAFT agents have been reported to have a higher stability<sup>41</sup> and to be less susceptible to hydrolysis<sup>42–44</sup> and oxidation<sup>45</sup> compared to xanthates, which had been previously used to polymerize NVP.

Herein, we present the preparation of various homotelechelic PVP oligomers via trithiocarbonate-mediated RAFT polymerization. The symmetrical bis(carboxymethyl)-trithiocarbonate RAFT agent was used as the chain-transfer agent to synthesize well-defined oligomers with a minimal production of unsaturated dimers. Molar masses of the oligomers were measured by size exclusion chromatography (SEC) and ranged from 550 to 5800 g/mol but should not be regarded as a limitation. A high purity of the oligomers was determined by <sup>1</sup>H NMR spectroscopy; further, they exhibited a similar surface activity as commercial surfactants according to spinning-drop measurements. One of the oligomers was used as a stabilizer in a typical radical aqueous miniemulsion polymerization of methyl methacrylate (MMA) to produce well-defined nanoparticles. Additionally, toxicity of PVP oligomers was tested toward bacteria (*E. coli*) and water fleas (*Daphnia pulex*). Such nontoxic oligomeric stabilizers based on *N*-vinylpyrrolidone could be safely used in various applications and released in wastewater systems without causing a lethal impact on aquatic wildlife.

## RESULTS AND DISCUSSION

**Trithiocarbonate-Mediated RAFT Polymerization of *N*-Vinylpyrrolidone.** Homotelechelic poly(*N*-vinylpyrrolidone) oligomers were synthesized via RAFT polymerization of *N*-vinylpyrrolidone (NVP) using bis(carboxymethyl)-trithiocarbonate as the chain-transfer agent (CTA) and 4,4-azobis(4-cyanovaleric acid) (VA-501) as the initiator in 1,4-dioxane at 80 °C (Scheme 1). A symmetrical CTA was employed to ensure the production of homotelechelic oligomers. VA-501 was chosen as the initiator to guarantee that the oligomer chains were terminated with carboxylic end-groups. Since it has been reported that the RAFT agent containing carboxylic acid can catalyze the dimerization of NVP, a minimal amount of pyridine was added to the reaction mixture to ensure a basic pH value.<sup>46–50</sup> A series of well-defined oligomers with degrees of polymerization ( $DP_n$ ) between 6 and 30 were prepared and obtained as yellow (typical color of trithiocarbonates)<sup>51</sup> and viscous materials at room temperature.

Oligomers were characterized by <sup>1</sup>H NMR spectroscopy, and their molar mass was determined by SEC in DMF (Table 1). In the case of PVP<sub>24</sub> (entry 4, Table 1), after ca. 3 h, a conversion of about 51% was reached. After precipitation into

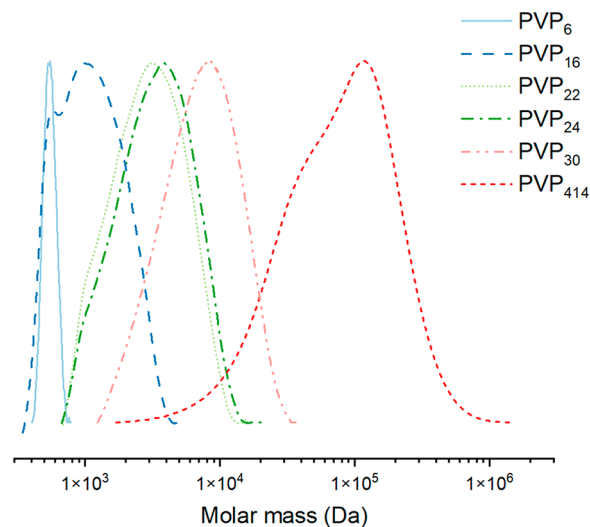


**Figure 1.**  $^1\text{H}$  NMR spectrum of PVP<sub>24</sub> (entry 4 in Table 1) in  $\text{CDCl}_3$ , 400 MHz, 40 °C.

diethyl ether, SEC chromatogram showed an apparent molar mass of  $M_n = 2700$  g/mol and a molar mass dispersity of  $\mathcal{D} = 1.47$ . The purity of the oligomers was confirmed by  $^1\text{H}$  NMR spectroscopy by integrating all the signals. For instance, for PVP<sub>24</sub>, signals were attributed to the presence of oligomer ( $\delta = 1.5\text{--}3.5$  ppm and  $\delta = 3.8$  ppm), dimer ( $\delta = 1.3$  and 6.9 ppm), monomer ( $\delta = 4.3$  and 7.0 ppm), 1,4-dioxane ( $\delta = 3.7$  ppm), and dichloromethane ( $\delta = 5.3$  ppm) (Figure 1). From NMR, a purity of ca. 98% was calculated for PVP<sub>24</sub>, with only ca. 0.3% of dimer formation during these conditions (see details in Supporting Information). Further NMR spectra proved the structure of the oligomer as expected (cf. Supporting Information for  $^{13}\text{C}$  NMR and DEPT 135 spectra, Figure S1).

In order to determine the limit of the efficiency of the trithiocarbonate agent, polymerization was carried out for a longer time. It was observed that the control of the polymerization was partly lost above 60% of conversion. However, a dimer content of ca. 1% was calculated according to NMR spectrum, so the rest of the study was performed with this symmetrical CTA. In addition, a polymerization was carried out on shorter time and stopped after 34% of conversion. From NMR analysis, a dimer content of ca. 1% was calculated.

As a comparison, high molar mass PVP was synthesized by conventional radical polymerization with a degree of polymerization of ca. 414. SEC analysis showed  $M_n = 45\,600$  g/mol and a molar mass dispersity of  $\mathcal{D} = 2.4$ . Polymer structure was checked by  $^1\text{H}$  NMR spectroscopy (Figure S2). SEC chromatograms of the oligomers and PVP<sub>414</sub> were plotted in Figure 2. Oligomers presented narrow to moderate molar mass distributions, while PVP<sub>414</sub> displayed a broad, multimodal distribution. The well-defined oligomers displayed molar masses ( $M_n$ ) between 550 and 5800 g/mol with molar mass distribution ( $\mathcal{D}$ ) between 1.01 and 1.48. Purities of oligomers were obtained between 95% and 99%. In addition, FTIR



**Figure 2.** Apparent molar masses of PVP oligomers and polymer (measured via SEC in DMF (0.1 M LiCl) at 60 °C vs PEG standards).

spectra of PVP<sub>24</sub> and PVP<sub>414</sub> were compared without showing any significant differences (Figures S3 and S4).

A control polymerization was performed in the same conditions as PVP oligomers without using pyridine. After ca. 3 h, the dimer formation was already observed via  $^1\text{H}$  NMR (Figure S5), while no polymerization occurred. However, the final product was purified by precipitation in diethyl ether to give a pale-yellow solid, and the presence of dimer was confirmed by  $^1\text{H}$  NMR (Figure S5). Hence, pyridine significantly reduces the unfavorable dimer formation while promoting the polymer formation.

**Thermal and Surfactant Properties.** The PVP oligomers and the polymer were characterized by thermal gravimetric analysis (TGA) under nitrogen with a heating rate of 10 °C/



min in order to follow their thermal degradation (Figure S6). PVP<sub>414</sub> showed a two-step degradation profile with a first weight loss corresponding to the loss of water, since high molar mass PVPs present hygroscopic properties,<sup>52</sup> and a second weight loss corresponding to the degradation of polymer backbone and occurring at 350 °C. PVP oligomers showed various thermal degradation profiles with several degradation steps. For instance, PVP<sub>24</sub> degraded with a three-step degradation profile. In general, polymers formed by LAMs have higher thermal stability than the one formed by MAMs.<sup>53</sup> However, low molar mass polymers are less stable than high molar mass polymers. These various thermal degradation profiles could be due to the presence of the trithiocarbonate RAFT unit in the center of the oligomer chain with weak C–S bonds in its structure. Stace et al. showed that the degradation of PVP containing dithiocarbamate end-groups starts with the homolysis of the C–S bond related to the end-group loss and depends on the nature of the Z-group.<sup>54</sup> Then, thermal properties of the materials were assessed by differential scanning calorimetry (DSC) under nitrogen at a heating rate of 20 °C/min. On their second heating thermograms, PVP oligomers displayed low glass-transition temperatures ( $T_g$ ) ranging from –26 to –10 °C and increasing with the number of repeating units (Figure S7). PVP<sub>414</sub> showed a high  $T_g$  around 165 °C which was similar to the glass-transition temperature of a commercial PVP (Figure S8).

The interfacial tension between water and cyclohexane was determined via spinning-drop tensiometry for one oligomer. The oligomer PVP<sub>24</sub> was dissolved in water at various concentrations, and the interfacial tension was measured against cyclohexane. The interfacial tension was compared to common nonionic surfactants for direct oil-in-water emulsions and to the PVP polymer (Table 2). For the highest concentrations of oligomer (i.e., 10, 15, and 30 g/L), the interfacial tensions were detected between 25.6 and 22.2 mN/m, similar to the commercial surfactants Lutensol AT50 and SDS at 0.1 g/L. For the lowest concentrations of oligomer (i.e.,

5, 1, 0.5, 0.1), the interfacial tensions were similar to PVP<sub>414</sub>. Interfacial tensions were plotted against oligomer concentrations (Figure S9).

**Stabilization of Radical Miniemulsion Polymerization of Methyl Methacrylate.** One of the synthesized oligomers was used to stabilize the radical miniemulsion polymerization of methyl methacrylate in water and to produce poly(methyl methacrylate) (PMMA) nanoparticles. The oil-in-water miniemulsion polymerization was conducted by dissolving PVP<sub>22</sub> and 2,2'-azobis[2-(2-imidazolin-2-yl)propane] dihydrochloride (VA-44) as the initiator in water, while the dispersed phase consisted of methyl methacrylate as the monomer and *n*-hexadecane as ultrahydrophobe. After sonication, a stable miniemulsion was obtained without any signs of phase separation. PVP<sub>22</sub> was able to sterically stabilize the methyl methacrylate nanodroplets and the resulting PMMA nanoparticles effectively. Dynamic light scattering (DLS) and scanning electron microscopy (SEM) proved the successful formation of spherical PMMA particles (Figure 3). DLS of the resulting dispersion revealed well-defined particles with diameters of ca. 631 nm and a PDI = 0.118 (Figure 3a).

**Toxicity Tests.** PVP oligomers were tested for bacterial toxicity. PVP<sub>24</sub> was incubated at two different concentrations (100 and 500 mg/L) with the strain NovaBlue of *E. coli* in a rich culture medium. Two controls were performed: a positive control with *E. coli* in a rich culture medium and a negative control containing antibiotics. The growth of *E. coli* was monitored by measuring the optical density at 600 nm. The corresponding growth curves were plotted in Figure 4. No difference was found between the positive control and the cultures containing PVP<sub>24</sub>: the bacterial growth curves look similar. Hence, oligomeric PVP does not present any toxicity toward *E. coli* contrary to high molar mass PVP which can be toxic toward Gram-negative bacteria.<sup>55,56</sup>

Toxicity study was also performed using *Daphnia pulex*. Daphnids were exposed to different concentrations of PVP<sub>16</sub> and acute toxicity effects were followed over 48 h. The test is considered valid if not more than 10% of the control Daphnids show immobilization. The percentages of immobilized Daphnids after 24 and 48 h were plotted against the concentration of the oligomer (Figure 5). None of the PVP<sub>16</sub> concentrations was highly toxic to *D. pulex*. These different concentrations (100, 50, 25, 12.5, and 6.25) did not show a lethal effect after 24 h; thus, no EC50s were obtained. After 48 h, only the concentrations above 25 mg/L showed a percentage of immobilization superior than or equal to 10%. A maximum immobilization of 20% was reached for the highest concentration (i.e., 100 mg/L) after 48 h; hence, no EC50s could be calculated. In comparison, Baumann et al. showed that high molar mass PVP was toxic toward *Daphnia magna* with an EC<sub>50</sub> after 48 h superior to 9750 mg/L.<sup>57</sup>

The concentration of PVP in river water was measured by Antić et al. and ranged from 0.9 to 7.1 mg/L after wastewater treatment plant.<sup>58</sup> In our study, oligomeric PVP did not show any toxicity toward *E. coli* at 500 mg/L after 8 days and showed no lethal effect toward *D. pulex* at 25 mg/L after 48 h. Therefore, we hypothesized that our oligomeric PVP can be safely released in wastewater treatment systems without causing lethal damage to aquatic wildlife.

## CONCLUSIONS

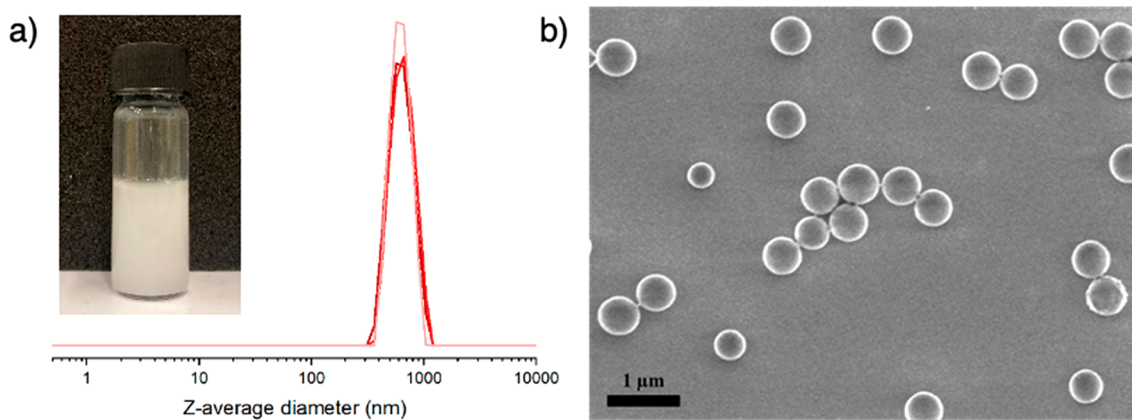
This work presents the synthesis of homotelechelic poly(*N*-vinylpyrrolidone) oligomers via trithiocarbonate-mediated

**Table 2. Interfacial Tension Values from Spinning-Drop Measurements**

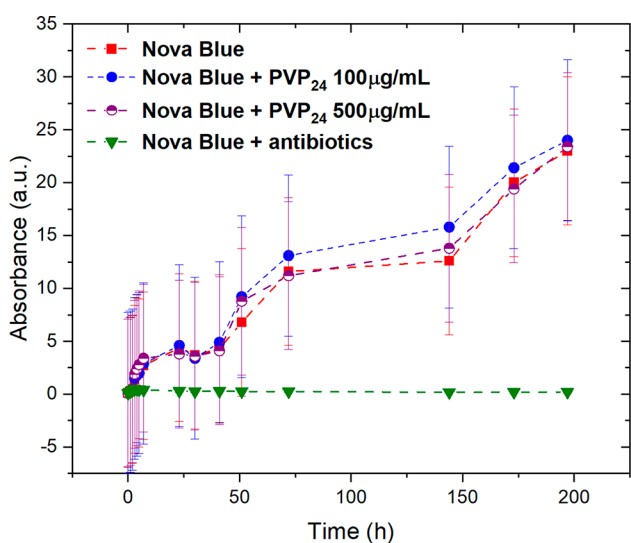
Sample <sup>a</sup>	Concentration g/L	Interfacial Tension <sup>b</sup> mN/m
PVP <sub>414</sub>	10	67.2 ± 1.2
PVP <sub>24</sub>	30	22.2 ± 0.8
PVP <sub>24</sub>	15	20.9 ± 0.4
PVP <sub>24</sub>	10	25.6 ± 0.2
PVP <sub>24</sub>	5	64.1 ± 0.9
PVP <sub>24</sub>	1	72.1 ± 1.0
PVP <sub>24</sub>	0.5	73.4 ± 1.0
PVP <sub>24</sub>	0.1	74.4 ± 1.1
Lutensol AT50	10	27.2 ± 0.5
Lutensol AT50	5	27.2 ± 0.4
Lutensol AT50	1	26.6 ± 0.4
Lutensol AT50	0.5	27.6 ± 0.6
Lutensol AT50	0.1	27.4 ± 0.5
SDS	10	6.6 ± 0.9
SDS	5	9.1 ± 0.2
SDS	1	7.5 ± 0.1
SDS	0.5	10.3 ± 0.2
SDS	0.1	32.4 ± 0.5

<sup>a</sup>Cyclohexane droplet spinning in the aqueous polymer solution.

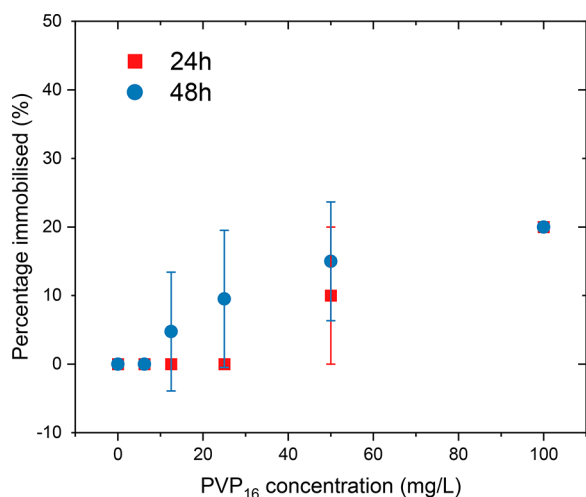
<sup>b</sup>Interfacial tension evaluated by the Laplace–Young method.



**Figure 3.** (a) DLS (size distribution by intensity, repeated scans) and photo of the PMMA nanoparticles prepared by radical miniemulsion polymerization, stabilized with PVP<sub>22</sub>. (b) SEM images of the PMMA nanoparticles (scale bar = 1 μm).



**Figure 4.** Microbial growth curves of *E. coli* bacteria grown at 37 °C, 300 rpm for 200 h.



**Figure 5.** Toxicity test of PVP<sub>16</sub> at different concentrations against *Daphnia pulex* after 24 and 48 h.

RAFT polymerization. The use of such symmetrical and commercially available trithiocarbonate RAFT agents reduced the acid-catalyzed dimer formation considerably. The obtained

oligomers displayed similar properties as the commercial Lutensol AT50 surfactant. PVP oligomers were able to stabilize the miniemulsion polymerization of methyl methacrylate and produced well-defined PMMA model nanoparticles. The PVP oligomers did not show toxicity toward *E. coli* and *D. pulex* up to 500 mg/L and 25 mg/L, respectively. PVP oligomers could be used to replace high molar mass poly(*N*-vinylpyrrolidone) as stabilizers for dispersions without having a lethal impact on aquatic environments in wastewater. In addition, such oligomers may present better biodegradability compared to high molar mass PVP, and the hydrolysis-labile trithiocarbonate can further reduce the molar mass during the degradation process. The biodegradation of PVP prepared by RAFT should be analyzed in future works to reduce bioaccumulation of this widely applied water-soluble polymer.

## EXPERIMENTAL SECTION

**Synthesis.** All manipulations involving air-sensitive reagents were carried out under a nitrogen atmosphere using a standard vacuum line and Schlenk techniques. All solvents and chemicals were purchased from Sigma-Aldrich, Acros Organics, Fluka, Fujifilm Wako Chemicals, or Fisher Scientific and used as received unless otherwise stated. Anhydrous deuterated chloroform ( $\geq 99.8$  atom % D) was purchased from Sigma-Aldrich and stored over activated molecular sieves (4 Å). Workup of polymeric materials was performed in air using lab-grade solvents. Milli-Q water was purified from a Milli-Q Advantage A10 purification system (Millipore, Billerica, Ma, USA).

To remove the stabilizers from 1,4-dioxane (Sigma-Aldrich,  $\geq 99.0\%$ ), *N*-vinylpyrrolidone (NVP, Sigma-Aldrich, 99.0%), and methyl methacrylate (MMA, Sigma-Aldrich, 99.0%), these were passed through basic alumina plugs in Pasteur pipettes and stored at 4 °C before use.

**General Procedure for the Trithiocarbonate-Mediated RAFT Polymerization of *N*-Vinylpyrrolidone.** Bis(carboxymethyl)-trithiocarbonate (470 mg, 2 mmol, 1 equiv), *N*-vinylpyrrolidone (4.4 mL, 41.5 mmol, 20 equiv), 4,4'-azobis(4-cyanovaleric acid) (VA-501, 192 mg, 0.6 mmol, 0.33 equiv), and pyridine (168 μL, 2 mmol, 1 equiv) were dissolved in 1,4-dioxane (2.2 mL) in a round-bottom 25 mL flask equipped with a magnetic stirring bar. The solution was stirred few minutes at room temperature and degassed under nitrogen for 20 min. The solution was then stirred for 3 h at 80 °C. The kinetics of the polymerization was followed by periodic extraction of aliquots from the reaction mixture, followed by dissolution in CDCl<sub>3</sub>. Each sample was analyzed by <sup>1</sup>H NMR spectroscopy. Finally, the flask was placed in liquid nitrogen until frozen and opened to air to terminate the polymerization. The crude product was purified by precipitation into cold diethyl ether (ca. -28 °C) two times, recovered in dichloromethane, and dried *in vacuo* to yield PVP<sub>24</sub>

Table 3. Overview of Conducted Polymerizations in This Study

Sample	Polymer composition <sup>a</sup>	Monomer	RAFT agent	Initiator	Pyridine	Dioxane	t (min)
1	PVP <sub>6</sub>	6.2 mL, 58.2 mmol, 14 eq	940 mg, 4.1 mmol, 1 eq	383 mg, 1.4 mmol, 0.33 eq	335 μL, 4.1 mmol, 1 eq	6.2 mL	360
2	PVP <sub>16</sub>	1 mL, 9.3 mmol, 15 eq	142 mg, 0.6 mmol, 1 eq	58 mg, 0.2 mmol, 0.33 eq	50 μL, 0.6 mmol, 1 eq	0.5 mL	140
3	PVP <sub>22</sub>	8.8 mL, 83 mmol, 20 eq	940 mg, 4.1 mmol, 1 eq	383 mg, 1.4 mmol, 0.33 eq	335 μL, 4.1 mmol, 1 eq	4.4 mL	180
4	PVP <sub>24</sub>	4.4 mL, 41.5 mmol, 20 eq	470 mg, 2 mmol, 1 eq	192 mg, 0.6 mmol, 0.33 eq	168 μL, 2 mmol, 1 eq	2.2 mL	180
5	PVP <sub>30</sub>	2.3 mL, 21.8 mmol, 35 eq	142 mg, 0.6 mmol, 1 eq	58 mg, 0.2 mmol, 0.33 eq	50 μL, 0.6 mmol, 1 eq	1.2 mL	140

<sup>a</sup>From SEC in DMF (vs PEG standards).

oligomer as a yellow honey-like product (yield: 65%; 3.01 g) (Table 3).

**General Procedure for the Radical Miniemulsion Polymerization of Methyl Methacrylate.** PVP<sub>22</sub> (115 mg) was dissolved in 2.5 mL of deionized water. A solution of 800 μL of methyl methacrylate (MMA) and 44 μL of *n*-hexadecane was prepared and added dropwise to the stirred solution containing the poly(*N*-vinylpyrrolidone) surfactant. The emulsion was stirred for 1 h at 1000 rpm. The emulsion was ultrasonicated (450 W, 3 min, 70% amplitude) to produce a stable miniemulsion. A solution of 25 mg of 2,2'-azobis[2-(2-imidazolin-2-yl)propane] dihydrochloride (VA-44) in 0.5 mL of deionized water was added to the miniemulsion. The miniemulsion was sealed and placed in an oil bath at 80 °C and the polymerization was allowed to proceed for 5 h. DLS: Particle size  $\bar{D}$  = 631 nm, PDI = 0.118.

**Characterization. Nuclear Magnetic Resonance (NMR) Spectroscopy.** <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded in deuterated chloroform as the solvent using a 400 MHz Bruker AVANCE III Nanobay spectrometer at room temperature. TopSpin 4.1.1. from Bruker was used for the analysis of all measured spectra. The spectra were calibrated against the solvent signal (Residual CHCl<sub>3</sub>;  $\delta$ H = 7.26 ppm).

**Size-Exclusion Chromatography (SEC).** Size-exclusion chromatography was performed in DMF (0.1 M LiCl) at 60 °C with an Agilent Technologies 1260 Infinity II, PSS SECurity system at a flow rate of 1 mL·min<sup>-1</sup>. Each sample injection volume was 50 μL, performed by Agilent 1260-ALS autosampler. 2 GRAM columns (PSS) in series with dimensions of 8 × 300 mm<sup>2</sup>, 10 μm particle size, and pore sizes of respectively 1000 and 30 Å, including a 10 μm GRAM guard column, were employed. Calibration was carried out using polyethylene glycol standards between 1,090,000 and 1620 g/mol supplied by Polymer Standards Service. The SEC data were plotted using the software OriginPro 2019b from OriginLab Corporation.

**Fourier Transform InfraRed (FTIR).** FTIR measurements were performed with an Alpha spectrometer from Bruker.

**Thermal Gravimetric Analysis (TGA).** TGA was performed on a TGA550 from TA Instruments at a heating rate of 10 °C·min<sup>-1</sup> under nitrogen from 25 to 600 °C.

**Differential Scanning Calorimetry (DSC).** DSC experiments were performed using a Pyris 1 from PerkinElmer under nitrogen. Aluminum pans were used with ca. 5 mg of the sample. For each oligomer, the temperature was increased from -50 to 50 °C with a ramp of 20 °C·min<sup>-1</sup>, then cooled to -50 °C at the same ramp. This was repeated during a second cycle with the same parameters. For each polymer, the temperature was increased from 0 to 200 °C with a ramp of 20 °C·min<sup>-1</sup>, then cooled to 0 °C at the same ramp. This was repeated during a second cycle with the same parameters.

**Spinning-Drop Measurements.** Spinning drop experiments were performed with the Spinning Drop video tensiometer SVT 20 N from DataPhysics; the evaluation was done by the Laplace–Young method.

**Dynamic Light Scattering (DLS).** Dynamic light scattering (DLS) was performed on a Zetasizer Nano S90 submicron particle sizer (Malvern Panalytical, UK) at a fixed angle of 90° and a laser diode running at 633 nm.

**Scanning Electron Microscopy (SEM).** Samples for SEM were prepared by drop-casting the sample solution onto a graphite SEM sample stub. Imaging was performed using a JEOL JSM-7610 F Plus ultrahigh resolution SEM microscope operated at 1.5 kV accelerating voltage to obtain the different structures/images.

**Toxicity Tests. Bacterial Assay.** Precultures and main cultures of *Escherichia coli* Nova Blue were prepared in a Luria–Bertani medium. Precultures were incubated in 50 mL shaking flasks at 37 °C for 24 h, with a shaking speed of 300 rpm. Main cultures were cultivated in 50 mL shaking flasks at 37 °C for 200 h, with a shaking speed of 300 rpm. Some of the main culture media contained different concentrations of PVP<sub>24</sub> oligomer (100 and 500 μg/mL) or antibiotics as negative control. The bacterial growth was followed by measuring the optical density at 600 nm (OD<sub>600</sub>).

**Daphnia sp., Acute Immobilization Test.** Acute toxicity testing was conducted according to OECD 202<sup>59</sup> to determine the acute lethal toxicity of PVP<sub>16</sub> on the juvenile *D. pulex* (age <24 h). Four replicates of five daphnids were exposed to 6.25, 12.5, 25, 50, and 100 mg/L of PVP<sub>16</sub> in reconstituted water (CaCl<sub>2</sub>, 2H<sub>2</sub>O; MgSO<sub>4</sub>, 7H<sub>2</sub>O; NaHCO<sub>3</sub>; KCl). The presence of oligomer did not alter the pH of solutions, and tests were run in the pH range of 7.5 to 8.5. In addition, a control was prepared with reconstituted water only. Solvents were not used to dissolve the oligomer. Experiments were conducted in glass test tubes in a temperature-controlled cabinet at 20 ± 1 °C in complete darkness. Tests were carried out under static conditions. After 24 and 48 h, each solution was checked for immobilized Daphnids, meaning Daphnids not able to swim within 15 s after gentle agitation.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsapm.2c00796>.

Additional <sup>1</sup>H and <sup>13</sup>C NMR spectra, purity calculation details, FTIR spectra, thermal characterizations results, interfacial tension measurements, and additional SEM images (PDF)

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### Author Contributions

A.G. and F.R.W. conceived of and designed the experiments. A.G. carried out the syntheses and characterizations and



analyzed the experimental results. The manuscript was written and edited through contributions of A.G. and F.R.W. All authors have given approval to the final version of the manuscript.

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## REFERENCES

- (1) Bajpai, D.; Tyagi, V. K. Nonionic Surfactants: An Overview. *Tenside Surfactants Detergents* **2010**, *47* (3), 190–196.
- (2) Rheinberger, T.; Wolf, T.; Wurm, F. R. Nonionic Surfactants Based on Amphiphilic Polyphosphonate Copolymers Prepared via Anionic Ring-Opening Copolymerization. *Eur. Polym. J.* **2020**, *131*, 109700.
- (3) Lam, S.-M.; Kee, M.-W.; Sin, J.-C. Influence of PVP Surfactant on the Morphology and Properties of ZnO Micro/Nanoflowers for Dye Mixtures and Textile Wastewater Degradation. *Mater. Chem. Phys.* **2018**, *212*, 35–43.
- (4) Wen, T.; Lu, L.; Dong, C.; Luo, Y. Investigation on the Regeneration Performance of Liquid Desiccant by Adding Surfactant PVP-K30. *Int. J. Heat Mass Transfer* **2018**, *123*, 445–454.
- (5) Shao, X.-F.; Yang, S.; Lin, J.-C.; Teng, H.-R.; Fan, L.-W.; Chiu, J. N.; Yuan, Y.-P.; Martin, V. Polyvinylpyrrolidone (PVP)-Enabled Significant Suppression of Supercooling of Erythritol for Medium-Temperature Thermal Energy Storage. *Journal of Energy Storage* **2022**, *46*, 103915.
- (6) Awasthi, R.; Manchanda, S.; Das, P.; Velu, V.; Malipeddi, H.; Pabreja, K.; Pinto, T. D. J. A.; Gupta, G.; Dua, K. Poly(Vinylpyrrolidone). In *Engineering of Biomaterials for Drug Delivery Systems*; Elsevier, 2018; pp 255–272. DOI: 10.1016/B978-0-08-101750-0.00009-X.
- (7) Makhayeva, D. N.; Filippov, S. K.; Yestemes, S. S.; Irmukhametova, G. S.; Khutoryanskiy, V. V. Polymeric Iodophors with Poly(2-Ethyl-2-Oxazoline) and Poly(N-Vinylpyrrolidone): Optical, Hydrodynamic, Thermodynamic, and Antimicrobial Properties. *Eur. Polym. J.* **2022**, *165*, 111005.
- (8) Vanharova, L.; Julinova, M.; Slavik, R. PVP Based Materials: Biodegradation in Different Environments. *Ecological Chemistry and Engineering S* **2017**, *24* (2), 299–309.
- (9) Julinova, M.; Kupec, J.; Slavik, R.; Vaskova, M. Initiating Biodegradation of Polyvinylpyrrolidone in an Aqueous Aerobic Environment: Technical Note/Zainicjowanie Biodegradacji Poliwinylpiperolidonu W Środowisku Wodno-Tlenowym: Notatki Techniczne. *Ecological Chemistry and Engineering S* **2013**, *20* (1), 199–208.
- (10) Julinová, M.; Vaňharová, L.; Jurča, M. Water-Soluble Polymeric Xenobiotics – Polyvinyl Alcohol and Polyvinylpyrrolidone – And Potential Solutions to Environmental Issues: A Brief Review. *Journal of Environmental Management* **2018**, *228*, 213–222.
- (11) Akashi, M.; Kirikihira, I.; Miyauchi, N. Synthesis and Polymerization of a Styryl Terminated Oligovinylpyrrolidone Macromonomer. *Angew. Makromol. Chem.* **1985**, *132* (1), 81–89.
- (12) Andreani, F.; Salatelli, E.; Ferruti, P. Synthesis of Functionalized End-Capped N-Vinylpyrrolidone Telomers with Potential Utility as Drug-Binding Matrices. *J. Bioact. Compat. Polym.* **1986**, *1* (1), 72–78.
- (13) Veronese, F. M.; Sartore, L.; Caliceti, P.; Schiavon, O.; Ranucci, E.; Ferruti, P. Hydroxyl-Terminated Polyvinylpyrrolidone for the Modification of Polypeptides. *J. Bioact. Compat. Polym.* **1990**, *5* (2), 167–178.
- (14) Schiavon, O.; Veronese, F. M.; Sartore, L.; Ranucci, E.; Ferruti, P.; Caliceti, P. Low Molecular Weight End-Functionalized Poly(N-Vinylpyrrolidone) for the Modification of Polypeptide Aminogroups. *J. Bioact. Compat. Polym.* **1994**, *9* (4), 411–428.
- (15) Chung, T. W.; Cho, K. Y.; Lee, H.-C.; Nah, J. W.; Yeo, J. H.; Akaike, T.; Cho, C. S. Novel Micelle-Forming Block Copolymer Composed of Poly( $\epsilon$ -Caprolactone) and Poly(Vinyl Pyrrolidone). *Polymer* **2004**, *45* (5), 1591–1597.
- (16) Ranucci, E.; Capuano, G.; Manfredi, A.; Ferruti, P. One-Step Synthesis of Poly(Lactic- Co -Glycolic Acid)- *g* -Poly-1-Vinylpyrrolidin-2-One Copolymers. *J. Polym. Sci., Part A: Polym. Chem.* **2016**, *54* (13), 1919–1928.
- (17) Kratz, K. Surface Hydrophilization of Highly Porous Poly(Ether Imide) Microparticles by Covalent Attachment of Poly(Vinyl Pyrrolidone). *Polymer* **2020**, *210*, 123045.
- (18) Ranucci, E.; Spagnoli, G.; Sartore, L.; Bignotti, F.; Ferruti, P.; Schiavon, O.; Caliceti, P.; Veronese, F. M. Synthesis and Molecular Weight Characterization of End-Functionalized N-Vinyl-2-Pyrrolidone Oligomers. *Macromol. Chem. Phys.* **1995**, *196* (3), 763–774.
- (19) Baldoli, C.; Oldani, C.; Maiorana, S.; Ferruti, P.; Ranucci, E.; Bencini, M.; Contini, A. Functionalization and Molecular Dynamics Study of Carboxy-Terminated Poly(1-Vinylpyrrolidin-2-One): A Potential Soluble Carrier of Biomolecules. *J. Polym. Sci. A Polym. Chem.* **2008**, *46* (5), 1683–1698.
- (20) Lu, X.; Gong, S.; Meng, L.; Li, C.; Yang, S.; Zhang, L. Controllable Synthesis of Poly(N-Vinylpyrrolidone) and Its Block Copolymers by Atom Transfer Radical Polymerization. *Polymer* **2007**, *48* (10), 2835–2842.
- (21) Vivek Mishra; Rajesh Kumar. Cyclic Polymer of N-Vinylpyrrolidone via ATRP Protocol: Kinetic Study and Concentration Effect of Polymer on Click Chemistry in Solution. *Polym. Sci. Ser. B* **2019**, *61* (6), 753–761.
- (22) Huang, Y.-S.; Chen, J.-K.; Kuo, S.-W.; Hsieh, Y.-A.; Yamamoto, S.; Nakanishi, J.; Huang, C.-F. Synthesis of Poly(N-Vinylpyrrolidone)-Based Polymer Bottlebrushes by ATRPA and RAFT Polymerization: Toward Drug Delivery Application. *Polymers* **2019**, *11* (6), 1079.
- (23) Huang, C.-F.; Nicolaÿ, R.; Kwak, Y.; Chang, F.-C.; Matyjaszewski, K. Homopolymerization and Block Copolymerization of N -Vinylpyrrolidone by ATRP and RAFT with Haloxanthate Inifers. *Macromolecules* **2009**, *42* (21), 8198–8210.
- (24) Schultz, T. W.; Yarbrough, J. W. Trends in Structure–Toxicity Relationships for Carbonyl-Containing  $\alpha,\beta$ -Unsaturated Compounds. SAR and QSAR in *Environmental Research* **2004**, *15* (2), 139–146.
- (25) Reader, P. W.; Pfuëkwa, R.; Jokonya, S.; Arnott, G. E.; Klumperman, B. Synthesis of  $\alpha,\omega$ -Heterotelechelic PVP for Bioconjugation, via a One-Pot Orthogonal End-Group Modification Procedure. *Polym. Chem.* **2016**, *7* (42), 6450–6456.
- (26) Popp, B. V.; Miles, D. H.; Smith, J. A.; Fong, I. M.; Pasquali, M.; Ball, Z. T. Stabilization and Functionalization of Single-Walled Carbon Nanotubes with Polyvinylpyrrolidone Copolymers for Applications in Aqueous Media. *J. Polym. Sci., Part A: Polym. Chem.* **2015**, *53* (2), 337–343.
- (27) Pound, G.; Aguesse, F.; McLeary, J. B.; Lange, R. F. M.; Klumperman, B. Xanthate-Mediated Copolymerization of Vinyl Monomers for Amphiphilic and Double-Hydrophilic Block Copolymers with Poly(Ethylene Glycol). *Macromolecules* **2007**, *40* (25), 8861–8871.
- (28) Pound, G.; McKenzie, J. M.; Lange, R. F. M.; Klumperman, B. Polymer–Protein Conjugates from  $\omega$ -Aldehyde Endfunctional Poly-(N-Vinylpyrrolidone) Synthesized via Xanthate-Mediated Living Radical Polymerisation. *Chem. Commun.* **2008**, No. 27, 3193.
- (29) Johnson, I. J.; Khosravi, E.; Musa, O. M.; Simnett, R. E.; Eissa, A. M. Xanthates Designed for the Preparation of N -Vinyl Pyrrolidone-Based Linear and Star Architectures via RAFT Polymerization. *J. Polym. Sci., Part A: Polym. Chem.* **2015**, *53* (6), 775–786.
- (30) Yin, F.; Nguyen, H. H.; Coutelier, O.; Destarac, M.; Lauth-de Viguier, N.; Marty, J.-D. Effect of Copolymer Composition of



- Controlled (N-Vinylcaprolactam/N-Vinylpyrrolidone) Statistical Copolymers on Formation, Stabilization, Thermoresponsiveness and Catalytic Properties of Gold Nanoparticles. *Colloids Surf., A* **2021**, *630*, 127611.
- (31) Schmitt, J.; Blanchard, N.; Poly, J. Controlled Synthesis of Branched Poly(Vinyl Acetate)s by Xanthate-Mediated RAFT Self-Condensing Vinyl (Co)Polymerization. *Polym. Chem.* **2011**, *2* (10), 2231.
- (32) Peña, J. A.; Gutiérrez, S. J.; Villamil, J. C.; Agudelo, N. A.; Pérez, L. D. Policaprolactone/Polyvinylpyrrolidone/Siloxane Hybrid Materials: Synthesis and in Vitro Delivery of Diclofenac and Biocompatibility with Periodontal Ligament Fibroblasts. *Materials Science and Engineering: C* **2016**, *58*, 60–69.
- (33) Aroua, S.; Tiu, E. G. V.; Ayer, M.; Ishikawa, T.; Yamakoshi, Y. RAFT Synthesis of Poly(Vinylpyrrolidone) Amine and Preparation of a Water-Soluble C<sub>60</sub>-PVP Conjugate. *Polym. Chem.* **2015**, *6* (14), 2616–2619.
- (34) Tilottama, B.; Manojkumar, K.; Haribabu, P. M.; Vijayakrishna, K. A Short Review on RAFT Polymerization of Less Activated Monomers. *Journal of Macromolecular Science, Part A* **2022**, 1–22.
- (35) Wan, D.; Satoh, K.; Kamigaito, M.; Okamoto, Y. Xanthate-Mediated Radical Polymerization of N-Vinylpyrrolidone in Fluoroalcohols for Simultaneous Control of Molecular Weight and Tacticity. *Macromolecules* **2005**, *38* (25), 10397–10405.
- (36) Fandrich, N.; Falkenhagen, J.; Weidner, S. M.; Staal, B.; Thünemann, A. F.; Laschewsky, A. Characterization of New Amphiphilic Block Copolymers of N-Vinylpyrrolidone and Vinyl Acetate, 2 - Chromatographic Separation and Analysis by MALDI-TOF and FT-IR Coupling. *Macromol. Chem. Phys.* **2010**, *211* (15), 1678–1688.
- (37) Pound, G.; Eksteen, Z.; Pfkwa, R.; Mckenzie, J. M.; Lange, R. F. M.; Klumperman, B. Unexpected Reactions Associated with the Xanthate-mediated Polymerization of N-vinylpyrrolidone. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 6575–6593.
- (38) Sigma Aldrich. *Controlled Radical Polymerization Guide*; p 52.
- (39) Liu, W.; Zhang, S.; Liu, S.; Wu, Z.; Chen, H. Efficient Heterodifunctional Unimolecular Ring-Closure Method for Cyclic Polymers by Combining RAFT and SuFEx Click Reactions. *Macromol. Rapid Commun.* **2019**, *40* (20), 1900310.
- (40) Nandy, K.; Srivastava, A.; Afgan, S.; Deepak, Kumar, R.; Kumar Rawat, A.; Singh, R.; Singh, R. K. The Benzyl Ethyl Trithiocarbonate Mediated Control Synthesis of a Block Copolymer Containing N-Vinyl Pyrrolidone by RAFT Methodology: Influence of Polymer Composition on Cell Cytotoxicity and Cell Viability. *Eur. Polym. J.* **2020**, *122*, 109387.
- (41) Legge, T. M.; Slark, A. T.; Perrier, S. Thermal Stability of Reversible Addition–Fragmentation Chain Transfer/Macromolecular Architecture Design by Interchange of Xanthates Chain-Transfer Agents. *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44* (24), 6980–6987.
- (42) Cortez-Lemus, N. A.; Hermosillo-Ochoa, E.; Licea-Claverie, Á. Effective End-Group Modification of Star-Shaped PNVCL from Xanthate to Trithiocarbonate Avoiding Chemical Crosslinking. *Polymers* **2021**, *13* (21), 3677.
- (43) Matioszek, D.; Dufils, P.-E.; Vinas, J.; Destarac, M. Selective and Quantitative Oxidation of Xanthate End-Groups of RAFT Poly(n-Butyl Acrylate) Latexes by Ozonolysis. *Macromol. Rapid Commun.* **2015**, *36* (14), 1354–1361.
- (44) Moad, G.; Rizzardo, E.; Thang, S. H. End-Functional Polymers, Thiocarbonylthio Group Removal/Transformation and Reversible Addition–Fragmentation–Chain Transfer (RAFT) Polymerization. *Polym. Int.* **2011**, *60* (1), 9–25.
- (45) Chen, M.; Moad, G.; Rizzardo, E. Thiocarbonylthio End Group Removal from RAFT-Synthesized Polymers by a Radical-Induced Process. *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47* (23), 6704–6714.
- (46) Breitenbach, J. W.; Galinovskiy, F.; Nesvadba, H.; Wolf, E. Über ein Dimeres N-Vinylpyrrolidon und das 1,1-Bis-(1'-pyrrolidonyl)-äthan. *Monatshefte für Chemie* **1956**, *87*, 580–592.
- (47) Breitenbach, J. W. Polymerization and Polymers of N-Vinylpyrrolidone. *J. Polym. Sci.* **1957**, *23* (104), 949–953.
- (48) Kaupp, G.; Matthies, D. Organische Gas-Festkörper-Reaktionen mit Stilbenen, Chalkonen und Enamiden. *Chem. Ber.* **1987**, *120* (11), 1897–1903.
- (49) Zhuo, J.-C. 1,3-Bis(Pyrrolidin-2-on-1-Yl)but-1-Ene. *Molecules* **1999**, *4* (12), M117.
- (50) Madl, A.; Spange, S. On the Importance of the Amide-Bonded Hydrogen Atom in the Cationically Induced Oligomerization of N-Vinylamides. *Macromolecules* **2000**, *33* (15), 5325–5335.
- (51) Barner, L.; Perrier, S. Polymers with Well-Defined End Groups via RAFT– Synthesis, Applications And Postmodifications. In *Handbook of RAFT Polymerization*; Barner-Kowollik, C., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2008; pp 455–482. DOI: 10.1002/9783527622757.ch12.
- (52) Rask, M. B.; Knopp, M. M.; Olesen, N. E.; Holm, R.; Rades, T. Influence of PVP/VA Copolymer Composition on Drug–Polymer Solubility. *European Journal of Pharmaceutical Sciences* **2016**, *85*, 10–17.
- (53) Chernikova, E. V.; Kudryavtsev, Y. V. RAFT-Based Polymers for Click Reactions. *Polymers* **2022**, *14* (3), 570.
- (54) Stace, S. J.; Fellows, C. M.; Moad, G.; Keddie, D. J. Effect of the Z- and Macro-R-Group on the Thermal Desulfurization of Polymers Synthesized with Acid/Base “Switchable” Dithiocarbamate RAFT Agents. *Macromol. Rapid Commun.* **2018**, *39* (19), 1800228.
- (55) Nair, B. Final Report On the Safety Assessment of Polyvinylpyrrolidone (PVP). *Int. J. Toxicol* **1998**, *17*, 95–130.
- (56) Luo, X.; Xu, S.; Yang, Y.; Li, L.; Chen, S.; Xu, A.; Wu, L. Insights into the Ecotoxicity of Silver Nanoparticles Transferred from Escherichia Coli to Caenorhabditis Elegans. *Sci. Rep* **2016**, *6* (1), 36465.
- (57) Baumann, J.; Köser, J.; Arndt, D.; Filser, J. The Coating Makes the Difference: Acute Effects of Iron Oxide Nanoparticles on Daphnia Magna. *Science of The Total Environment* **2014**, *484*, 176–184.
- (58) Antić, V. V.; Antić, M. P.; Kronimus, A.; Oing, K.; Schwarzbauer, J. Quantitative Determination of Poly-(Vinylpyrrolidone) by Continuous-Flow off-Line Pyrolysis-GC/MS. *Journal of Analytical and Applied Pyrolysis* **2011**, *90* (2), 93–99.
- (59) OECD. *OECD Guideline for Testing of Chemicals - Daphnia Sp., Acute Immobilisation Test*, 2004.