

# Particulate Precipitation Polymerization: A Convenient Procedure for the Synthesis of Crosslinked Polymers Useful as Polymeric Supports

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## Synopsis

Suitable choice of monomer/nonsolvent and monomer plus solvent/nonsolvent ratios affords a very simple and convenient laboratory scale method for the synthesis of functionalized crosslinked polymers suitable as polymeric supports in a wide variety of applications. The method involves an initially homogeneous solution polymerization which, because of the presence of nonsolvents ultimately produces insoluble, particulate (i.e., nonswollen) resin. Advantages over the usual suspension polymerization processes include the absence of stabilizers and suspension agents and complete freedom to utilize water soluble or water insoluble monomers, or mixtures of the two. Reaction conditions must be determined experimentally for individual systems and a number of representative examples are given.

## INTRODUCTION

Suspension polymerization,<sup>1</sup> as applied originally to the preparation of polystyrene ion-exchange resins, is a well-established procedure which has now become more widely employed in the formation of resins for use as polymeric reagents and supports.<sup>2</sup> This latter development was stimulated by the work of Merrifield who showed that lightly crosslinked polystyrenes were effective supports for step-wise synthesis of polyaminoacids.<sup>3,4</sup> Nowadays it is commonplace to utilize crosslinked polymeric resins (mainly based on polystyrenes) for attachment of a very wide variety of reagents employed in the usual range of organic synthetic transformations<sup>5</sup> and transition metal catalyzed processes.<sup>6</sup>

The main advantage arising from the use of polymeric supports lies in the convenience of separation, recovery, and recycling of polymer-attached reaction products from unused reactants, and a potential problem is associated with the presence of residual impurities from the stabilizing/suspension agents (inorganic and colloidal) required in the suspension polymerization procedure. Suspension polymerizations may be controlled to give products with relatively uniform particle and pore sizes but require stabilized oil droplet-in-water or water droplet-in-oil suspensions for water insoluble and water soluble monomers, respectively. Considerable difficulties are encountered when it is necessary to copolymerize, by suspension polymerization, mixtures of water-soluble and water-insoluble monomers.<sup>1</sup>

While the suspension method yields polymeric products having regular spherical shapes and surface areas, it is the swellability and particle size which are more important in determining reaction rates and ease of manipulation, for most applications of polymeric supports.

In order to overcome some of the difficulties encountered in the synthesis of polymeric resins by suspension polymerization, we have developed a simple laboratory procedure which permits the synthesis of a very wide range of cross-linked and functionalized lyophobic and lyophilic resins, having relatively high purity, and with reasonably controlled particle sizes.

## EXPERIMENTAL

### Materials

Styrene, acrylonitrile, methyl methacrylate, 2-hydroxy ethyl methacrylate, methacrylic acid, *N*-vinyl pyrrolidone, and *N*-vinyl imidazole monomers were commercial materials purified by the usual methods and distilled under reduced pressure before use. *p*-Acetoxystyrene was prepared and purified as described previously.<sup>7</sup> *N*-Acryloylmorpholine was a gift from Dr. R. Epton (Wolverhampton Polytechnic) and was used as supplied.

Divinylbenzene (BDH) was washed with 5% aqueous NaOH solution followed by distilled water, dried over CaCl<sub>2</sub> and then over CaH<sub>2</sub>, and finally distilled under reduced pressure, without fractionation, so as to maintain the initial composition of divinylbenzene (DVB) in ethylvinylbenzene. Mass spectrometric data for the purified DVB showed 56.8% of DVB in the mixture (71.5% para, 28.5% ortho isomers) and 43.2% ethyl vinyl benzenes in unknown isomer ratios.

Azobisisobutyronitrile (AIBN) was twice recrystallized from ethanol. All solvents were purified by the usual techniques.

### Analytical Methods

Analyses of some monomers including divinylbenzene and vinylbenzyl chloride were carried out in a Micromass 12 mass spectrometer with electron impact ionization and a Pye Unicam series 104 gas chromatogram with a Watson Biemann molecular separation interface.

Purity of the monomers and some of the intermediates for monomer synthesis was checked by NMR spectroscopy using a Perkin-Elmer R12B 60-MHz spectrometer. This method was also applied for monitoring some reaction stages during synthesis.

All GLC experiments were performed in a Pye Unicam series 104 gas chromatogram with flame ionization detector using a column made from 3% OV-225 on Supelcoport (100-120 mesh).

Molecular weight measurements were made in toluene solution at 25°C in a gel permeation chromatograph (Waters Associates model 200) fitted with a differential refractometer detector. Standard samples of polystyrene (Waters Associates) were used for calibration.

Copolymer composition of the polymers of styrene-acrylonitrile-divinylbenzene were determined by elemental analysis for nitrogen.

### Polymerization Technique

The polymerization experiments were generally carried out at the desired temperature in a round bottom flask with continuous stirring using a magnetic stirrer. In a typical polymerization procedure, appropriate amounts of monomer or monomer mixture along with the initiator (AIBN) were placed in the flask under nitrogen and the requisite amount of solvent/nonsolvent mixture was added before closing the flask with a rubber septum. The reaction vessel was then placed in a constant-temperature bath maintained at the desired temperature with continuous stirring for the specified time. When the reaction was complete, the material was filtered, washed thoroughly with the solvent/nonsolvent mixtures and finally with the nonsolvent before drying in a vacuum oven. For the preparation of polymers with larger amounts of materials, an apparatus suitable for a typical suspension polymerization under inert atmosphere may be used.<sup>7</sup>

### Examples of Particulate Precipitation Polymerization

Examples given in Tables I–III illustrate applications of the technique to polymerization of some vinyl monomers and illustrate the effects of monomer/solvent, solvent/nonsolvent ratios, and crosslink density on the nature of the products. Since the polymerizations become heterogeneous at an appropriate time/conversion for individual systems, it was of obvious interest to determine whether this resulted in abnormal molecular weight distributions. Experimentally this can only be accomplished for noncrosslinked reaction products, so the same precipitation technique was applied to homopolymerization of styrene in the absence of DVB. Results are indicated in Table IV.

Another matter for concern was whether, in a typical crosslinked system, individual reaction components were consumed at differential rates. This was investigated using styrene–DVB at a representative combination of reactants. Figure 1 shows GLC analytical data confirming that relative rates of consumption of individual reacting components (styrene, divinylbenzenes, ethylstyrenes) do not vary in any dramatic way throughout the reaction.

Possible variation of resin composition during polymerization was investigated using the styrene–acrylonitrile–DVB system as representative (Table V).

### General Aspects of Particulate Precipitation Polymerization

The method adapted for synthesis of crosslinked polymers consists essentially of the usual homogeneous solution phase process modified by inclusion of a nonsolvent for the expected (noncrosslinked) product polymer. Thus, all monomers, initiators (usually AIBN), additional solvents, and nonsolvents, constitute a true solution at the start of each polymerization. Additives such as stabilizers and suspension agents are completely avoided, and while purging with nitrogen, has the expected beneficial effect on reproducibility of reaction rates, it is not essential. Additionally, there are no complications when using mixtures of water-soluble and water-insoluble monomers. The ratio of nonsolvent to solvent components in the reaction mixture is critical and must be carefully adjusted by trial and error to cause the crosslinked particles to precipitate at the desired stage of the polymerization. Some control of particle size

TABLE I  
 Polymerization of Vinyl Monomers in Presence of Divinylbenzene at 65°C

Experiment No.	Reaction components	Volume (ml)	Reaction time (hr)	% Conversion	Nature of product
1	Methyl methacrylate	3	6-8	90-100	hard particles 60-100 mesh
	Divinylbenzene	0.15			
	Benzene	1			
	Hexane	3			
	Isopropyl alcohol	10			
2	AIBN	0.05(g)	2	90	hard 60-100 mesh
	Hydroxyethyl methacrylate	2			
	DVB	0.1			
	Benzene	3			
	Hexane	9			
3	AIBN	0.03(g)	4	90	very fine particles
	Acrylonitrile	3			
	Benzene (or hexane)	25			
	AIBN	0.1(g)			
4	AIBN	0.025(g)	5	80	hard particles, 60-100 mesh
	N-Vinyl pyrrolidone	2			
	DVB	0.05			
	Benzene	6			
	Hexane	6			
5	AIBN	0.1(g)	10-12	90-100	hard, fine particles
	Methacrylic acid	5			
	DVB	0.1			
	Benzene	50			
	AIBN	0.1(g)			

TABLE II  
Effect of Monomer/Solvent Ratio on Acrylonitrile-*p*-Acetoxystyrene-DVB Polymerization at 60°C

	Experiment No.		
	6	7	8
Materials used (ml):			
Acrylonitrile	3	3	2
<i>p</i> -Acetoxystyrene	1	1	2
Styrene	—	—	1
Hexane	5	15	5
Benzene	5	15	5
DVB	0.15	0.15	0.15
AIBN	0.05(g)	0.05(g)	0.05(g)
Reaction time (hr)	8-10	10-12	6-8
Conversion (%)	70-80	80-90	80-90
Nature of the product	slightly hard beads, 60-100 mesh	fine powder, 200 mesh	hard, spherical beads, 15-30 mesh

can be accomplished by adjusting the rate of stirring but the nature of the solvent, nonsolvent, and crosslinker components mainly determine the physical characteristics of the final product. Overall, the method involves typical solution polymerization in the presence of a nonsolvent, which causes the product, crosslinked polymer, to precipitate in a readily handled particulate form at an easily adjusted stage of the polymerization.

Choice of solvent (including monomers) and nonsolvent components is obviously vital for successful resin formation and cannot be generalized. Each combination of monomers will have one or more solvent/nonsolvent systems giving satisfactory results and these must be determined experimentally. The experimental and results section gives representative examples of monomer mixtures which have successfully been converted into particulate resin particles, but the list is not to be regarded as restrictive, nor should the particular experimental conditions be regarded as properly optimized for any system. Resin particles were obtained using commercial divinylbenzene as the crosslinking agent but other types of crosslinker would be equally applicable, subject to the usual reactivity ratio conditions. Examples of monomer mixtures yielding resin particles include acrylonitrile-styrene, acrylonitrile-*p*-acetoxystyrene, chloro-

TABLE III  
Effect of Solvent/Nonsolvent Composition on Styrene-DVB copolymerization at 70°C

	Experiment No.		
	9	10	11
Materials used (ml):			
Styrene	3	3	3
DVB	0.15	0.15	0.25
Toluene	1	1	1
Isoamyl alcohol	10	—	4
Ethanol	—	10	—
Heptane	—	—	10
AIBN	0.05(g)	0.05(g)	0.10(g)
Nature of the product	hard particles, 60-100 mesh	soft particles, 60-100 mesh	hard particles, 25-60 mesh

TABLE IV  
 Precipitation Polymerization of Styrene in the Absence of DVB at 70°C

	Experiment No.				
	12	13	14	15	16
Styrene (ml)	3	3	3	3	3
<i>n</i> -Heptane (ml)	10	20	0	toluene(2)	toluene(0.5)
Isopropyl alcohol (ml)	15	5	25	23	24.5
AIBN (g)	0.1	0.1	0.1	0.1	0.1
Time of polymerization (hr)	27	25	19	20	25
Yield (g)	1.38	1.37	1.69	1.60	1.78
$10^{-3}\overline{M}_w$ (GPC)	9.3	10.0	9.4	8.8	9.9
$10^{-3}\overline{M}_n$ (GPC)	5.9	5.7	6.1	5.6	5.5
$\overline{M}_w/\overline{M}_n$	1.6	1.8	1.5	1.6	1.8

methylstyrene-2-hydroxyethylmethacrylate, styrene-*p*-acetoxystyrene, and *N*-acryloylmorpholine-styrene. Similarly, crosslinked resins were obtained from essentially homopolymerizations of styrene, methacrylic acid, *N*-vinyl imidazole, 2-hydroxyethylmethacrylate, *N*-vinyl pyrrolidone, and methyl methacrylate.

Data given in the Experimental and Results sections indicate the effects of stirring rate, crosslinker concentration, and solvent/nonsolvent ratios on the physical characteristics of resin particles obtained from some of the systems listed above, and this range, together with the further examples given below, clearly demonstrate applicability of the method to both hydrophobic and hydrophilic monomers.

Even with the limited and entirely empirical nature of the results presented, it is possible to draw some conclusions as to the general mechanistic features of particulate precipitation polymerization. Copolymer composition does not

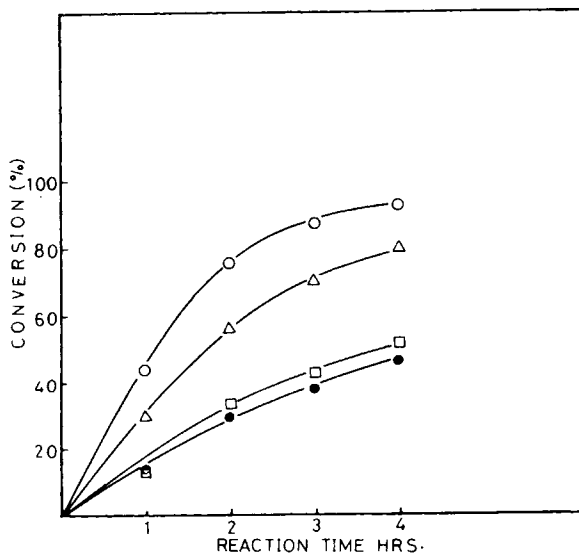


Fig. 1. Relative rates of consumption of polymerizable components at 70°C. Reaction mixture contains styrene(□)(3 ml); DVB [(○) *o*-DVB; (Δ) *p*-DVB] (1 ml); isopropanol (20 ml); *n*-hexane (5 ml); AIBN (0.1 g). Commercial DVB contains *ortho*- and *para*-divinylbenzenes and a mixture of ethyl vinyl benzenes (●). Analysis by GLC.

TABLE V  
Composition of Resins Obtained from Polymerization<sup>a</sup> of Styrene-Acrylonitrile-DVB at 60°C

	Experiment No.			
	17	18	19	20
Polymerization time (hr)	1	2	3	4
Polymer yield (g)	0.26	0.56	1.12	1.63
Conversion (%)	7.4	15.5	31.2	45.4
Nitrogen content (%)	8.20	8.72	8.60	9.16

<sup>a</sup> Styrene 2 ml; acrylonitrile 2 ml; DVB 0.12 ml; benzene 5 ml; *n*-hexane 5 ml; AIBN 0.05 g.

change dramatically with reaction time (Table V), but this must depend to some extent on reactivity ratios for individual systems. It is important that, although divinylbenzene is more reactive than styrene, the relative rates of incorporation of DVB and styrene change only slightly for very high conversions (Fig. 1), indicating that the crosslink density in the product resins does not change significantly with reaction time or conversion.

The general conclusion therefore, must be that these polymerizations proceed as essentially true solution phase processes until, according to the choice of solvent/nonsolvent ratio, the crosslinked products precipitate in particulate (i.e., nonswollen) forms suitable for use as polymeric supports. Data obtained for polymerization of styrene in the absence of crosslinker (Table IV) show that the molecular weight distribution is normal and does not vary with conversion.

It follows that polymerization proceeds with the usual termination steps until the resin particles separate from solution at which point the growing radicals become trapped. This point was checked by the synthesis of block polymers. For example, a reaction mixture containing styrene (3 ml), DVB (1 ml), isopropanol (10 ml), *n*-hexane (5 ml), and AIBN (0.1 g) typically yielded 0.7 g of resin after 2 hr polymerization at 70°C. In a special experiment after cooling to room temperature, excess monomers, initiator, etc. were removed by means of a syringe inserted into the serum cap enclosing the reaction vessel. Methyl methacrylate monomer (4 ml) was added via the syringe in order to swell the polystyrene resin. The mixture was then allowed to stand at room temperature and the products ultimately poured into methanol and washed carefully. Starting with 0.7 g of resin, the final product [polystyrene resin grafted with poly(methyl methacrylate)] showed weight increases of 0.13 g (18.6%) and 0.43 g (61.4%) after 20 and 40 hr, respectively. Swelling of the particulate resin particles by additional monomer or solvent makes the trapped radicals available for reaction and hence affords a simple method of grafting an additional polymeric component.

### Applications of Particulate Precipitation Polymerization

Previously<sup>7</sup> we have been concerned with the synthesis of polystyrene-based resins having phenolic groups for use in the Merrifield type of peptide synthesis. These resins were obtained by the usual suspension copolymerization of styrene, *p*-acetoxystyrene, and divinylbenzene, the required phenolic functionality being readily available via hydrolysis of the acetoxyl protecting group. We now report that a reaction mixture containing styrene (16 ml), *p*-acetoxystyrene (0.2 ml), DVB (0.15 ml), isoamylalcohol (5 ml), methanol (15 ml), and AIBN (0.1 g) when allowed to polymerize at 70°C for 8 hr yielded 1.0 g of resin particles (60–200

mesh) suitable for use in solid phase peptide synthesis.<sup>8</sup> This procedure is very much more convenient than the suspension process already reported.<sup>7</sup>

Similarly, the precipitation method was used (Table II) to prepare phenolic resins based on polyacrylonitrile rather than on styrene in anticipation of enhanced performance in peptide synthesis due to the more polar polymer backbone.<sup>9</sup> Both the polystyrene based and polyacrylonitrile phenolic resins have been employed successfully in reactions of protected amino acids, and full details are given in a separate publication.<sup>10</sup>

As an example of resin formation from a mixture of water soluble and water insoluble monomers, the copolymerization of styrene with *N*-acryloylmorpholine was studied, the latter being an important constituent of many hydrophilic resins used in column separation procedures.<sup>11</sup> Typically styrene (0.5 g), *N*-acryloylmorpholine (2 g), DVB (0.075 g), benzene (5 ml), *n*-hexane (5 ml), and AIBN (0.03 g) polymerized at 65°C for 9 hr gave hard particles (70% conversion) having 30–60 mesh.

Very recently the applicability of polymer-bound sensitizers for the generation of singlet molecular oxygen has been extended to a hydrophilic resin derived by suspension polymerization of chloromethylstyrene and 2-hydroxyethylmethacrylate.<sup>12</sup> For comparison we have synthesized a related water-swellaable resin by the particulate precipitation technique. Chloromethylstyrene (60% meta, 40% para) (2 ml), 2-hydroxyethylmethacrylate (1 ml), DVB (0.1 ml), *n*-hexane (14 ml), methanol (1 ml), and AIBN (0.06 g) were allowed to polymerize at 70°C for 4 hr. The product (1.2 g) consisted of water-swellaable resin particles having 60–200 mesh size. The resin was then allowed to react with Rose Bengal in dimethylformamide at 60°C and washed as described<sup>12</sup> to yield bright red particles suitable for application as sensitizer in an aqueous environment.

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