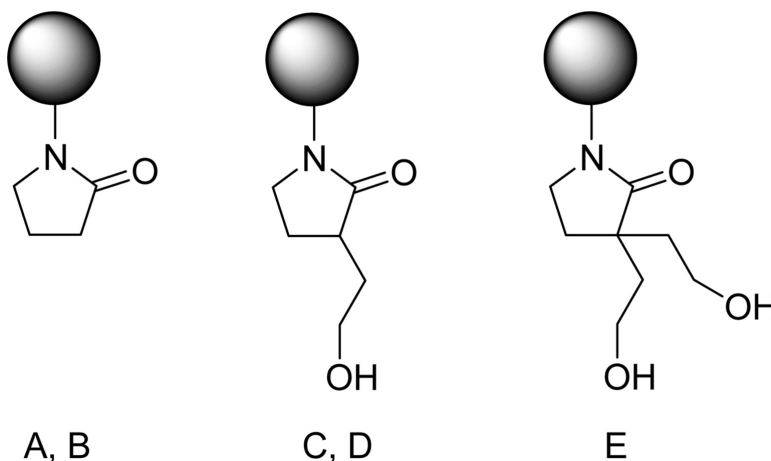


## Hydrophilic Polymer Supports for Solid-Phase Synthesis: Hydroxyl-Functional Beads of Poly(vinylpyrrolidone)

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# Hydrophilic Polymer Supports for Solid-Phase Synthesis: Hydroxyl-Functional Beads of Poly(vinylpyrrolidone)

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Poly(vinylpyrrolidone) (PVP) has solubility properties that make it an attractive material for polymer-assisted synthesis applications; however, the naked polymer lacks reactive groups upon which to do chemistry. Furthermore, large differences in radical reactivity between 1-vinylpyrrolidin-2-one (NVP) and most other monomers lead to compositional drift during copolymerization, further complicating the introduction of functional groups into the polymer using this method. Monomers that are derivatives of NVP itself are expected to show smaller differences in radical reactivity and therefore provide a way of preparing PVP with adjustable properties. Three monomers introducing hydroxyl-functional groups and a new cross-linker, all derivatives of NVP, were synthesized and used in the preparation of a new type of hydrophilic polymer beads by aqueous suspension polymerization. These lightly cross-linked beads contain hydroxyl groups at a functional loading of 0.21–0.29 mmol/g and swell extensively in a broad range of solvents.

## Introduction

Ever since Merrifield<sup>1</sup> introduced the technique of solid-phase peptide synthesis in 1963, this technique has been utilized in a large variety of chemical reactions. In general, polymer-assisted synthesis methods utilize the physical properties of the polymer, which provide the chemist with a handle by which the polymer-bound compound can easily be separated from complex reaction mixtures. Both cross-linked and soluble polymers are used in organic synthesis as support materials for substrates, reagents, catalysts, and scavengers.<sup>2</sup> Although soluble polymers ideally provide a more homogeneous reaction mixture in which all reacting species are in solution,<sup>3</sup> these supports are used to a much lesser extent than the cross-linked polymers. The main reason for this is that the soluble polymers generally require a more complicated separation procedure than the cross-linked materials do while also exhibiting a low substitution level.<sup>4</sup>

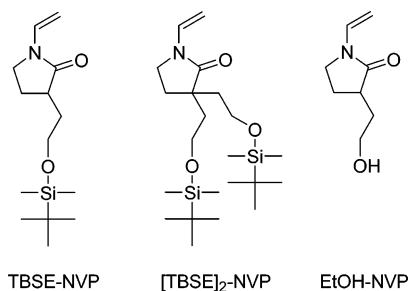
Cross-linked polymer supports are generally used in the form of beads that are easily isolated by simple filtration techniques. Macroporous beads have a high degree of cross-linking and are often rigid materials that preserve their porosity regardless of the chemical environment to which they are subjected.<sup>5</sup> Although the permanent porosity permits easy access to the reactive sites on the surface, the inability to swell prevents access to sites imbedded in the polymer.<sup>6</sup> Lightly cross-linked beads expand or collapse, depending on the surrounding chemical environment, and once these materials are swollen by an appropriate solvent, virtually all reactive sites within the beads are chemically accessible.

By far, the most widely used cross-linked supports are made from polystyrene cross-linked with divinylbenzene

(PS–DVB). These materials are easily swollen by a range of low-polarity solvents, but their hydrophobic nature hinders swelling in most polar solvents, such as methanol and water, and consequently, using such materials in polar solvents is virtually impossible. A number of different strategies have been employed to prepare alternative supports that avoid the limitations of PS–DVB.<sup>7</sup> Apart from copolymerization of hydrophilic monomers,<sup>8–16</sup> two other general methods have been used to achieve this. The first employs grafting of poly(ethylene glycol) (PEG) chains onto beads of PS–DVB.<sup>17–21</sup> The second utilizes PEG chains as cross-linking units within the resins.<sup>22–25</sup>

Although it is necessary for a lightly cross-linked polymer support to be able to swell in the reaction medium, this ability is not the only important feature of the material. In a solid-phase reaction, the swollen polymer is the equivalent of the solvent in the corresponding solution-phase reaction.<sup>26</sup> Because of this, the specific properties of each polymer support provide unique reaction conditions, which may or may not be suitable for a certain reaction. Since poly(vinylpyrrolidone) (PVP) is soluble in water and methanol as well as a number of other organic solvents,<sup>27</sup> this polymer offers an interesting alternative support material. However, PVP lacks the reactive functional groups necessary for attaching organic compounds to the polymer. Furthermore, the radical reactivity of 1-vinylpyrrolidin-2-one (NVP) is different from most other monomers.<sup>28,29</sup> This difference leads to compositional drift during copolymerization, which complicates the introduction of reactive groups into the polymer by means of this method. For the same reason, it is also difficult to cross-link PVP using any of the standard (meth)acrylate- or divinylbenzene-based cross-linkers.<sup>29,30</sup> A copolymerization of functional monomers based on NVP itself is not expected to suffer from these problems.<sup>31,32</sup>

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**Figure 1.** Functional monomers prepared from 1-vinylpyrrolidin-2-one (NVP): 3-[2-(*tert*-butyl-dimethylsilyloxy)-ethyl]-1-vinylpyrrolidin-2-one (TBSE-NVP), 3,3-bis-[2-(*tert*-butyl-dimethylsilyloxy)-ethyl]-1-vinylpyrrolidin-2-one, ((TBSE)<sub>2</sub>-NVP), and 3-(2-hydroxyethyl)-1-vinylpyrrolidin-2-one (EtOH-NVP).

Having a functional group attached to the  $\alpha$ -position of NVP should not significantly affect the reactivity of the vinyl bond, and little compositional drift would be expected to occur during copolymerization of such monomers and NVP.<sup>33</sup>

To evaluate the copolymerization of functional derivatives of NVP, we have previously synthesized and copolymerized a number of such monomers.<sup>34</sup> Here, we present the synthesis of a new cross-linker and its use in the successful preparation of a new type of hydrophilic polymer beads by suspension polymerization. Our initial experiments afforded lightly cross-linked functional beads that swelled extensively in a range of organic solvents as well as water and methanol.

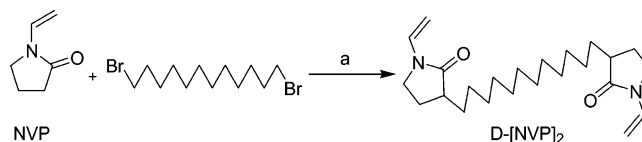
### Results and Discussion

**Monomers Used.** To test the possibility of introducing functionality into PVP by copolymerization a number of functional monomers were synthesized based on NVP. The general synthesis method is similar to earlier reported procedures in which the main purpose was to produce monofunctional monomers.<sup>31,32,35</sup> Regardless of the starting molar ratio of NVP to the compound carrying the functional group, the crude product mixture always contained both mono- and difunctional monomers (Figure 1). To ensure excess amounts of the NVP anion over the compound containing the functional group, slow addition of the latter compound was also tried to favor the formation of the monofunctional monomers. However, these experiments also gave a mixture of mono- and difunctional monomers. Since both products are useful for the preparation of functional beads, no optimization of the reaction conditions to get only mono- or only difunctional monomers has been performed.

The synthesis of TBSE-NVP and (TBSE)<sub>2</sub>-NVP has been reported earlier.<sup>34</sup> EtOH-NVP was easily obtained by a simple removal of the *tert*-butyl-dimethylsilyl (TBS) protecting group from TBSE-NVP using ammonium fluoride in methanol.<sup>36</sup>

**Cross-Linker Synthesis.** Like the monomer syntheses, the first attempts to synthesize a cross-linker were inspired by previously published work by White et al.<sup>31,32</sup> In light of the monomer syntheses, in which the difunctional monomers were always a significant part of the product mixture, 1,12-dibromododecane was used as the bridging unit between the two NVP units instead of 1,6-dibromohexane, which was used by White et al. (Scheme 1), to possibly reduce the risk of intramolecular ring-formation. As soon as one end of the

**Scheme 1.** Synthesis of 1,12-Bis(2-oxo-1-vinylpyrrolidin-3-yl)-dodecane, (D-(NVP)<sub>2</sub>)<sup>a</sup>



<sup>a</sup> Reaction conditions: (a) lithium bis(trimethylsilyl) amide (LBTMSA), THF, 0 °C–room temperature, 15 h.

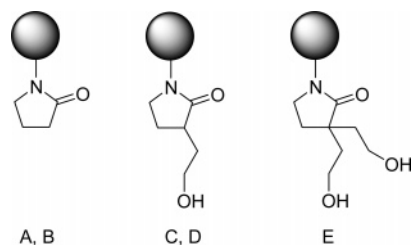
bridging unit has been attached to an NVP molecule, removal of the remaining  $\alpha$ -proton gives a nucleophilic anion that can react with the second bromine in the other end of the alkyl chain. In the case of 1,6-dibromohexane, this reaction will result in a seven-membered ring attached to the NVP molecule. By using 1,12-dibromododecane, the yield of the cross-linker was increased, possibly as an effect of ring-closing reactions occurring to a lesser extent. To further increase the probability of attaching two molecules of NVP to each molecule of the bridging unit, the former were used in large excess. The overall yield of D-(NVP)<sub>2</sub> after purification by column chromatography was 49%.

### Preparation of Beads by Suspension Polymerization.

Naturally, the problems of copolymerizing NVP with most other monomers also aggravate the preparation of cross-linked materials including this monomer. Compositional drift during the copolymerization leads to uneven distribution of cross-links and, hence, heterogeneous materials. In addition to these problems, using NVP to prepare spherical beads by suspension polymerization is further aggravated by its solubility in water. Nevertheless, the production of highly cross-linked beads of PVP, using either ethylene dimethacrylate or divinylbenzene as cross-linkers, has been reported.<sup>29,30,37,38</sup> To the best of our knowledge, there are no previous publications concerning lightly cross-linked beads of PVP. Preparing such materials requires that the difference in reactivity ratios between the cross-linker and NVP be small, and therefore, D-(NVP)<sub>2</sub> should be ideal for this purpose.

A thorough optimization of reaction conditions for the suspension polymerization of NVP and ethylene dimethacrylate has been reported by Horák et al.<sup>29</sup> By modifying the conditions developed therein, a series of lightly cross-linked beads were prepared using the novel NVP-based monomers together with the cross-linker D-(NVP)<sub>2</sub>. In the initial experiments, the functional monomers were omitted when trying to find suitable conditions for the suspension polymerization. Using only NVP and the cross-linker, beads with a particle size distribution between 50 and 300  $\mu\text{m}$  were obtained. It was found that small amounts of sodium dodecylsulfate (0.05 wt %) and decanoic acid (0.05 wt %) in the aqueous phase were crucial to avoid aggregate formation. On the basis of these results, the experiments were repeated with various amounts of the functional NVP-based monomers added. Figure 2 shows a schematic representation of the different beads prepared with the general composition of the suspension polymerization mixture presented in Table 1.

The beads were not tacky, and therefore, size fractionation presented no problems. The beads also were robust, and no



**Figure 2.** Schematic representations of the PVP beads. Apart from the different functional monomers, all beads were prepared from NVP and D-(NVP)<sub>2</sub>. (A) PVP-0-(2%), no functional monomer, 2 mol % of cross-linker; (B) PVP-0-(1%), no functional monomer, 1 mol % of cross-linker; (C) PVP-EtOH, functional monomer is TBSE-NVP; (D) PVP-EtOH, functional monomer is EtOH-NVP; (E) PVP-(EtOH)<sub>2</sub>, functional monomer is (TBSE)<sub>2</sub>-NVP.

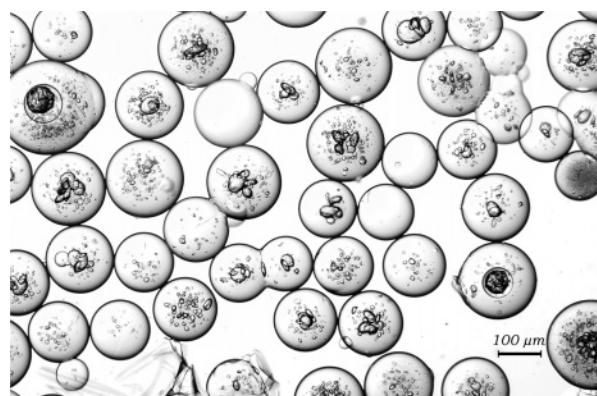
**Table 1.** Composition of the Suspension Polymerization Mixtures

	concn
Organic Phase	
1-vinylpyrrolidin-2-one (NVP)	88–98 mol %
cross-linker (D-(NVP) <sub>2</sub> )	1–2 mol %
functional monomer <sup>a</sup>	0–10 mol %
initiator (AIBN)	1.5 wt % rel to monomers
monomers in organic phase	40 wt %
dodecanol in diluent mixture	20 wt %
Aqueous Phase	
NaCl	20 wt %
Mg(OH) <sub>2</sub>	0.8 wt %
sodium dodecylsulfate	0.05 wt %
decanoic acid	0.05 wt %
phase ratio (organic/aqueous)	1:8 by volume

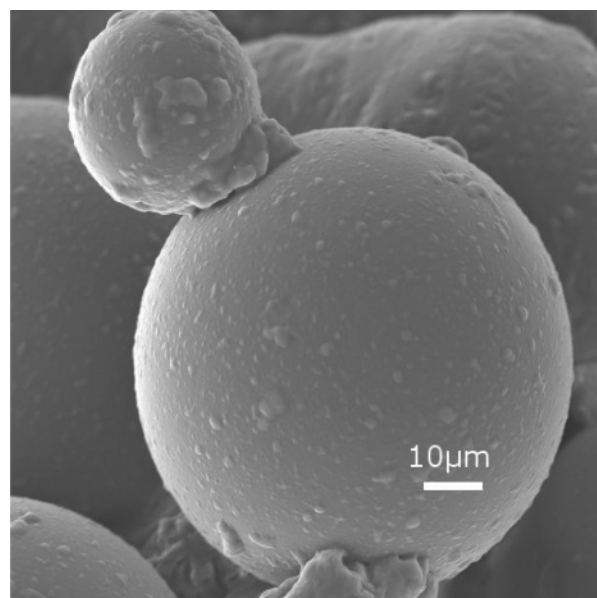
<sup>a</sup> EtOH-NVP, TBSE-NVP, or (TBSE)<sub>2</sub>-NVP.

indications of ruptured beads from normal handling could be seen, either when swollen or when dry. Figure 3 shows a photograph of the fractionated beads (150–300 μm) partly swollen in water. A scanning electron micrograph of the beads in the dry state is shown in Figure 4.

**Swelling Measurements.** One of the most important properties of lightly cross-linked polymer beads for solid-phase synthesis is the ability to swell in the reaction solvent. The typical way of measuring swelling is to put the beads in a graduated cylinder and compare the visual readings of the volume, before and after adding the solvent.<sup>39</sup> A similar method instead measures the weight difference between dry and swollen beads.<sup>12</sup> To be accurate, both these methods require at least a few hundred milligrams of beads. Here, a typical experiment produced 2–3 g of beads, and therefore, determining the swelling in seven different solvents using any of these methods would be laborious and require reuse of the beads several times. Instead, the swelling was measured using a microscope by comparing the diameter of a dry bead with the diameter of the same bead after addition of the solvent. It has previously been shown that the degree of swelling is independent of the original bead diameter.<sup>40</sup> Still, to avoid biasing the results in any way, beads of varying sizes were chosen for each determined swelling ratio. Used correctly, this method requires only a few beads (~10–20) for each solvent and provides reproducible and accurate swelling data. By dividing the diameter of the swollen bead by the diameter of the corresponding dry bead, the result is obtained as a swelling ratio. From the determined densities



**Figure 3.** Photograph of fractionated (150–300-μm) beads of cross-linked PVP, partly swollen in water.

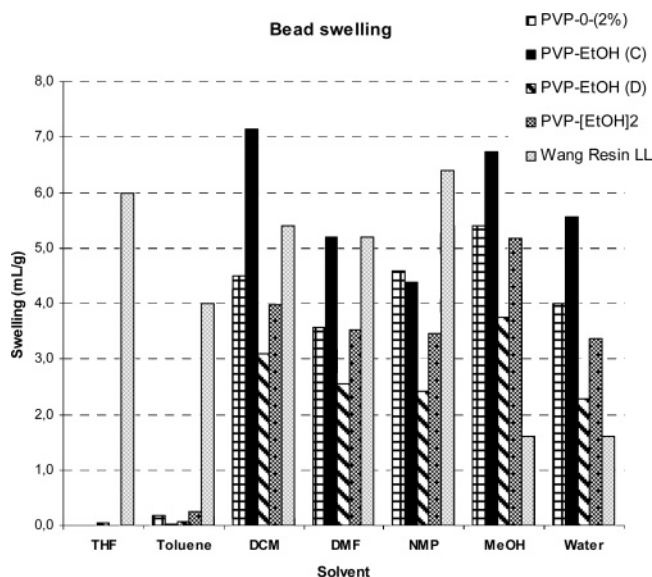


**Figure 4.** Scanning electron microscopy image of cross-linked PVP beads in the dry state.

of the beads, the swelling ratios were used to calculate the corresponding solvent uptake (in mL/g) so that the results could be compared to swelling measurements reported in the literature. The results from these measurements are shown in the diagram in Figure 5 together with literature data for Wang Resin LL (LL for low loading) representing a typical PS–DVB-based support material for comparison.<sup>39</sup>

From the diagram in Figure 5, it is obvious that the PVP-beads swell considerably in all the tested solvents except toluene and tetrahydrofuran (THF). This is expected, since both toluene and THF are thermodynamically poor solvents for PVP. Water, dichloromethane (DCM), 1-methylpyrrolidin-2-one (NMP), *N,N*-dimethylformamide (DMF), and methanol (MeOH) are good solvents for PVP, and as expected, the swelling in these solvents is much better. Since the swelling data for the PVP beads were obtained using a different method, as compared to the method used by Santini et al.<sup>39</sup> for Wang Resin LL, a direct comparison of individual values for the different types of materials should be done with some caution. Still, it is clear that the swelling of the PVP beads in DCM, NMP, and DMF is comparable to the swelling of Wang Resin LL. It is also clear that the PVP beads show better swelling than the PS–DVB-based material





**Figure 5.** Swelling of cross-linked PVP beads in some common reaction solvents. Swelling data for Wang Resin LL are given for comparison.<sup>39</sup>

in methanol and water. The extent of swelling is determined not only by the chemical characteristics of the beads but also by the degree of cross-linking. In all experiments but PVP-0-(1%), the molar fraction of cross-linker in the suspension polymerizations was kept at the same level (2 mol %). A lower degree of cross-linking should give better swelling; however, swelling tests on PVP-0-(1%) showed more or less the same extent of swelling as PVP-0-(2%) in all the tested solvents.

The ability to swell in solvents covering such a broad range of polarity suggests the possibility of performing multistep solid-phase syntheses in which different steps of the synthesis require different solvents.

**Density Measurements.** In the literature, swelling data are normally reported as volume of solvent per gram of beads (mL/g). To be able to compare the obtained results (obtained as a swelling ratio) with literature data, the densities of the beads were determined. The measured densities were 1.10 g/mL (PVP-0-(2%)), 1.08 g/mL (PVP-0-(1%)), 1.06 g/mL (PVP-EtOH (C)), 1.32 g/mL (PVP-EtOH (D)), and 1.25 g/mL (PVP-(EtOH)<sub>2</sub>).

**Loading Capacity.** The amount of available hydroxyl groups in the beads was determined by reacting these groups with excess of trityl chloride, washing the beads, cleaving the trityl cation, and detecting the amount of chromophore by UV spectrophotometry.<sup>41</sup> The results from these measurements are shown in Table 2. Our first experiments were performed without any functional monomers as exemplified by PVP-0-(2%). As expected, PVP-0-(2%) showed no loading capacity at all, but this result confirmed the efficiency of the bead washing procedure after cleaving the trityl cation.

Looking at the different functional beads, it is obvious that the determined loading capacities are lower than the theoretical values calculated from the composition of monomers in the suspension polymerizations. These lower than expected values could be the result of several effects. One possible explanation is steric hindrance from the polymer matrix in the reaction of trityl chloride with the hydroxyl

**Table 2.** Loading Capacities of Hydroxyl Groups

	loading capacity (mmol/g)	
	determined <sup>a</sup>	theoretical <sup>b</sup>
PVP-0-(2%)	0.006	0
PVP-(EtOH) <sub>2</sub>	0.21	0.53
PVP-EtOH (C)	0.29	0.43
PVP-EtOH (D)	0.29	0.71

<sup>a</sup> The results are averages of three separate measurements.

<sup>b</sup> Calculated from the percentage of functional monomer in the polymerization mixture.

groups. In the case of PVP-EtOH (C) and PVP-(EtOH)<sub>2</sub>, another possibility could be incomplete removal of TBS-protecting groups during the preparation of the beads. However, further deprotection reactions on these materials have not resulted in a changed loading capacity. The lower value for PVP-(EtOH)<sub>2</sub> is possibly an effect of steric hindrance from the trityl group itself. Once the first hydroxyl group has reacted with one molecule of trityl chloride, the adjacent hydroxyl group is shielded by that trityl group, and hence, it will be less prone to react. The same effect is not applicable to the monofunctional monomers used in PVP-EtOH (C) and PVP-EtOH (D). Despite the somewhat lower than theoretical loading capacities, all of the suspension copolymerizations in which functional monomers were used have a loading capacity. PVP-0-(2%) does not have a loading capacity. This proves that the functional monomers have been incorporated into the polymer beads.

In an attempt to prepare beads with higher loading of hydroxyl groups, more of the functional monomer TBSE-NVP (10 mol %) was used in one suspension copolymerization. However, after only a few minutes of stirring, the suspension was no longer stable and separated into two phases. To alter the mass composition of the original organic phase as little as possible, while still using an increased amount of functional monomer, EtOH-NVP (10 mol %) was used instead in a second attempt to increase the loading capacity (PVP-EtOH (D)). This time, the suspension was stable throughout the whole of the reaction time. Unfortunately, the loading of hydroxyl groups turned out to be the same as for PVP-EtOH (C), that is, 0.29 mmol/g. A possible explanation for this result could be the better solubility in water for EtOH-NVP, as compared with TBSE-NVP. If a large portion of the EtOH-NVP is present in the water phase, less functional monomers are available for the copolymerization in the organic phase.

Although the obtained loading capacities are on the low side of the spectrum for polymer support materials, the main objective is to show that we are able to prepare functional hydrophilic beads of PVP.

## Experimental Section

**Materials and Equipment.** Tetrahydrofuran (THF) was dried by distillation over sodium and benzophenone prior to use. All other chemicals were obtained from Sigma-Aldrich and used without further purification. On-bead reactions were performed in empty reservoirs (6 mL) fitted with frits (polyethylene, 20 μm) from Isolute SPE Accessories. <sup>1</sup>H (300 MHz) and <sup>13</sup>C (75.4 MHz) NMR spectra were recorded on a Varian VXR-300S NMR spectrometer in CDCl<sub>3</sub> at ambient

temperature. Chemical shifts are reported for solutions in  $\text{CDCl}_3$  [residual  $\text{CHCl}_3$  ( $\delta_{\text{H}}$  7.26 ppm) and  $\text{CDCl}_3$  ( $\delta_{\text{C}}$  77.16 ppm) as internal standard]. UV spectra were recorded on a Perkin-Elmer Lambda 20 UV/Vis Spectrometer. Thin-layer chromatography was performed on silica gel plates (Merck, silica gel 60 F<sub>254</sub>). Microscopy images for the swelling measurements were taken using a Nikon Coolpix 4500 digital camera attached to an Olympus BH2-UMA microscope via Scopetronix Maxview Plus equipment. SEM images were obtained using a Zeiss Scanning Electron Microscope (DSM 940).

**Synthesis of 3-[2-(*tert*-Butyl-dimethylsilyloxy)-ethyl]-1-vinylpyrrolidin-2-one (TBSE-NVP) and 3,3-Bis-[2-(*tert*-butyl-dimethylsilyloxy)-ethyl]-1-vinylpyrrolidin-2-one, ((TBSE)<sub>2</sub>-NVP).** The synthesis of these monomers has previously been published elsewhere.<sup>34</sup>

**Synthesis of EtOH-NVP: Removal of TBS-Protecting Group from TBSE-NVP.**<sup>36</sup> 3-[2-(*tert*-Butyl-dimethylsilyloxy)-ethyl]-1-vinylpyrrolidin-2-one (TBSE-NVP, 0.914 g, 3.39 mmol) was dissolved in methanol (10 mL). Ammonium fluoride (0.628 g, 17.0 mmol) was added, and the mixture was stirred for 48 h. The reaction progress was monitored by TLC. Silica gel (0.53 g) was added, and the solvent was removed from the reaction mixture by rotary evaporation. The remaining material was then put on top of a short column of silica gel, and the deprotected monomer was eluted using ethanol (100 mL), followed by a mixture of ethanol/methanol (50 mL, 9/1 by volume). Finally, the solvents were removed by rotary evaporation, affording 3-(2-hydroxy-ethyl)-1-vinylpyrrolidin-2-one (EtOH-NVP) (0.49 g, 3.16 mmol, 93%, purity >99% (GC));  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 1.60–1.84 (2H, m,  $-\text{CH}_2\text{CH}_2\text{O}-$ , and  $-\text{CH}_2\text{CH}_2\text{N}-$ ), 1.88–2.04 (1H, m,  $-\text{CH}_2\text{CH}_2\text{N}-$ ), 2.24–2.38 (1H, m,  $-\text{CH}_2\text{CH}_2\text{O}-$ ), 2.60–2.74 (1H, m,  $-\text{CH}-(\text{C}=\text{O})-$ ), 3.31–3.56 (2H, m,  $-\text{CH}_2\text{N}-$ ), 3.61–3.81 (2H, m,  $-\text{CH}_2\text{OH}$ ), 3.87 (1H, broad s,  $-\text{OH}$ ), 4.39 (1H, app. d,  $J = 16.0$  Hz,  $-\text{CH}=\text{CH}_2$ ), 4.43 (1H, app. d,  $J = 9.0$  Hz,  $-\text{CH}=\text{CH}_2$ ), 7.01 (1H, dd,  $J = 9.0$  Hz and  $J = 16.0$  Hz,  $-\text{CH}=\text{CH}_2$ );  $\delta_{\text{C}}$  (75.4 MHz,  $\text{CDCl}_3$ ) 25.15 ( $-\text{CH}_2\text{CH}_2\text{N}-$ ), 34.18 ( $-\text{CH}_2\text{CH}_2\text{O}-$ ), 41.39 ( $-\text{CH}_2\text{N}-$ ), 43.32 ( $-\text{CH}-(\text{C}=\text{O})-$ ), 61.20 ( $-\text{CH}_2\text{O}-$ ), 95.17 ( $-\text{CH}=\text{CH}_2$ ), 129.55 ( $-\text{CH}=\text{CH}_2$ ), 175.93 (C=O).

**Synthesis of 1,12-Bis(2-oxo-1-vinylpyrrolidin-3-yl)-dodecane, (D-(NVP)<sub>2</sub>) (Scheme 1).** The reaction flask was sealed with a rubber septum and connected to a vacuum pump. The flask was dried by simultaneous evacuation and heating with a hot-air gun for ~3 min. The flask was then filled with nitrogen gas. This drying procedure was repeated three times at the start of each experiment. Dry THF (50 mL) was added, and the flask was placed in an ice bath. Lithium bis(trimethylsilyl) amide (LBTMSA, 60.0 mL, 1.0 M solution in THF) was then added, followed by NVP (7.2 mL, 66.7 mmol) using disposable syringes. The solution was stirred in the ice bath for 1 h and then for 1 h at room temperature. Finally, 1,12-dibromododecane (2.00 g, 6.1 mmol, dissolved in 20 mL of THF) was added dropwise over 15 min using a disposable syringe. The reaction mixture was stirred for 15 h at room temperature and then quenched with distilled water and extracted three times with equal volumes

of diethyl ether. The combined ether extracts were dried using anhydrous  $\text{MgSO}_4$ , and the solvent was evaporated. The crude product mixture was purified by column chromatography on silica gel (petroleum ether/ethyl acetate 5/1 v/v, followed by petroleum ether/ethyl acetate/methanol 5/1/0.2 v/v/v until TLC showed spots from unreacted NVP). Evaporation of the eluent from the appropriate fractions gave the crude product as a white solid. Finally, the crude product was recrystallized from a mixture of pentane and dichloromethane, yielding D-(NVP)<sub>2</sub> (1.16 g, 49%, purity >99% (GC));  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 1.20–1.42 (24H, m,  $-\text{CH}_2-$ ), 1.66–1.81 (2H, m,  $-\text{CH}_2\text{CH}_2\text{N}-$ ), 2.22–2.34 (2H, m,  $-\text{CH}_2\text{CH}_2\text{N}-$ ), 2.44–2.56 (2H, m,  $-\text{CH}-(\text{C}=\text{O})-$ ), 3.32–3.54 (4H, m,  $-\text{CH}_2\text{N}-$ ), 4.35–4.45 (4H, m,  $-\text{CH}=\text{CH}_2$ ), 7.10 (2H, dd,  $J = 8.7$  Hz and  $J = 15.6$  Hz,  $-\text{CH}=\text{CH}_2$ );  $\delta_{\text{C}}$  (75.4 MHz,  $\text{CDCl}_3$ ) 24.50, 27.25, 29.58, 29.62, 29.67, 29.69 ( $-\text{CH}_2-$ ), 42.52 ( $-\text{CH}_2\text{N}-$ ), 42.97 ( $-\text{CH}-(\text{C}=\text{O})-$ ), 94.06 ( $-\text{CH}=\text{CH}_2$ ), 129.70, ( $-\text{CH}=\text{CH}_2$ ), 175.40 (C=O); MS (EI, 70 eV)  $m/z$  388 (81%,  $\text{M}^+$ ), 278 (24), 124 (58), 111 (90), 69 (100), 56 (53). HRMS (EI) calcd for  $\text{C}_{24}\text{H}_{40}\text{N}_2\text{O}_2$  ( $\text{M}^+$ ): 388.309. Found: 388.312.

**Typical Suspension Polymerization Experiment.** A 100-mL spherical reaction vessel with a flat flange and a three-necked lid was fitted with an anchor-type mechanical stirrer and a condenser. The vessel was charged with NaCl (15.53 g) and  $\text{MgCl}_2 \times 6\text{H}_2\text{O}$  (4.23 g, 20.8 mmol), followed by distilled water (41.61 g), decanoic acid (0.042 g), and sodium dodecylsulfate (0.042 g). This mixture was then stirred (~500 rpm) under nitrogen atmosphere and heated to 70 °C using an oil bath. A disposable syringe was used for the dropwise addition of NaOH (23.0 mL, 1.0 M) to form  $\text{Mg}(\text{OH})_2$  in situ. The organic phase was prepared by mixing azobisisobutyronitrile (AIBN, 0.068 g, 0.41 mmol), NVP (4.28 g, 38.1 mmol), D-(NVP)<sub>2</sub> (0.25 g, 0.76 mmol) and an appropriate amount of functional monomer with the inert diluents, cyclohexanol (5.38 g) and 1-dodecanol (1.34 g). The organic phase was swirled and heated carefully to get a homogeneous solution. This solution was then added to the reaction vessel using a disposable syringe, and the polymerization was allowed to proceed for 8 h. The reaction mixture was then allowed to cool to room temperature before HCl (3 mL, concentrated) was added to dissolve the  $\text{Mg}(\text{OH})_2$  and to simultaneously remove *tert*-butyl-dimethylsilyloxy (TBS) protecting groups if applicable. The polymer beads were collected and washed with distilled water (6 × 100 mL). The beads were sieved into appropriate size fractions (>500, 500–300, 300–150, and 150–38 μm) in their water-swelled state. The separated fractions were finally washed with THF (3 × 100 mL), followed by diethyl ether (3 × 100 mL), and dried in a vacuum oven (40 °C, 1h).

**Swelling Measurements.** The ability of the polymer beads to swell in seven different solvents (toluene, THF, DMF, MeOH, DCM, NMP, and water) was analyzed using a published procedure.<sup>37</sup> Individual beads were first photographed in their dry states and then after the addition of the solvent. Bead diameters were measured from the microscopy images (640 × 480 pixels, magnification 250 times) using ImageJ 1.32j computer software. The swelling ratio was calculated as the ratio between the diameter of the swollen

bead and the diameter of the corresponding dry bead. The given swelling ratios are the averages of at least 10 measurements for each sample and solvent. Beads of varying sizes were used in the measurements.

**Density Measurements.** To be able to determine the density of the beads, the tip of a volumetric pipet (3.00 mL) was sealed using a small amount of Araldite epoxy adhesive. The true volume of this modified pipet was determined from several measurements of the mass of diethyl ether needed to fill it to the calibration mark. Previous swelling measurements had shown that the beads do not swell at all in this solvent. Bead densities were then determined by weighing in a known amount of beads (~200 mg) into the pipet, filling it to the calibration mark with diethyl ether, and weighing the pipet again. Care was taken to remove any air bubbles from inside the pipet. From the weight of the beads and diethyl ether (density 0.714 g/mL), and the total volume of the mixture, the bead densities could be calculated. Each reported density is the average of three separate measurements.

**Determination of Loading Capacity.** The loading capacities of the beads were determined by reacting the accessible hydroxyl groups with an excess of trityl chloride.<sup>38</sup> First, the beads (5–10 mg) were weighed into a disposable SPE cartridge (volume 6 mL) and washed with DCM (3 × 6 mL). The beads were then swollen in a solution containing ~50 equiv of trityl chloride and triethylamine (as calculated from the composition of the monomer feed) in DCM (3 mL). The reaction was allowed to proceed for 2 h. Unreacted compounds were then removed by washing the beads with DCM (3 × 6 mL), MeOH (2 × 6 mL), and DCM (3 × 6 mL) again. Finally, the trityl groups were cleaved from the beads by washing with a mixture of DCM and trifluoroacetic acid (TFA, 1.0 vol %). This was continued until the yellow color of the washing extract was no longer visible. Finally, the yellow extract was diluted with the washing mixture to a total volume of 100 mL in a volumetric flask. The concentration of the trityl cation was quantified by measuring the maximum UV absorption intensity at 400–430 nm and comparing the obtained value with a calibration curve.

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