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Gram-Scale Synthesis of Suspension-Polymerized Styrene–Divinylbenzene-Based Resins Using an Oscillatory Baffled Reactor

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The use of spherical particulate cross-linked vinyl polymer beads or resins produced by free-radical suspension polymerization is now widespread in both synthetic and screening methodologies.[1–3] Increasingly, however, they are also being exploited as the basis of heterogeneous reagents, catalysts, and scavengers to facilitate the synthesis of target molecules in solution.[4,5] The work-horse species are styrene–divinylbenzene-based resins, which are synthesized on a large industrial scale (ca. 1000 kg) by using a batch polymerization procedure carried out in steel, stirred-tank reactors (STR).[6] Laboratory-scale syntheses are performed similarly by using a glass reactor typically of 0.5–2.0 L in volume.[7] A major technical challenge is to avoid particle aggregation, and this is usually achieved by dissolving a suitable suspension stabilizer in the aqueous phase, coupled with efficient stirring. In practice, stabilization conditions are usually optimized by experimentation, and no universal procedure is available that is suitable for all polymerization mixtures. Since aggregation is associated primarily with surface phenomena, that is, particle–particle, particle–reactor, and particle–stirrer interactions, and since the surface/volume ratio increases as the scale of the process is reduced, aggregation becomes more problematic. Suspension polymerization to produce high-quality beads in good yield on a gram scale is therefore difficult to achieve. This situation is unfortunate because an attractive strategy for synthesizing complex functional resins is to use an appropriate functional (for example, styryl) monomer in a suspension polymerization to produce resin beads with a predetermined loading, cross-link ratio, and morphology. Since laboratory resin synthesis is problematic below the 10–20 g scale, and some optimization program is almost always necessary for each functional comonomer, there is a considerable deterrent to investing in complex monomer synthesis in view of the likely wastage that will ensue in implementing successful suspension polymerization.

We have now developed a robust suspension polymerization procedure by using a small oscillatory baffled reactor (OBR) capable of providing good yields of high-quality resin beads, of both gel-type and various macroporous morphologies, and operating on a gram scale. We have also shown that a functional styryl co-monomer can be employed in the system with no deterioration in the yield nor physical quality of the resin beads obtained.

The design and underlying principles of the OBR have been reported by Mackley and co-workers,[8–10] and the appropriate choice of the dimensions of the reactor and the oscillating baffles, together with the frequency and amplitude of oscillation, leads in effect to each baffled cell acting as if it were a continuously stirred tank.[9,10] Ni et al. have reported the results of remarkable flow-visualization experiments[11] and computational fluid-dynamic simulations[12] which confirm this picture. The successful application of OBRs in suspension polymerization by the same group[13–16] prompted us to investigate the possibility of scaling down the reactor size to carry out gram-scale suspension polymerizations.

Accordingly, the glass OBR shown in Figures 1 and 2 was constructed. The reactor consists of a vertical glass tube 25 mm in diameter and 137 mm tall (ca. 70 mL volume) with a water jacket 53.5 mm in diameter and 158 mm tall. The top of the reactor is a conventional glass flange arrangement that allows the use of an N_2 supply and a condenser. The oscillatory motion in the reaction mixture is achieved by moving a set of stainless steel baffles up and down. The set consists of two or three orifice baffles (with orifice diameters of 11 mm) and an upper coupling plate into which is located the driving con-rod. The latter is 6.3 mm in diameter and 190 mm in length and is connected non-centrally to a rotating wheel which thus provides the oscillatory vertical motion. The con-rod moves within a long teflon bearing in the glass flange lid so as to maintain a vertical alignment of the baffles within the reactor. The baffles are made of 3-mm thick stainless-steel plate, and are connected to each other and the coupling plate by two 1.5-mm stainless-steel rods. The distance between the lower baffle and the reactor bottom is 6 mm (at full extension) and the oscillation amplitude is set at 21 mm. The free baffle area ratio (defined as the ratio of baffle orifice area to the tube

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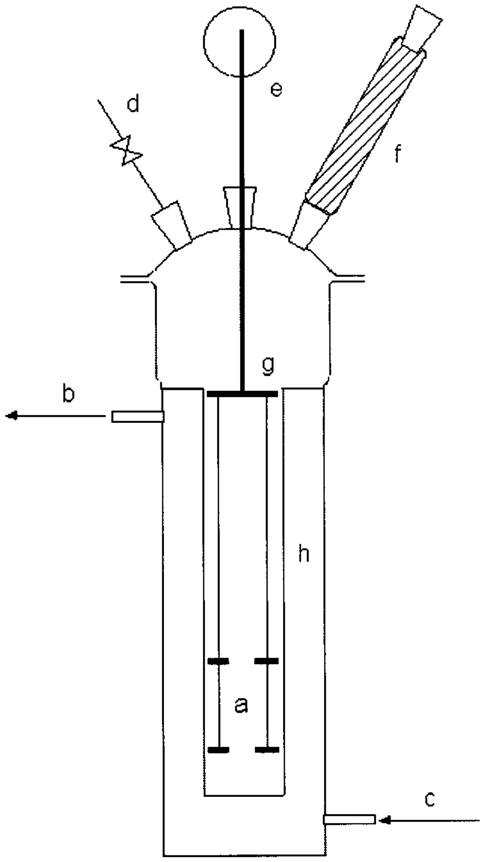


Figure 1. Schematic representation of small-scale oscillatory baffled reactor (OBR): a) orifice baffles; b) port to water bath; c) port from water bath; d) N_2 supply; e) off-centered drive coupled to con-rod; f) condenser; g) coupling plate; h) water jacket.

area) is fixed at 19 %, with a baffle spacing of 32 mm. Perhaps somewhat counter intuitively, optimum suspension conditions are provided by low frequency oscillation, typically about 2–8 Hz.

Data for the synthesis of representative macroporous resins are shown in Table 1. Earlier experiments utilized 40–65 mL of aqueous phase and 10 mL of organic phase (5 mL of co-monomer and 5 mL of porogen) with the triple baffle set arrangement. The yields of high-quality spherical beads are generally good or very good, and this is consistent with the results obtained using a laboratory-scale stirred-tank-type reactor,[7] where it is normally found that high-quality macroporous resins are easier to produce than gel types. Oscillation frequencies in the range 2.5–6 Hz were found to be suitable with tylose MH1000 (methyl cellulose) as the suspension stabilizer. Excessive foaming and particle aggregation occurred above 6.5 Hz, and likewise particle aggregation started to occur at 2.5 Hz. Particle diameters fall in a similar range to those found using a laboratory-scale stirred-tank reactor[7] and the breadth of the distribution also seems similar. Additional fractionation by sieving would be necessary to achieve narrower distributions than those indicated in Table 1. The nature of the stabilizer did not prove to be too crucial, with good quality products also being obtained using poly(vinyl alcohol) (PVA, 88 % hydrolyzed, M_{wt} = ca. 125 000) or xanthan gum (kelzan) as the primary stabilizer. Both toluene and 2-ethylhexan-1-ol were employed as porogens. The former interacts quite well (relatively thermodynamically "good"

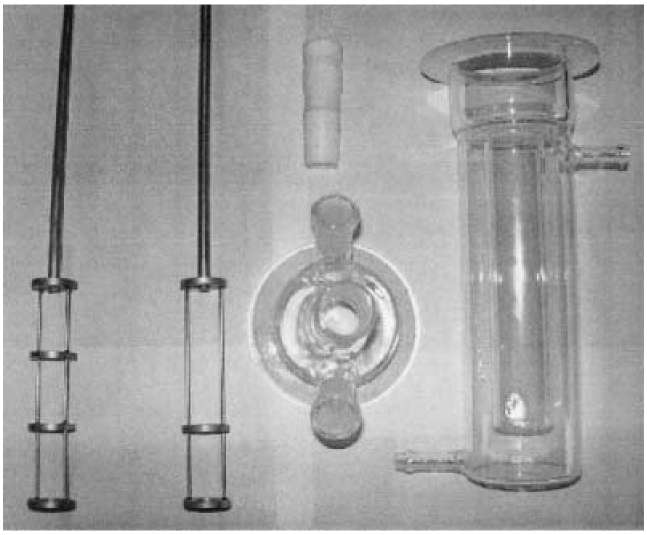


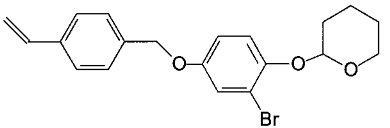
Figure 2. Actual OBR reactor, flange top, con-rod teflon guide, and 3 × orifice baffle arrangement/2 × orifice baffle arrangement.

Table 1. Macroporous styrene/DVB based beads prepared by suspension polymerization in a small oscillatory baffled reactor (OBR).[a]

Resin	Co-monomer composition [mL, vol %]			Porogen [mL][d]	Aqueous phase (mL, stabilizer)	Set of baffles	Oscillation frequency [Hz]	Reaction time [h]	Reaction temperature [°C]	Yield [%][e]	Bead characteristics	
	styrene	DVB[b]	CMS[c]								diameter [µm]	analysis [%] found/calcd
M1	2.00, 40	3.00, 60	–	T (5)	40, 0.44 % tylose MH1000	3	6	8	70	95	106–710[f]	–
M2	2.00, 40	3.00, 60	–	T (5)	65, 0.44 % tylose MH1000	3	6	7	80	84	–	–
M3	2.00, 40	3.00, 60	–	T (5)	40, 0.44 % tylose MH1000	3	5	8	70	96	106–710[f]	–
M4	2.00, 40	3.00, 60	–	T (5)	40, 0.44 % tylose MH1000	3	4	8	70	89	106–710[f]	–
M5	2.00, 40	3.00, 60	–	T (5)	40, 0.44 % tylose MH1000	3	3	8	70	92	212–710[f]	–
M6	2.00, 40	3.00, 60	–	T (5)	40, 0.44 % tylose MH1000	3	2.5	8	70	91	300–710[f,g]	–
M7	–	1.00, 100	–	T (1)	25, 0.75 % PVA/3.3 % NaCl[j]	2	6	5	70	85	99–147[h]	
M8	4.80, 87	0.70, 13	–	EH (4.5)	40, 0.44 % tylose MH1000	3	3	8	70	71	106–710[f]	–
M9	0.88, 88	0.20, 12	–	EH (1)	25, 0.75 % PVA/3,3 % NaCl[j]	2	6	5	70	71	119–257[h]	–
M10	3.65, 73	0.60, 12	0.75, 15	EH (5)	65, 0.44 % tylose MH1000	3	3	7	80	75	–	Cl, 3.8/4.1
M11	3.65, 73	0.60, 12	0.75, 15	EH (5)	65, 0.75 % PVA/3.3 % NaCl	3	3.5	7	80	67	62–151[h]	Cl, 3.9/4.1
M12	4.55, 77[k]	0.76, 10[k]	0.81, 13[i,k]	EH (5)	65, 0.44 % tylose, MH1000	3	3.5	7	80	78	85–191[h]	Br, 2.4/2.7

[a] 1 wt % azobisisobutyronitrile (AIBN), relative to monomer. [b] DVB, 80 % grade. [c] CMS = chloromethylstyrene (mixed isomers). [d] T = toluene; EH = 2-ethylhexan-1-ol. [e] Yield of isolated high-quality spherical beads. [f] By sieving into fractions. [g] Larger fractions aggregated. [h] Optical microscopic observation. [i] functional comonomer, (**1**), replacing CMS. [j] Additional 5 mL added during reaction. PVA = poly(vinyl alcohol). [k] g, wt %.

solvent) with polystyrene-based resins and is known to generate high surface area macroporous resins when used with relatively large levels of divinylbenzene.[17] In this instance resin M7 (Figure 3a) has a dry-state surface area of 659 $m^2 g^{-1}$ as determined from a BET analysis of N_2 sorption data (Micromeritics ASAP 2000), and so the morphology of this species is totally as anticipated. 2-Ethylhexan-1-ol is, in contrast, a relatively thermodynamically "poor" solvent and is known to generate macroporous resins with modest surface area when used with rather low levels of divinylbenzene.[17] Here resin M9 (Figure 3b) has a dry-state surface area of 64 $m^2 g^{-1}$, and so again this is consistent with similar resins prepared in a stirred-tank reactor. Replacement of part of the styrene feed with chloromethylstyrene (M10 and M11; Figure 3c) or with functional co-monomer **1**[18] (M12; Figure 3d) does not disturb the suspension system and good yields of high-quality resins are obtained in each case. Elemental microanalysis of the resins confirmed the incorporation of these monomer residues at a level close to the feed composition and we anticipate that the distribution and accessibility of functional groups will be similar to that in analogous resins prepared in a stirred-tank reactor. Finally it is important to note that high quality macroporous beads can be obtained in good yield on a one-gram scale (M7 and M9) by reducing the volume of the aqueous phase to 25 mL and employing the double baffle set arrangement.



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Data for the synthesis of representative gel-type resins are shown in Table 2. In general, high-quality lightly cross-linked spherical gel-type resins are more difficult to synthesize in good yield than are macroporous species. This is because gel-type species show a higher tendency to aggregate and the suspension conditions required to avoid this are somewhat more rigorous. Our initial attempts to produce 2% cross-linked styrene/DVB resins in our small OBR are exemplified by entries G1 and G2 in Table 2 using xanthan gum as a primary stabilizer. Though beads were obtained (with this and

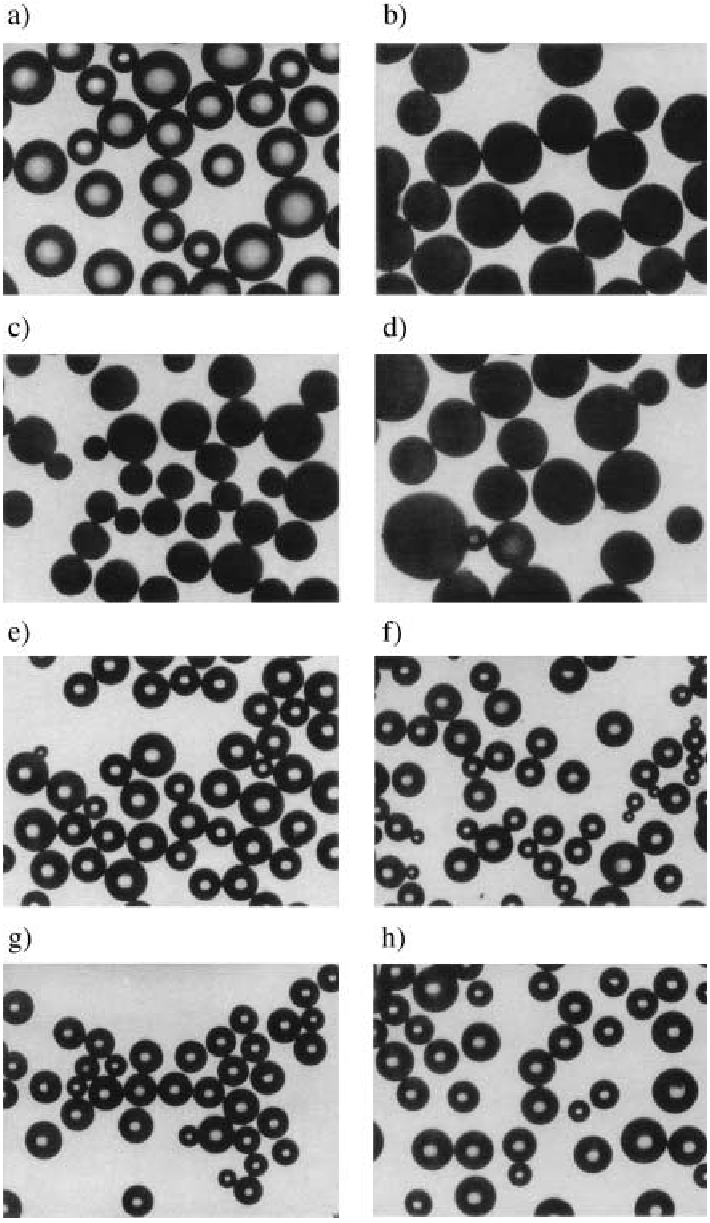

Figure 3. Optical micrographs: a) macroporous resin M7; b) macroporous resin M9; c) macroporous resin M11; d) macroporous functional resin M12; e) gel-type resin G4; f) gel-type resin G7; g) gel-type resin G8; h) gel-type functional resin G9. (Typical diameters ca. 150 μm.)

Table 2. Gel-type styrene/DVB-based beads prepared by suspension polymerization in small oscillatory baffled reactor (OBR).[a]

Resin	Co-monomer composition [mL, vol %]			Aqueous phase [mL, stabilizer]	Set of baffles	Oscillation frequency [Hz]	Reaction time [h]	Reaction temperature [°C]	Yield [%][c]	Bead characteristics	
	styrene	DVB[b]	functional monomer							diameter [μm][d]	analysis found/calcd
G1	4.92, 98	0.08, 2	–	65, xanthan gum[e]	3	8	7	80	36	62–136	
G2	3.40, 68	0.08, 2	1.52,30[f]	65, xanthan gum[e]	3	8	7	80	44	–	Cl, 9.9/7.9
G3	1.90, 95	0.10, 5	–	25,[i] 0.75% PVA/3.3% NaCl	2	6	5	70	67	–	–
G4	1.90, 95	0.10, 5	–	25,[i] 0.75% PVA/3.3% NaCl	2	6	5	70	77	129–248	–
G5	1.90, 95	0.10, 5	–	25,[i] xanthan gum[e]	2[g]	6	5	70	53	59–110	–
G6	1.90, 95	0.10, 5	–	25,[i] 0.75% PVA/3.3% NaCl	2	6	5	70	60	–	–
G7	1.96, 98	0.04, 2	–	25,[i] 0.75% PVA/3.3% NaCl	2	6	5	70	70	83–248	–
G8	1.98, 99	0.02, 1	–	25,[i] 0.75% PVA/3.3% NaCl	2	6	5	70	54	101–202	–
G9	1.17, 59[j]	0.05, 2[j]	0.78,40[h,j]	25,[i] 0.75% PVA/3.3% NaCl	2	6	5	70	74	119–257	Br, 8.8/8.0

[a] 0.7 wt% AIBN. [b] 80% grade DVB; figure quoted refers to actual DVB isomers. [c] Yield of isolated high-quality spherical beads. [d] Optical microscopic observation. [e] 1.6 wt% boric acid, 0.01 wt% cellosize, 0.08 wt% xanthan gum, 16 wt% NaCl. [f] Chloromethylstyrene, mixed isomers. [g] Oscillation frequency, 8 Hz. [h] Functional co-monomer (**1**). [i] Additional 5 mL added during reaction; PVA = poly(vinyl alcohol). [j] g, wt%.

other stabilizers), the yield of the isolated high-quality spherical resin was rather low, too low to allow economic adaptation for use with complex functional co-monomers. However, it was realized that a major contribution to the seeding of aggregation was irregular agitation at the liquid–gas interface, especially when this interface was located too close to one of the oscillating baffles. Accordingly, therefore the two baffle set arrangement was designed, built, and commissioned and the volume of the total liquid phase adjusted to be sufficiently remote from the upper baffle to allow for efficient suspension within the bulk of the liquid and yet to avoid induction of particle aggregation at the surface. Since evaporative losses were also significant with an aqueous phase volume of only 25 mL, the level of liquid was maintained during the reaction by gradual addition of more aqueous phase (5 mL). These simple design and operational changes led to a significant improvement in the yields of the isolated high quality beads, despite the polymerization being performed with only approximately 2 g of comonomers (for example, G4, G7, and G8, Figure 3 e–g). The most robust stabilizer used was poly(vinyl alcohol) (PVA, 88 % hydrolyzed, $M_{\text{wt}} =$ ca. 125000 Aldrich) at 0.75 wt %, with 3.3 wt % of NaCl in the aqueous phase, and with a baffle oscillation frequency of 6 Hz. Xanthan gum was also a useful stabilizer (G5) but a higher oscillation frequency, 8 Hz, was required because of the larger viscosity of this aqueous solution. By using the optimized procedure 2 % cross-linked gel-type resin G9 was prepared using functional co-monomer **1**, with a good yield of isolated quality beads of about 1.5 g (ca. 75 %; Figure 3 h). Resins G1–G9 are all lightly cross-linked (DVB $\leq$ 5 vol %) and have been prepared in the absence of any porogen. Each would therefore be expected to have a gel-type morphology and a correspondingly very low dry-state surface area. This was confirmed for resin G8 whose dry-state surface area is less than $5\,\text{m}^2\,\text{g}^{-1}$. The volume swelling of G4, G7, and G8 with cross-link ratios of 5, 2, and 1 %, respectively, in toluene are 3.05, 4.52, and $7.59\,\text{mL}\,\text{g}^{-1}$, which is again consistent with the gel-type morphology of these species. Interestingly the corresponding swelling figure for the 2 % cross-linked functional resin G9 is $3.37\,\text{mL}\,\text{g}^{-1}$, which suggests that the presence of the residues from the functional co-monomer **1** reduces somewhat the ability of toluene to solvate this resin.

In summary, we have developed a robust small-scale experimental procedure for synthesizing both macroporous and gel-type high-quality spherical particulate styrene–divinylbenzene resins in good yield. The methodology is tolerant to the use of functional co-monomers, and now offers the prospect of exploiting complex, structurally well-characterized monomers in suspension polymerization to produce resins for use in high-throughput discovery programs.

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An Azulene Dimer as a Near-Infrared Quencher[**]

Wellington Pham, Ralph Weissleder, and Ching-Hsuan Tung[*]

Highly sensitive, efficient, and quenchable fluorochromes have become essential for acquiring genomic and proteomic data from biological samples.[1] Fluorescent compounds also have many other useful applications in medicine, biotechnology, and biological science.[2,3] Specifically, fluorochromes attached to various ligands have been used for detecting nucleic acid hybridization (molecular beacons),[4,5] in drug discovery,[6] for sensing molecular interactions,[7,8] and for deciphering biological pathways.[9] Typically, molecular DNA beacons[4,5] and enzyme-sensing probes[10] primarily rely on the fluorescence resonance energy transfer (FRET) between

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author. It contains detailed information on the synthesis and characterization of the compounds discussed.

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