

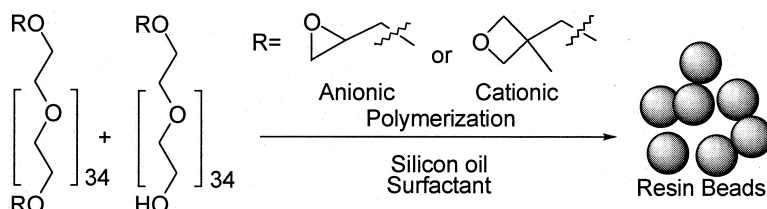
Article

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Surfactant Mediated Cationic and Anionic Suspension Polymerization of PEG-Based Resins in Silicon Oil: Beaded SPOCC 1500 and POEPOP 1500

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A novel surfactant has been synthesized for use in cationic and anionic ring-opening suspension polymerization of PEG-based macromonomers in silicon oil. A polymer of acrylate esters containing pentamethyldisiloxane and PEG was prepared by radical polymerization. The surfactant can stabilize an emulsion of PEG-based macromonomers, initiator, and solvent in silicon oil such that polymer beads are obtained by ring-opening polymerization, initiated either by a Lewis acid (cationic ring opening) or potassium *tert*-butoxide (anionic ring opening). The average bead size could be controlled by varying the stirring rate and the amount of surfactant and solvent. The surfactant does not interfere with the polymerization and can be removed together with residual silicon oil by a simple washing procedure.

Introduction

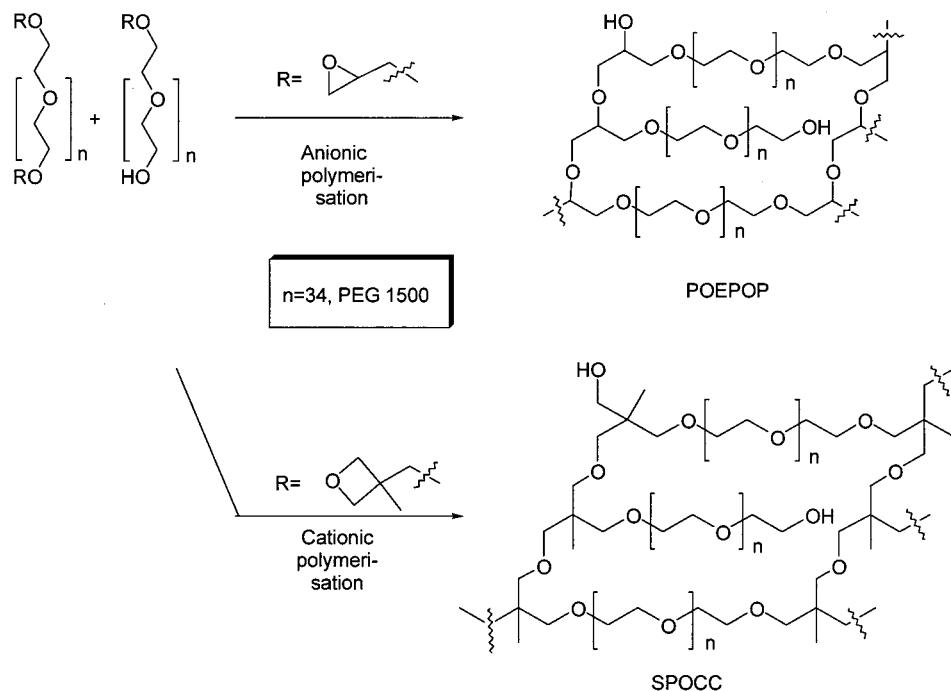
The recent renaissance of solid-phase organic chemistry for small molecule generation has created an increasing demand for new solid supports. Traditionally, polystyrene-divinylbenzene (PS-DVB) has been used as a support for solid-phase chemistry because of its high thermal stability, chemical inertness, and mechanical robustness. However, the limited swelling of PS-DVB supports in polar media can limit reagent accessibility and prevent chemical applications in which complete solvation of the polymer matrix is essential for the reactivity.² For example, the poor swelling of conventional PS-DVB in polar solvents such as aqueous buffers results in limited diffusion of reagents and low yields for reactions performed in these media. Although increased swelling in polar solvents can be achieved by grafting poly(ethylene glycol) (PEG) to chloromethylated PS-DVB, the resulting PEG-grafted PS-DVB supports such as TentaGel and ArgoGel³ have also been demonstrated to have limitations for use in aqueous solvents and for enzymatic chemistry.⁴

Our interest in solid-phase synthesis and enzymatic reactions on solid phase has resulted in the development of several novel PEG-based resins, including POEPOP, SPOCC (Scheme 1), and POEPS-3.⁵ Exhibiting high swelling volumes in both nonpolar solvents and water, these PEG-based resins have been successfully applied in solid-phase organic reactions in both aqueous and organic media.⁶ Furthermore, enzymatic reactions have been successfully performed using POEPOP,⁷ POEPS-3,⁷ and SPOCC^{5b} resins. The PEG-based supports thus exhibit several advantages for application in solid-phase organic chemistry, solid-phase enzymatic reactions, and on-bead screening assays.

The solid-phase chemistry performed previously with PEG-based resins has employed mainly polymer prepared by bulk polymerization, followed by mechanical grinding and sieving to afford an appropriate particle size. However, the grinding process is labor-intensive and generates irregular particles as well as a considerable quantity of fines which has to be removed by sedimentation. Due to these limitations and because irregular and more fragile particles may later prove troublesome for on-bead screening assays, we have pursued the production of beaded polymers.

Inverse suspension polymerization methods for producing beads from acrylic monomers are well established⁸ and can produce a higher yield of particles possessing uniform shape and size. Initially, we found that POEPS-3 could be prepared in beaded form by inverse suspension polymerization using water to generate stable emulsion droplets in a mixture of carbon tetrachloride and heptane.^{5c} Water is, however, incompatible with the cationic and anionic ring-opening polymerization methods to prepare SPOCC and POEPOP polymers, respectively. To circumvent the problems of using dispersants that interfered with the cationic and anionic reactions, an entirely new suspension polymerization technique was developed based on the reaction of emulsions of the PEG-macromonomers in silicon oil.^{5b} Because silicon oil is generally immiscible with organic compounds, it serves as an appropriate inert phase for this suspension polymerization. This technique has worked well on a 1–2 g scale with short PEG-monomers such as PEG-194 and PEG-400 chains. However, aggregation occurred when the process was scaled up and when longer PEG-monomers such as PEG 900 and PEG 1500 was employed.⁹ Recently, an acrylate copolymer containing perfluorocarbon and PEG esters was shown to stabilize an emulsion of functional monomers, cross-linkers, imprinting molecules, initiator, and solvents in perfluoro(methylcyclohexane).¹⁰ We reasoned that a

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Scheme 1. Synthesis of SPOCC and POEPOP

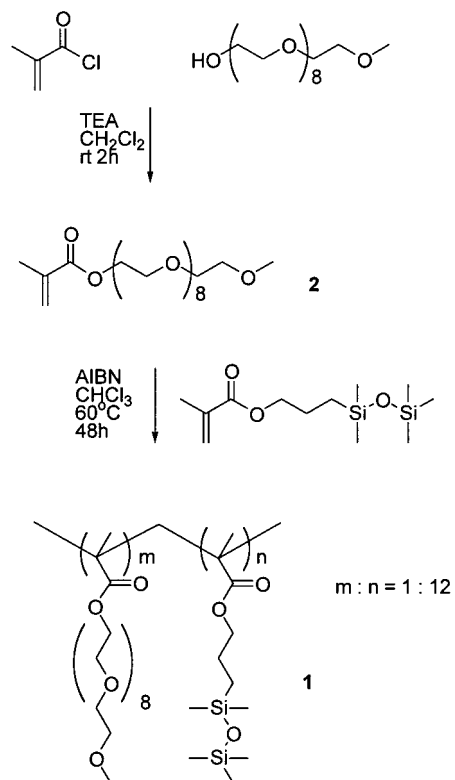
similar approach could be developed for cationic and anionic ring-opening suspension polymerization of PEG-based macromonomers in silicon oil. Using this concept, stable emulsion droplets at high density can now be obtained even with the longer PEG-macromonomers without aggregation by application of a novel surfactant for suspension polymerization in silicon oil. This technique was demonstrated by the synthesis of beaded SPOCC 1500 and POEPOP 1500 resins for solid-phase organic chemistry.¹¹

Result and Discussion

Surfactant **1** was synthesized by a two-step process featuring acylation of PEG 350 monomethyl ether with methacryloyl chloride in the presence of triethylamine to give methoxyxypolyoxyethylenyl methacrylate **2** followed by copolymerization with 9 equiv of trimethylsilyloxydimethylsilylpropyl methacrylate (Scheme 2). Nanoprobe magic angle spinning (MAS) ¹H NMR of surfactant **1** showed a 1:12 ratio between the PEG- and trimethylsilyloxydimethylsilylpropyl-building blocks (based on the integral for the PEG signal and the signal for the CH₃-Si groups). Surfactant **1** was subsequently used for all of the beaded polymerization reactions presented in this paper.

The most frequently used resins for solid-phase synthesis have particle sizes ranging from 40 to 200 μm and a loading on the order of 10–300 pmol per bead. Beads with a size range of 300–750 μm have a higher loading per bead that has enabled reaction monitoring on single beads by magic angle spinning (MAS) ¹H NMR spectroscopy.¹² An important goal was to prepare uniformed beads of this size.

The NMR properties of SPOCC and POEPOP has been studied extensively in this laboratory as reported previously.⁹ SPOCC 1500 and POEPOP 1500 with moderate cross-linking exhibited better resolution and narrow line widths compared to the spectra of SPOCC and POEPOP resins with short tether length (PEG-400 and PEG-900) or high cross-

Scheme 2. Synthesis of Surfactant

linking, when examined by magic angle spinning nanoprobe NMR spectroscopy. Furthermore, SPOCC 1500 and POEPOP 1500 will allow larger molecules to penetrate the resin compared to SPOCC and POEPOP resins with short tether length. This will be an advantage in enzymatic reactions. In this context all the polymerization reactions were carried out with either 3-methyloxetanylmethyl PEG 1500 macromonomers (SPOCC) or methyloxirane PEG 1500 macromonomers (POEPOP) with 75% incorporation of oxetanyl or oxiranyl groups, respectively.

Table 1. Suspension Polymerization of SPOCC Monomers^{a]}

entry	monomer, g	surfactant, mg/g monomer	solvent, mL	stirring, rpm	size distribution of dry beads, μm^b				yield, % ^c
					% > 1000	% > 500	% > 300	% 300>	
1	2	100	DCM 2	300				100	73
2	2	50	DCM 2	300				100	68
3	2	25	DCM 2	300				100	71
4	2	12.5	DCM 2	300				100	27
5	2	25	DCE 2	200		6.7	73.3	20	75
6	2	25	MeCN 2	200		20	66.7	13.3	75
7	2	25	DMTG 2	200					
8	4	25	DCM 4					100	78
9	4	25	DCM 2.4	200				29	78
10	4	25	DCM 1.5	200	13	13	58		80
11	4	25	DCM 1.5	100	72	28	15		80
12	4	25	DCM 1.5	300	1.5	11.9	77.6	9	84
13	20	25	DCM 7.5	300		20	74	6	89

^{a]} In all entries, 50 μL of $\text{BF}_3\cdot\text{OEt}_2$ /g macromonomer and 20 mL of silicon oil/g macromonomer were used. ^{b]} Determined by weight after sieving. ^{c]} Determined after sieving.

SPOCC resins were synthesized by anionic polymerization of 3-methyloxetanylmethyl PEG 1500 macromonomers with a Lewis acid as a catalyst. $\text{BF}_3\cdot\text{OEt}_2$ was added to a solution of macromonomers and surfactant **1** in the desired solvent at 0 °C, and the mixture was suspended in silicon oil at room temperature. After 2 h of stirring at room temperature, the temperature was increased to 60 °C, and the polymerization was left overnight for curing without stirring. The resulting polymer particles were filtered on a sintered glass funnel, and the silicon oil was collected for recycling.

Initially, the amount of surfactant needed to produce beads of the SPOCC 1500 type was examined by polymerization of 3-methyloxetanylmethyl PEG 1500 macromonomers in the presence of varying amounts of surfactant and subsequent measurement of the bead size distribution (Table 1, entry 1–4). Small beads with a diameter of less than 50 μm resulted from the use of 100 mg of surfactant/g macromonomer. Higher amounts of the surfactant gave only very small irregular particles. Stable emulsions were achieved using 25 and 50 mg of surfactant/g macromonomer. The bead size distribution increased with decreasing amount of surfactant, typically in the range 106–300 μm for 25 mg of surfactant/g macromonomer and 53–212 μm for 50 mg of surfactant/g macromonomer. A significant amount of aggregation was observed when the amount of surfactant was reduced to 12.5 mg/g macromonomer, indicating the lower limit for formation of stable emulsions.

Test polymerizations of 3-methyloxetanylmethyl PEG 1500 macromonomers were carried out in a range of solvents. Acetonitrile, dichloromethane, and dichloroethane have previously been used successfully in bulk polymerization of 3-methyloxetanylmethyl PEG 1500 macromonomers,^{5b,9} and dimethyl-triethylene glycol ether was tested since this solvent has properties similar to those of the macromonomer (Table 1, entries 3, 5–7). The polymerization method was applicable to all of these solvents except dimethyl-triethylene glycol ether, which solidified at the lower temperatures needed to control the initiation of the cationic ring-opening polymerization.

The amount of solvent in the cationic ring-opening polymerization also influenced the bead-size distribution (Table 1, entries 8–10). For example, 1 mL of dichlo-

romethane/g macromonomer gave a bead size of less than 300 μm when stirred at 200 rpm. Reducing the amount of dichloromethane to 0.6 mL/g macromonomer produced larger beads having diameters between 300 and 500 μm . Continued reduction of the volume of dichloromethane to 0.38 mL/g macromonomer resulted mainly in beads larger than 500 μm .

The stirring rate also had a significant influence on the bead size using 25 mg of surfactant and 0.38 mL of dichloromethane/g macromonomer (Table 1, entry 10–12). At 100 rpm, beads with a diameter above 1000 μm were obtained. At 200 and 300 rpm, the bead size was reduced to 500–1000 and 300–500 μm , respectively.

Using our optimal conditions (25 mg of surfactant and 0.38 mL of dichloromethane/g macromonomer; stirring at 300 rpm), a 20 g batch of SPOCC 1500 was produced (Table 1, entry 13), demonstrating that the procedure works equally well on a larger scale (Figure 1c).

Initially, anionic ring-opening polymerization of methyloxirane PEG 1500 macromonomers was performed by adding solid tBuOK to a melted mixture of macromonomers and surfactant **1**, followed by addition of the reaction mixture to silicon oil at 120 °C, with stirring. This resulted in an inhomogeneous mixture and resulted in beads exhibiting a large variation in size and quality. When different solvents were examined to improve homogeneity, small amounts of 1,2-dichloroethane, tetrahydrofuran, or acetonitrile inhibited the polymerization and no useful material was formed. High quality beads from a homogeneous solution were obtained after addition of tBuOH to the mixture containing 25 mg of surfactant/g macromonomer (Table 2, entries 1 and 5). Evaporation of the tBuOH before polymerization resulted in beads with a larger size distribution due to increased viscosity of the reaction mixture. To fine-tune the size distribution, different batches of macromonomers were mixed with surfactant, tBuOH and tBuOK, concentrated under high vacuum and polymerized at different stirring rates (Table 2, entries 2–4). Stirring at 100 and 200 rpm resulted in beads with diameters above 1000 μm and between 500 and 1000 μm , respectively. Increasing the stirring speed to 300 rpm resulted in a 3:1 ratio of beads between 1000 and 500 μm and 500–300 μm (Table 2, entry 4; Figure 1a). Stirring at

Table 2. Suspension Polymerization of POEPOP Monomers^a

entry	monomer, g	surfactant, mg/g monomer	solvent, mL	stirring, rpm	size distribution of dry beads, μm^c				yield % ^d
					% >1000	% >500	% >300	% 300>	
1	1	25	tBuOH 0.38	100		76	24		79
2	1	25	tBuOH 2 ^b	100	85	15			77
3	5	25	tBuOH 5 ^b	200	26	68	8		81
4	5	25	tBuOH 5 ^b	300	0.3	75	24	0.7	88
5	5	25	tBuOH 5	300				100	70
6	61	25	tBuOH 35 ^b	300	27	49	17	7	84

^a In all entries, 50 mg of tBuOK/g macromonomer and 20 mL of silicon oil/g macromonomer were used. ^b The tBuOH was evaporated in vacuo before polymerization. ^c Determined by weight after sieving. ^d Determined after sieving.

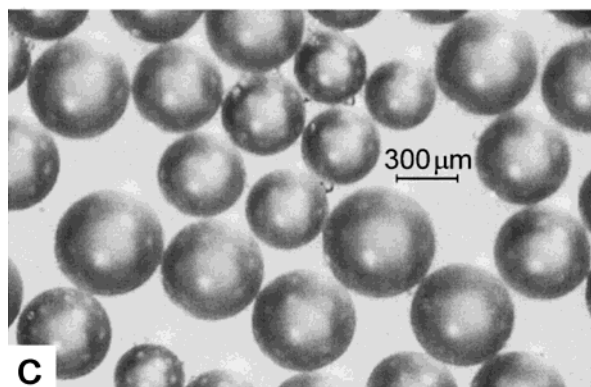
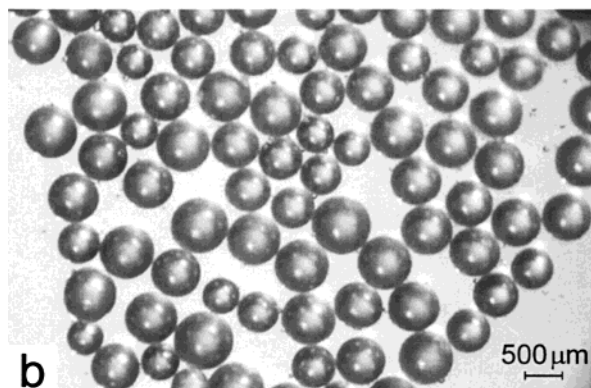
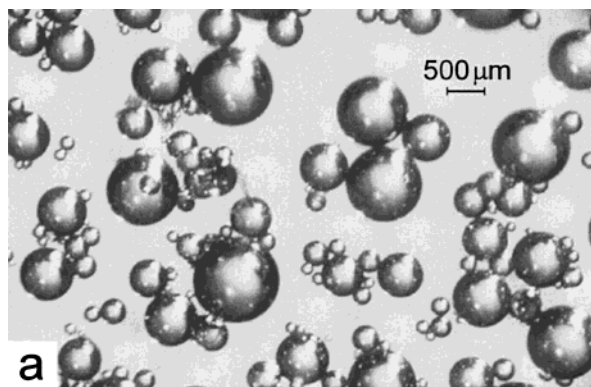


Figure 1. Beaded polymers: (a) POEPOP 1500 (Table 2, entry 4) before sieving; (b) POEPOP 1500 (Table 2, entry 6), 1000 μm > beads > 500 μm ; (c) SPOCC 1500 (Table 1, entry 13), 500 μm > beads > 300 μm .

300 rpm gave a larger size distribution when carried out on a large scale (Table 2, entry 6). However, high quality beads were obtained (Figure 1b).

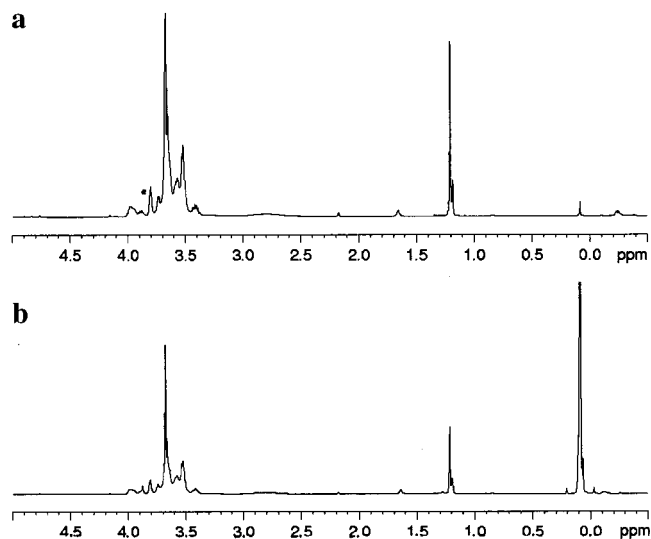


Figure 2. 500 MHz MAS ^1H NMR spectra of POEPOP 1500: (a) in CDCl_3 after the washing procedure to remove silicon oil and surfactant; (b) first swelled in CDCl_3 containing 1% silicon oil then in CDCl_3 .

The beaded resin batches were washed extensively with dichloromethane to remove silicon oil and surfactant, followed by washing with methanol and water to remove unreacted macromonomers. To open residual oxetane and epoxide rings in the beaded resins, SPOCC and POEPOP were treated with 4 M HCl and 4 M NaOH, respectively. The treatment of POEPOP with 4 M NaOH also destroyed any products formed from transesterification reaction between a deprotonated alcohol and esters of the surfactant during the polymerization. Nanoprobe ^1H NMR spectroscopy showed only traces or complete removal of remaining silicon-containing compounds in any of the resins (Figure 2).

The swelling of the resins were measured in tetrahydrofuran (THF), MeCN, dimethylformamide (DMF), water, and dichloromethane (DCM) by the syringe method (Table 3).¹³ The PEG-based resins swelled best in CH_2Cl_2 , somewhat less in DMF and water, and much less in THF and MeCN. The small difference in swelling between small and large beads was probably due to different packing characteristics. Only small variations in swelling was observed between the beaded resin and granulated resin⁹ made from the same monomers, typically in the range between 3 and 5%.

The loading was determined as described in the Experimental Section and presented in Table 3. The SPOCC and the POEPOP resins exhibited loadings between 0.49 and 0.53 mmol/g and resembled closely the loading of the material obtained by bulk polymerization.⁹

Table 3. Swelling and Loading of Resin Beads

resin	bead size, μm	swelling					loading mmol/g
		THF mL/g	MeCN mL/g	DMF mL/g	water mL/g	DCM mL/g	
SPOCC 1	300>	7.4	6.8	8.7	8.4	11.6	0.51
SPOCC 2	300>	7.3	6.7	8.7	8.5	11.7	0.50
SPOCC 3	300>	7.3	6.8	8.8	8.4	11.6	0.49
SPOCC 4	300>	7.3	6.7	8.7	8.4	11.6	0.50
SPOCC 5	>300	7.4	6.8	8.8	8.5	11.7	0.51
SPOCC 6	>300	7.5	6.9	8.8	8.5	11.7	0.51
SPOCC 8	300>	7.3	6.7	8.7	8.4	11.6	0.52
SPOCC 9	>300	7.4	6.8	8.8	8.5	11.8	0.50
SPOCC 10	>500	7.5	6.9	8.9	8.6	11.8	0.49
SPOCC 11	>1000	7.7	7.1	9.0	8.7	11.9	0.50
SPOCC 12	>300	7.4	6.7	8.8	8.5	11.7	0.49
SPOCC 13	>300	7.4	6.8	8.8	8.6	11.8	0.51
POEPOP 1	>500	7.6	8.0	8.4	7.9	10.0	0.52
POEPOP 2	>1000	7.8	8.2	8.6	8.1	10.2	0.51
POEPOP 3	>500	7.6	8.0	8.5	8.0	10.1	0.53
POEPOP 4	>500	7.5	8.0	8.4	8.0	10.0	0.50
POEPOP 5	300>	7.4	7.9	8.3	7.8	9.9	0.51
POEPOP 6	>500	7.5	8.1	8.4	7.9	10.1	0.52

Conclusion

A surfactant suitable for cationic and anionic ring-opening suspension polymerization of PEG-based macromonomers has been synthesized for stabilizing an emulsion of PEG-based macromonomers, initiator, and solvent in silicon oil. The average bead size could be controlled by varying stirring rate and the amount of surfactant and solvent. Beads were obtained in high yields.¹⁴ The surfactant does not interfere with the polymerization and can be removed together with residual silicon oil by a simple washing procedure. The polymerization could be performed at a high density of macromonomer droplets in the suspension medium. Because the silicon oil can be recovered by filtration at the end of polymerization and reused, this process is viable for large scale polymer production. Since surfactant **1** can be easily synthesized from commercially available material, this technique should make beaded PEG-based resins readily accessible.

Experimental Section

All solvents were purchased from Labscan Ltd. (Dublin, Ireland) and stored over molecular sieves. Methacryloyl chloride and poly(ethylene glycol) 350 monomethyl ether were purchased from Fluka (Buchs, Switzerland). Trimethylsilyloxydimethylsilylpropyl methacrylate was purchased from ABCR (Karlsruhe, Germany). PEG-macromonomers were synthesized as previously described.^{5,8} The quantity of hydroxyl groups available for substrate attachment (loading) of the resins was determined by esterification with Fmoc-Gly activated by MSNT in the presence of *N*-methyl imidazole in CH_2Cl_2 and subsequent measurement of the UV-absorbency of the adduct of dibenzofulvene and piperidine formed on treatment of a weighed polymer sample with 20% piperidine in DMF. Swelling was determined by the syringe technique.¹³ Selected resins were characterized by ¹H MAS nanoprobe NMR spectroscopy on a Varian Unity Inova 500 MHz spectrometer as described in ref 9.

Polymerization reactions were carried out in a 150 or 800 mL beaker with a 7 cm long stirring bar.

Methoxyxypolyoxyethylenyl Methacrylate 2. Methacryloyl chloride (0.67 mL, 5.9 mmol) was added dropwise to a solution of PEG 350 monomethyl ether (2.0 g, 5.7 mmol) and triethylamine (1.7 mL, 12.2 mmol) at 0 °C with stirring and exclusion of moisture. The reaction mixture was stirred for 5 h and then filtered, and the solvent was evaporated in vacuo. The resulting pale white/yellow oil was used without further purification. ¹H NMR, 250 MHz, $\delta(\text{CDCl}_3)$: 6.3 (1H, m), 5.9 (1H, m), 4.45 (2H, m), 3.81 (1H, m), 3.59–3.34 (32H, m), 3.25 (3H, m) and 1.82 (3H, s) ppm. ¹³C NMR, $\delta(\text{CDCl}_3)$: 167.20, 137.20, 124.10, 72.26, 70.80, 70.92, 68.80, 58.81, and 17.20 ppm.

Pentamethyldisiloxane Polymeric Surfactant 1. Trimethylsilyloxydimethylsilylpropyl methacrylate (4.0 mL, 13.1 mmol) and methoxyxypolyoxyethylenyl methacrylate **2** (0.6 g, 1.44 mmol) were dissolved in degassed chloroform (10 mL). AIBN (60 mg, 0.37 mmol) was added, and the reaction vial was sealed and heated at 60 °C for 48 h. The reaction mixture was diluted with chloroform (50 mL) and washed with 0.1 M aqueous NaHCO_3 (2×50 mL), the organic layer was separated, dried (MgSO_4), and filtered, and the solvent was removed by evaporation in vacuo. The resulting polymer was a yellow paste and was dried under high vacuum and used without further treatment. Nanoprobe MAS ¹H NMR, 500 MHz, $\delta(\text{CDCl}_3)$: 3.91 (2.6 H, m, $\text{CO}_2\text{CH}_2\text{CH}_2$), 3.79–3.55 (2.2 H, m, $[\text{CH}_2\text{CH}_2\text{O}]_8$), 3.40 (0.2H, s, OCH_3), 1.93 (2.5 H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.1 (1.4 H, m, CCH_2C), 0.95 (3 H, m, CH_3CH), 0.65 (2 H, m, $\text{CH}_2\text{CH}_2\text{Si}$), and 0.05 (15 H, m, $\text{CH}_2\text{Si}(\text{CH}_3)_2\text{OSi}(\text{CH}_3)_2$) ppm.

Suspension Polymerization. SPOCC. Surfactant **1** was dissolved in 1,2-dichloroethane and mixed with the 3-methyloxetanylmethyl PEG 1500 macromonomers under argon in amounts as illustrated in Table 1. After a homogeneous solution was obtained, the solution was cooled in an ice bath and $\text{BF}_3 \cdot \text{OEt}_2$ (0.1 mL/g macromonomer) was added with stirring and exclusion of moisture. After 2 min, the mixture was added to silicon oil (20 mL/g macromonomer) at room temperature with stirring (rate indicated in Table 1). After 2 h of stirring at room temperature, the temperature was increased to 60 °C and the polymerization was left overnight for curing without stirring. The resulting polymer particles were filtered on a sintered glass funnel, and the silicon oil was collected for recycling. The beads were washed with dichloromethane, dimethyl formamide, methanol, and water (3×5 mL/g macromonomer for each solvent), treated with 4 M HCl (8 mL/g macromonomer) for 2 h at 60 °C, washed extensively with water, methanol, dimethyl formamide, and dichloromethane (3×5 mL/g macromonomer for each solvent), dried under high vacuum for 24 h and sieved through the following sieves: 1000, 500, and 300 μm (see Table 1).

POEPOP. A solution of potassium *tert*-butoxide (50 mg/g macromonomer) in *tert*-butyl alcohol (Table 2) was mixed with the methoxyxirane PEG 1500 macromonomers at 40 °C and stirred for 10 min, and a solution of the surfactant (Table 2) in *tert*-butyl alcohol (0.1 mL/50 mg of surfactant) was added. The solvent was evaporated in vacuo at 50 °C, and the residue was added to silicon oil (20 mL/g macromonomer) at 120 °C with stirring (rate as indicated in Table

2). After stirring at 120 °C for 12 h and washing as above, the resin was treated with 4 M NaOH for 2 h at 60 °C and washed as above. Drying and sieving were performed as described for SPOCC above.

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References and Notes

- (1) Professor William Lubell, Université de Montréal, C. P. 6128, Succursale Centre Ville, Montréal, Québec, Canada H3C 3J7, is currently a visiting Professor at Carlsberg Laboratory.
- (2) (a) Adams, J. H.; Cook, R. M.; Hudson, D.; Jammalamadaka, V.; Lyttle, M. H.; Songster, M. F. *J. Org. Chem.* **1998**, *63*, 3706–3716. (b) Cilli, E. M.; Oliveira, E.; Marchetto, R.; Nakaie, C. R. *J. Org. Chem.* **1996**, *61*, 8992.
- (3) (a) Becker, H.; Lucas, H.-W.; Maul, J.; Pillai, V. N. R.; Anzinger, H.; Mutter, M. *Macromol. Chem., Rapid Commun.* **1982**, *3*, 217–223. (b) Hellermann, H.; Lucas, H.-W.; Maul, J.; Pillai, V. N. R.; Mutter, M. *Macromol. Chem.* **1983**, *184*, 2603–2617. (c) Rapp, W.; Zhang, L.; Häblich, R.; Bayer, E. In *Petides 1988, Proceedings of the European Peptide Symposium*; Jung, G., Bayer, E., Eds.; Walter de Gruyter: Berlin, 1989; 199–201. (d) Porco, J. A.; Deegan, T.; Devonport, W.; Gooding, O. W.; Heisler, K.; Labadie J. W.; Newcomb, B.; Nguyen, C.; van Eikeren, P.; Wong, J.; Wright, P. *Mol. Diversity* **1996**, *2*, 197–206.
- (4) (a) Burger, M. T.; Barlett, P. A. *J. Am. Chem. Soc.* **1997**, *119*, 12697–12698. (b) Leon, S.; Quarrell, R.; Lowe, G. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2997–3002. (c) Smith, H. K.; Bradley, M. *J. Comb. Chem.* **1999**, *1*, 326–332.
- (5) (a) Renil, M.; Meldal, M. *Tetrahedron Lett.* **1996**, *37*, 6185–6188. (b) Rademann, J.; Grøtli, M.; Meldal, M.; Bock, K. *J. Am. Chem. Soc.* **1999**, *121*, 5459–5466. (c) Buchardt, J.; Meldal, M. *Tetrahedron Lett.* **1998**, *39*, 8695–8698.
- (6) (a) Rademann, J.; Meldal, M.; Bock, K. *Chem. Eur. J.* **1999**, *5*, 1218–1225. (b) Schleyer, A.; Meldal, M.; Manat, R.; Paulsen, H.; Bock, K. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1976–1978. (c) Graven Sams, A.; Grøtli, M.; Meldal, M. *J. Chem. Soc. Perkin Trans. I.* **2000**, 955–962.
- (7) Unpublished results.
- (8) (a) Munger, M.; Trommsdorff, E. In *Polymerization Processes*; Schildknecht, C. E., Skeist, I., Eds.; Wiley-Interscience: New York, 1977; pp 106–142. (b) Kanda, P.; Kennedy, R. C.; Sparrow, J. P. *Int. J. Pept. Protein Res.* **1991**, *38*, 385–391. (c) Guyot, A. In *Synthesis and Separations using Functional Polymers*; Sherrington, D. C., Hodge, P., Eds.; John Wiley and Sons: London, 1988; pp 1–42.
- (9) Grøtli, M.; Gotfredsen, C. H.; Rademann, J.; Buchardt, J.; Clark, A. J.; Duus, J.Ø.; Meldal, M. *J. Comb. Chem.* **2000**, *2*, 108–119.
- (10) Mayes, A. G.; Mosbach, K. *Anal. Chem.* **1996**, *68*, 3769–3774.
- (11) Beaded SPOCC 400, SPOCC 900, POEPOP 400, and POEPOP 900 have also been obtained in high yields using this technique.
- (12) (a) Pursch, M.; Schlotterbeck, G.; Tseng, L.-H.; Albert, K.; Rapp, W. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2867–2869. (b) Sarkar, S. K.; Garigipati, R.; Adams, J. L.; Keifer, P. A. *J. Am. Chem. Soc.* **1996**, *118*, 2305–2306. (c) Gotfredsen, C. H.; Grøtli, M.; Willert, M.; Duus, J.; Meldal, M. *J. Chem. Soc. Perkin Trans. I.* **2000**, 1167–1171.
- (13) Auzanneau, F.-I.; Meldal, M.; Bock, K. *J. Pept. Sci.* **1995**, *1*, 31–44.
- (14) Some material remained in the reaction flask after transfer of the polymerization mixture into the oil. The actual yields are therefore higher than those shown in Tables 1 and 2.

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