

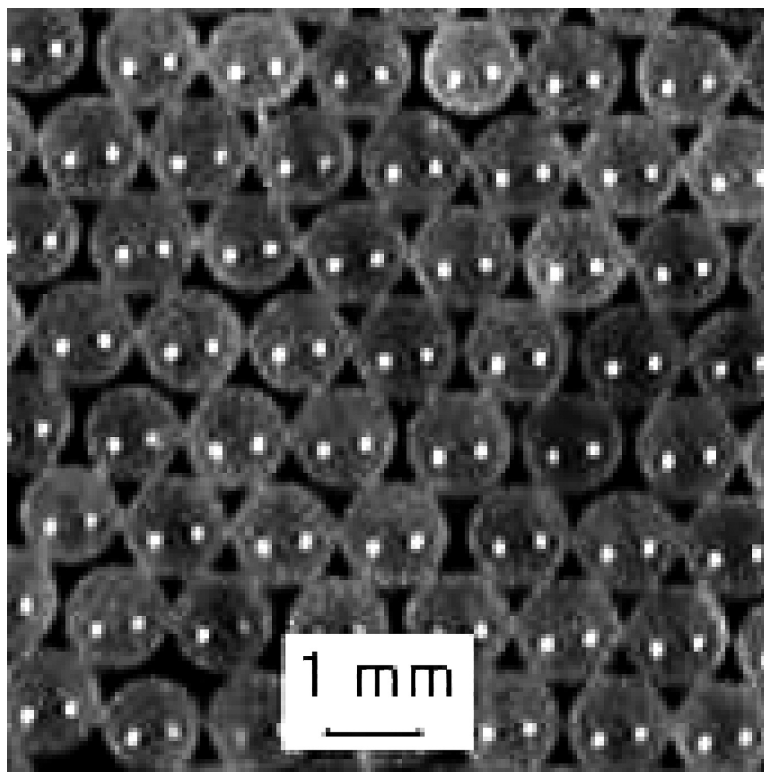
Article

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Large Uniform-Sized Polymer Beads for Use as Solid-Phase Supports Prepared by Ascension Polymerization

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Large uniform-sized polymer beads are desirable for “one-bead–one-compound” applications in the combinatorial synthesis of compound libraries. We have developed a technique for the preparation of large polymer spheres with narrow size distributions. Uniform-sized poly(styrene-*co*-divinylbenzene) beads with diameters in excess of 1 mm have been prepared by free radical polymerization in an ascension process through a heated column. The size of the beads can be adjusted by the diameter of the injection needle and the injection speed. The resin beads can be made porous by the incorporation of a porogen during the preparation; they reach a specific surface area in excess of 200 m²/g. The mechanical properties of the spheres and their use in organic synthesis have been studied.

Introduction

Polymer beads can be synthesized by emulsion, dispersion, suspension, and seed polymerization methods.^{1–4} They have been widely used for organic synthesis, separation, and treatment of wastewater.^{5–7} While it is relatively easy to prepare small monodispersed spheres by emulsion polymerization,^{8–10} larger polymer beads are desirable for certain applications, including the so-called “one-bead–one-compound” application in combinatorial synthesis involving solid-phase chemistry.^{11–13} Uniformity in bead size should ensure that similar amounts of library compounds are present on each bead. When the loading is high enough, the reaction on a bead may be monitored by high-resolution magic angle spinning experiments, and the quantity of the compounds may be sufficient for subsequent testings.

Large beads with diameters ranging from 50 to 2000 μm may be easily obtained by suspension polymerization, but the resulting spheres are not uniform in size. In 1984, Timm¹⁴ reported a method for the preparation of large polymer beads by polymerizing monomer droplets formed by the vibratory excitation of a laminar jet of monomeric material flowing through a continuous liquid medium containing a suitable suspending agent. The polymer beads obtained had a diameter ranging from 0.5 to 2 mm. The particle size distribution was still large with 90% of the particles having diameters in the range of 0.5 to 0.58 mm. In 1995, Ruckenstein and Hong¹⁵ reported a sedimentation polymerization method to prepare beads with a mean diameter reaching 1 to 2.5 mm and a relatively narrow size distribution. In this approach, droplets of an aqueous monomer solution containing an initiator and cross-linking agent are allowed to sediment through in a heated paraffin oil medium. The bead size can be adjusted by changing the needle

diameter. Using this method, Zhang and co-workers produced monodisperse highly porous emulsion-templated polymers¹⁶ and silica beads.¹⁷ However, this method is limited to hydrophilic monomers (not miscible with paraffin oil) that can be polymerized rapidly (typically acrylamide and *N,N*-methylenebisacrylamide) to avoid particle coalescence.¹⁰ In addition, the separation of the beads from the sedimentation medium is difficult. To alleviate this last problem, Zhang and Cooper also used compressed super critical CO₂ as the sedimentation medium.¹⁸

We report here a method for the preparation of large cross-linked polymer beads of uniform size through an ascension process. This method, named “ascension polymerization” in our lab, consists of injecting droplets of a hydrophobic monomer mixture (containing an initiator and cross-linking agent) at the bottom of a column containing a hydrophilic medium. Because of the difference in density of the two fluids, the monomer droplets rise through the heated medium and polymerize (Figure 1). Alternatively, the polymerization can be initiated by light irradiation during the ascension of the particles through the column. Once the beads reach the top of the column, they can be left there for a period of time to accumulate and to ensure a complete polymerization. In this study, we demonstrate the usefulness of ascension polymerization for preparing large poly(styrene-*co*-divinylbenzene) spheres (PS-DVB) with uniform size distributions. The validity of this method for preparing solid-phase supports for combinatorial chemistry is demonstrated by preparing a chloromethylated PS-DVB resin and carrying out a model solid phase synthetic procedure. Moreover, the mechanical properties of selected beads are tested and compared to those of a commercially available PS-DVB bead.

Results and Discussion

Ascension Polymerization. The density and viscosity of the aqueous medium in the column are fundamentally

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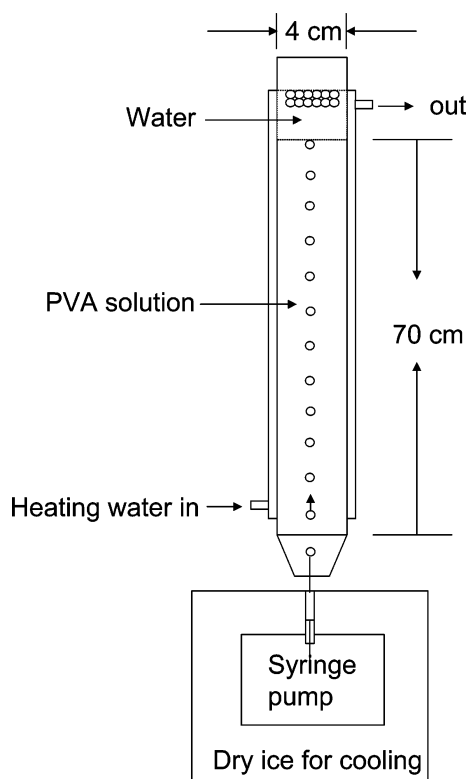


Figure 1. Experimental setup used for ascension polymerization. Droplets of a mixture of hydrophobic monomers are injected at the bottom of a heated column containing an aqueous solution of PVA. As the droplets rise through the column, they polymerize and accumulate at the top of the column where they can be collected. The column is heated by circulating hot water, and irradiation of the column is optional.

important factors because they determine the rate of ascension of the monomer droplets in the column. When pure distilled water was used as the ascension medium, the monomer droplets rose too rapidly and polymerization of the beads was incomplete. This caused significant coalescence of the beads at the top of the column. Poly(vinyl alcohol) (PVA) was added to the ascension medium; since it was chemically inert with respect to the polymerization reaction, it increased the viscosity of the medium but only had a small effect on the density. The density of the monomer solution is around 0.9 g/cm^3 , and that of a 15 wt % PVA aqueous solution is above 1 g/cm^3 . When a 15 wt % PVA solution was used as the medium, the ascension time was about 20 min for a typical monomer mixture, and no coalescence occurred at the top of the column. Given the interfacial tension between the monomer and the PVA solution, the monomer solution, once injected, formed droplets that gradually rose in the column. The density of

the droplets and the resulting beads is lower than that of the medium (even after complete polymerization); therefore the beads remain at the top of the column for easy retrieval. During the ascension of the droplets, their density decreased as they became polymerized and the ascension process slowed. This implies that the injection of droplets into the column must be relatively slow (0.3 mL/h) to avoid contact between the polymerizing spheres early in the ascension process. A multiple needle injection system may be considered for larger-scale applications.

The slow injection rate of the highly reactive monomer solution into the heated column required that certain precautions be made. Namely, it was noticed that if the tip of the needle from which the monomer fluid was ejected was placed too far into the column, premature polymerization of the mixture in the needle occurred. This was alleviated by inserting the needle into the column only as far as was absolutely necessary to clear the bottom seal. Furthermore, the syringe and syringe pump were both kept in an isothermal compartment cooled with dry ice during the injection process. While these methods yielded acceptable results, other injection devices¹⁹ may be considered for future experiments.

Bead Size and Porosity. Several polymer beads were prepared by this method under the reaction conditions outlined in Table 1. Figure 2 shows the optical images of the beads along with the scanning electronic microscopy (SEM) images of the inner structure of the beads. It is apparent that the beads are quite uniform in size with an average diameter ranging from 1.3 to 1.9 mm with standard deviations of less than 5%. The narrow size distribution for selected bead samples is shown in Figure 3, as obtained from image analysis.

When no porogen was added to the monomer mixture, highly spherical beads with a uniform size distribution were obtained as shown by optical (Figure 2 panel 1a) and electron (Figure 2 panel 1b) microscopy. These beads are gel-type (transparent) because of the low porosity observed by the imaging techniques as well as the low specific surface area measured by gas adsorption analysis (Table 1).

The addition of porogens to the monomer mixture had a pronounced effect on the morphology of the synthesized beads. When toluene was used as the porogen (PS-DVB/T), the beads remained spherical and monodisperse (Figure 2 panel 2a), yet the microstructure observed by SEM reveals a much rougher surface (Figure 2 panel 2b) than that of the beads obtained without porogen. This translates into a much larger specific surface area, ca. $201 \text{ m}^2/\text{g}$, as measured by gas adsorption (Table 1). When large amounts of toluene were used as the porogen (1.5 times the volume of the

Table 1. Characteristics of the Polymer Beads Prepared by the Ascension Polymerization Method

sample ^a	monomer mixture/porogen							mean diameter (mm)	surface area (m^2/g)
	S (mL)	DVB (mL)	S-Cl (mL)	toluene (mL)	H ₂ O (mL)	AOT (g)	Span 80 (g)		
PS-DVB	1.2	4.8	—	—	—	0.008	—	1.32 ± 0.04	0.14 ± 0.01
PS-DVB/T	1.2	4.8	—	9	—	0.008	—	1.50 ± 0.03	200 ± 20
PS-DVB/AOT	1.2	4.8	—	—	0.090	0.220	0.250	1.89 ± 0.09	0.36 ± 0.01
PS-DVB/T-AOT	1.2	4.8	—	3	0.090	0.220	0.250	1.74 ± 0.04	125 ± 4
PS-Cl	1.7	0.13	1.4	—	—	0.008	—	1.13 ± 0.08	4.3 ± 0.1

^a All monomer mixtures contained 0.05 g AIBN as polymerization initiator.

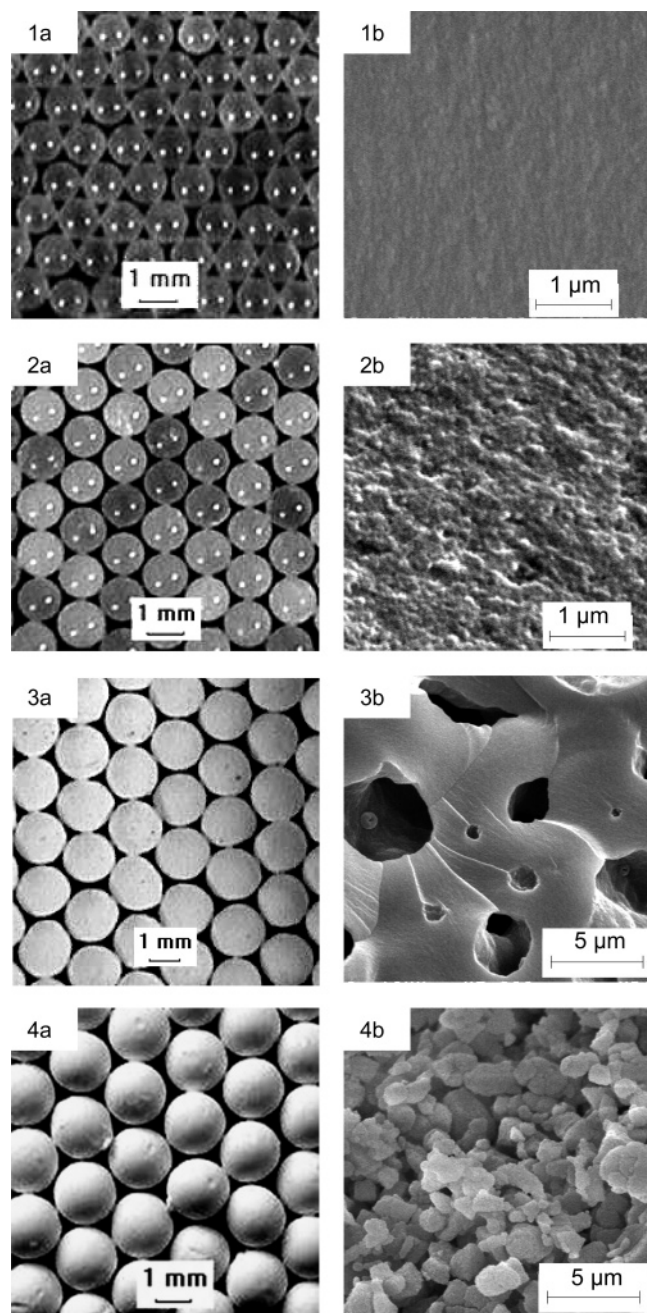


Figure 2. (a) Optical and (b) SEM images of the inner structure of the cross-linked polystyrene beads. PS-DVB: (1a–b) average diameter (d_{av}) is 1.32 mm, standard deviation (SD) is 2.7%. PS-DVB/T (toluene as porogen): (2a–b) d_{av} = 1.50 mm, SD = 2.2%. PS-DVB/AOT (AOT reverse micelles as porogen): (3a–b) d_{av} = 1.89 mm, SD = 4.8%. PS-DVB/T-AOT (toluene and AOT micelles as porogens): (4a–b) d_{av} = 1.74 mm, SD = 2.4%.

monomers), the ratio of DVB to styrene (4.8/1.2 mL, ~77 mol % DVB) was high for the ease of obtaining spherical droplets. By increasing the amount of cross-linking agent, the onset of gelation of the droplet occurred more rapidly in the column. It should be noted that, under other conditions, PS-DVB spheres containing as little as 2 mol % DVB can be successfully prepared (see subsequent sections).

We have used sodium bis(2-ethylhexyl) sulfosuccinate (AOT) reverse micelles to obtain porous polymers.²⁰ The use of AOT micelles alone (PS-DVB/AOT) lowered the interfacial tension between the monomeric fluid and the

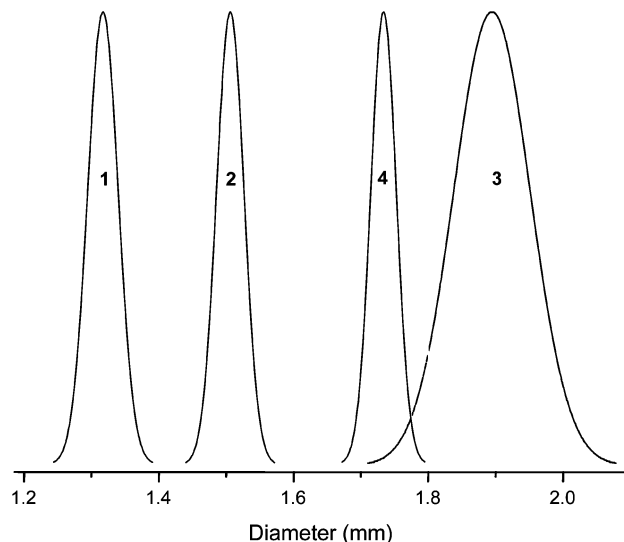


Figure 3. Size distribution curves for the cross-linked beads (Table 1) obtained by image analysis of images similar to those shown in Figure 2.

column medium significantly, and thus beads with irregular shapes and broad diameter distributions were obtained (data not shown). Therefore, Span 80 was added as a cosurfactant to adjust the interfacial tension between the monomeric fluid and the column medium. The resulting beads had pores in the 1–5 μ m range (Figure 2 panel 3b), likely resulting from the presence of micelles and aggregates of micelles in the monomer mixture during polymerization. However, the low surface area of these beads is indicative that this porogen alone is more effective in increasing the surface area. Furthermore, the beads still have a more irregular shape than when toluene was used as the porogen, and the distribution of the diameter of the particles remains broader than that for PS-DVB and PS-DVB/T (Figure 3).

The combination of toluene and AOT reverse micelles yielded polymer beads (PS-DVB/T-AOT) with a highly porous structure shown by optical (Figure 2 panel 4a) and electron (Figure 2 panel 4b) microscopy, as well as by gas adsorption analysis (surface area 125 m²/g). While the uniformity of bead diameter is improved relative to that of PS-DVB/AOT (Figure 3), their shape remains slightly irregular because of the presence of large amounts of surfactant.

AOT has a hydrophilic lipophilic balance (HLB) value between 14.9 and 10.5²¹ and is considered to be a hydrophilic surfactant. When AOT was used, the monomer solution after injection could not form monodisperse droplets because of the low interfacial tension caused by AOT. To solve this problem, a hydrophobic surfactant, Span 80, with an HLB value of 4,²² was introduced to adjust the interfacial tension. However, as reported by Korhonen,²³ when Span 80 was added, the monomer solution is unstable and becomes heterogeneous in time (typically after several hours). Therefore, a small amount of AOT (8 mg) can help ease this problem, since it helps lower the interfacial tension and stabilizes the solution.

Swelling and Mechanical Properties. The swelling of the beads in typical organic solvents is consistent with resins of similar composition. To obtain functionalized polymer

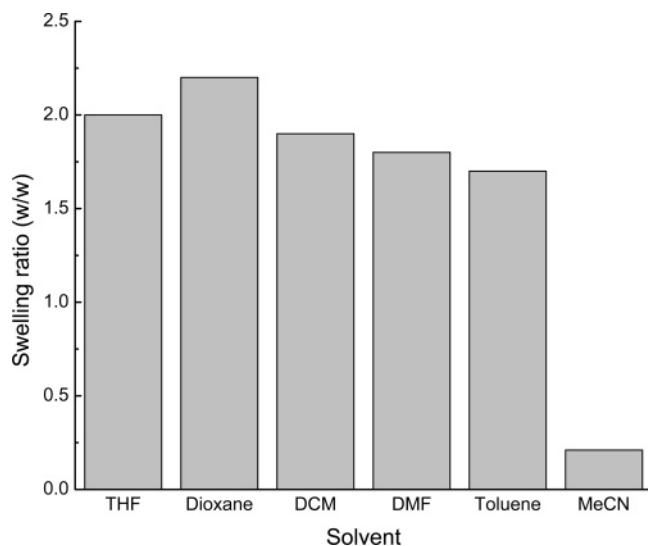


Figure 4. Swelling characteristics of a typical chloromethylated PS-DVB bead (PS-Cl) in selected organic solvents.

supports, chloromethylstyrene was incorporated into the monomer mixture along with styrene and DVB in the proportions listed in Table 1. The beads obtained (PS-Cl) were very uniform in size (average diameter 1.13 ± 0.08 mm). Its swelling characteristics in selected organic solvents are shown in Figure 4. Even though this resin was not made to be porous, they have good swelling in most organic solvents and they remain uniform in size in the swollen state.

The mechanical properties of the polymer beads in the swollen state were evaluated by a technique known as single-bead unconfined compression, described in much greater detail elsewhere.²⁴ The shear modulus of the bead can be obtained from the force response profile when an individual bead placed between two pistons was subject to a loading/unloading deformation. These experiments were performed to determine if the beads prepared by ascension polymerization have mechanical properties comparable to those of typical commercial materials. To do this, the large beads prepared with no porogen (PS-DVB), those prepared with toluene as the porogen (PS-DVB/T), and the commercial sulfonated PS-DVB resin were tested in DMF for comparison. They had similar swelling ratios in DMF (i.e., 1.1 ± 0.1 , 1.5 ± 0.1 , and 1.4 ± 0.1 (w/w) for PS-DVB, PS-DVB/T, and the commercial resin, respectively). The shear moduli of the three resins were measured as a function of strain amplitude. The shear moduli remained invariable with the strain (Figure 5), indicating that the beads were being tested in their linear elastic region. The shear moduli of all three resins were on the same order of magnitude. PS-DVB and the commercial resin had similar mechanical strength within the experimental error (moduli around 300 MPa), while the porous PS-DVB/T had a slightly lower shear modulus (ca. 120 MPa). All resins possessed good mechanical stability and remained intact under vigorous stirring during their use in solid-phase synthesis as shown in the next section.

Chemical Modification and Solid-Phase Synthesis. To validate the large resin beads obtained from ascension polymerization in solid phase synthesis and eventually in combinatorial chemistry, chloromethylstyrene was copolymerized with styrene and divinylbenzene as listed in Table

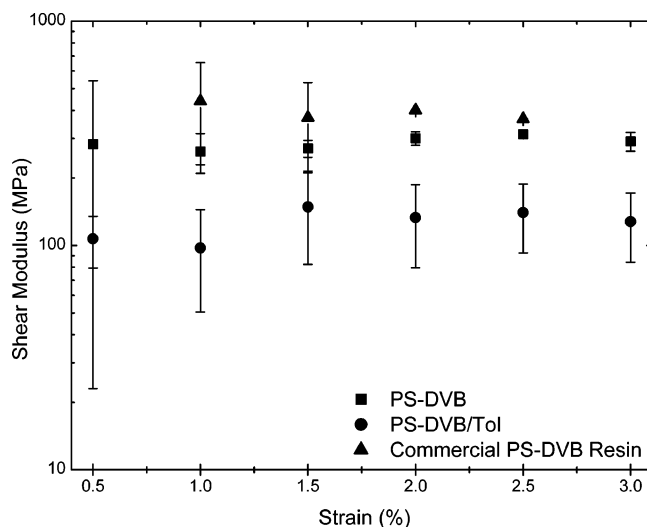


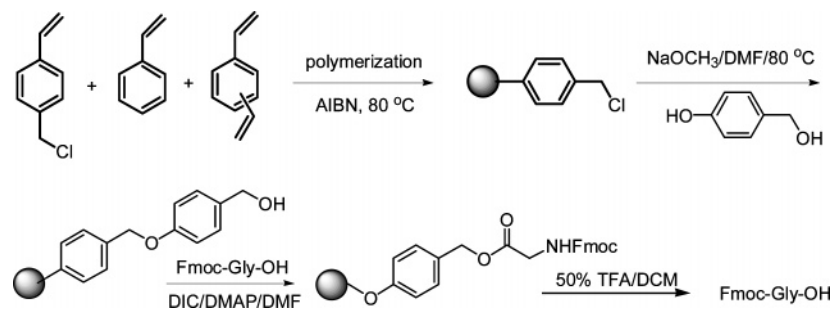
Figure 5. Mechanical properties of PS-DVB, PS-DVB/T, and a commercially available PS-DVB resin measured by unconfined compression in DMF.

1. The PS-Cl resin was then transformed into a Wang-type resin by a reaction with 4-hydroxybenzyl alcohol and MeONa at 80 °C for 24 h in dimethylformamide (DMF). Subsequently, *N*-Fmoc-glycine was coupled onto the latter overnight at room temperature in DMF using 3-diisopropylcarbodiimide (DIC) as the coupling agent and 4-(dimethylamino)pyridine (DMAP) as the catalyst. The loading of Fmoc-glycine on the resin was 1.13 mmol/g as determined by measuring the absorbance at 301 nm of an aliquot of the coupled resin which was cleaved in a piperidine/DMF (20/80) solution for 1 h at room temperature. This value is within the range expected for a typical Wang resin used for peptide synthesis, despite the low porosity of the bead. Please note that we did not attempt to optimize the porosity nor the loading of the functionalized beads. Obviously, higher loading beads may be prepared by incorporating porogens as seen in the previous discussion.

N-Fmoc-glycine, serving as a model “peptide”, was subsequently cleaved from the resin by reacting with trifluoroacetic acid (TFA) in dichloromethane (DCM) (50 vol %) for 30 min at room temperature. Fmoc-glycine was retrieved with an 80% yield and 91% purity (¹H NMR) demonstrating that the resins prepared by ascension polymerization can be used as supports for peptide synthesis.

Conclusion

We have demonstrated that ascension polymerization is a versatile and convenient method for preparing large uniform-sized polymeric spheres. Porous spheres can be prepared using different porogens (or mixtures of porogens), and these materials possess similar mechanical properties to the commercially available Merrifield-type resins. Moreover, the usefulness of this technique for the preparation of supports for combinatorial chemistry was demonstrated by introducing functional groups onto a model PS-DVB bead and carrying out a solid-phase synthesis. A styrene–DVB system is used in the current study, but it is easy to apply this method to other suitable organic monomers and cross-linkers. Other

Scheme 1. Solid-Phase Synthesis Using the Resin Bead Obtained from Ascension Polymerization

functional groups can also be introduced as in the case of conventional polymeric supports.

Experimental Section

Chemicals. Styrene (S), divinylbenzene (DVB), and chloromethylstyrene were purchased from Aldrich and washed with a 10 wt % NaOH aqueous solution and vacuum distilled to remove inhibitors. AOT and sorbitan monooleate (Span 80) were purchased from Sigma and were used as received. The free radical initiator, 2,2'-azoisobutyronitrile (AIBN, purchased from Eastman Kodak), was recrystallized from ethanol and stored in a refrigerated dark bottle until use. PVA, 99% + hydrolyzed, with an average molecular weight between 89 000 and 98 000, was purchased from Aldrich and used as received. Other reagents such as *N*-Fmoc-glycine (Aldrich), TFA (Aldrich), 4-hydroxybenzyl alcohol (Aldrich), DIC (Aldrich), and DMAP (Fluka) were used as received. For the study of mechanical properties, large commercial polystyrene beads cross-linked with 7 mol % DVB bearing sulfonic acid groups (from Hecheng Co., Tianjin, China) were selected for comparison purposes.

Ascension Polymerization. The ascension column was made of glass and is 70 cm in length and has a 4 cm internal diameter. A 15 wt % PVA solution in water was used as the medium. The monomer solutions were prepared by mixing together the monomers, the cross-linker, the initiator, the surfactants (AOT and Span 80), and the porogen reagents (toluene or AOT reverse micelles) as described in Table 1. The monomer solution was transferred into a syringe actuated by a syringe pump placed in an isothermal chamber cooled with dry ice. The column was heated to 80 °C by circulating hot water in the jacket surrounding the column, and the monomer solution was gradually injected into the column. Polymerization took place as the droplets traveled through the column. Irradiation with UV light is optional during this process.

Characterization of the Beads. Optical microscopy and image analysis were used to observe the beads and to calculate the average particle size and size distribution. The internal morphology of the beads was investigated with a JEOL JSM-840 scanning electron microscope (SEM). Gas adsorption measurements were performed on an Omnisorp Gas Adsorption Analyzer (Coulter Scientific, Miami, FL) with nitrogen gas as the adsorbate.

The mechanical properties of individual beads were evaluated using a model A300.100 MACH-1 Mechanical Tester (Biosyntech Inc., Laval, Canada). This instrument has a 100 nm displacement resolution and was equipped with a

150 g (7.5 mg sensitivity) load cell. The individual bead to be tested was transferred to the instrument's compression chamber which contained the same solvent in which it was swollen, and contact between the bead and compressing piston was achieved by lowering the piston at a rate of 8 $\mu\text{m s}^{-1}$ until a tare load of 10 mg was achieved. The distance separating the compressing platen at this point was then taken as the bead diameter for subsequent calculations. Strain amplitudes of 0.5, 1, 1.5, 2, 2.5, and 3% were applied at a rate of 1% s^{-1} to verify bead response linearity.

Solid-Phase Synthesis. The chloromethylated PS-DVB resin (0.3 g; 0.96 mmol of Cl groups, as determined hypothetically from the feed; PS-Cl in Table 1) was transformed into a Wang-type resin via reaction with 4-hydroxybenzyl alcohol (0.18 g, 1.44 mmol) and NaOCH₃ (0.09 g, 1.63 mmol) at 80 °C for 24 h. The resin was collected and washed with DMF, DCM, tetrahydrofuran (THF), and diethyl ether and dried under vacuum. This resin (0.1 g; 0.3 mmol OH groups based on 100% yield of the preceding reaction) was swollen in DMF for 30 min, and then it was reacted with *N*-Fmoc-glycine (0.70 g, 1.5 mmol) using DIC (0.23 mL, 1.5 mmol) as coupling agent and DMAP (15 mg, 0.15 mmol) as catalyst at room-temperature overnight. The coupled resin was washed with DMF, DCM, THF, and diethyl ether and dried under vacuum.

The loading of the coupled resin was determined as follows. Five milligrams of the coupled resin was suspended in 1 mL of a piperidine/DMF solution (20:80) and left at room temperature for 1 h. The solution was then diluted to 50 mL with ethanol, and the absorbance at 301 nm was measured using a UV-vis spectrophotometer. The cleavage of the amino acid Fmoc-glycine was performed by reacting 0.1 g (0.113 mmol, determined as described above) of the coupled resin with a 50% TFA in DCM solution at room temperature for 30 min. The filtrate was evaporated under vacuum to give the white solid Fmoc-glycine (26 mg, 80% yield, 91% purity by ¹H NMR).

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