Rigid Polar Composite Supports for Use in Solid Phase Synthesis

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Synopsis

A number of particulate polyethylene and polypropylene based matrices have been γ-radiation grafted with poly(acryloylsarcosine methyl ester). The resulting composite materials have physicochemical properties attractive for use in continuous solid phase synthesis. Three macroporous polystyrene resins have also been impregnated with a secondary polyamide network using thermal initiation. All of these retain their rigid spherical structure and the composite properties again make them good candidates for use under pressure. One of these has been used in a preliminary solid phase experiment and two successive amino acid residues coupled with ~100% yield.

INTRODUCTION

Polar polymeric supports based on poly(*N*,*N*-dimethylacrylamide)[1,2] have shown some advantages in solid phase synthesis over conventional polystyrene resin materials.[3] A functional comonomer, acryloyl sarcosine methyl ester (ASME), is added to the polymerization mixture to provide the site for oligomer assembly. Furthermore, when these essentially soft gels are impregnated into the macropores of a secondary rigid matrix, the resulting composite material is also suitable for application under moderate pressures in a continuous flow system.[4] We have recently been involved in a program aimed specifically at developing novel supports with technological as well as synthetic advantages and have already described some new macroreticular supports based on poly(aromatic amide)s.[5] The present report deals with our efforts to produce composite materials in which flexible polar polyamide species are (i) γ-ray radiation grafted onto rigid inert hydrocarbon polymer matrices and (ii) impregnated into the macropores of rigid macroreticular polystyrene resins.

EXPERIMENTAL

Materials

Polymers

Polytetrafluoroethylene (PTFE), ICI "Fluon," grade 301G, particle size, 200–500 μm; low density polyethylene (LDPE), British Drug House, particle size,

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Journal of Applied Polymer Science, Vol. 28, 3137–3144 (1983)
 CCC 0021-8995/83/103137-08$01.80

100–250 μm; high density polyethylene (HDPE), Hoechst "Hostalen GUR" 412, particle size, 50–150 μm; polypropylene from a gas phase reaction, PP–gas, ICI, grade 6082/17, particle size 150–375 μm; polypropylene from a diluent reaction, PP–diluent, ICI, grade HM20, particle size 150–375 μm; copolymer of propylene with 12% ethylene from a gas phase reaction, PP/PE–gas, ICI, grade CM10, particle size, 150–375 μm; copolymer of propylene with 12% ethylene from a diluent reaction, PP/PE–diluent, ICI, grade CM10, particle size, 150–375 μm; polystyrene resins (i) Rohm and Haas, XAD-4, particle size, 200–2000 μm, (ii) Bio-Beads, SM-2, particle size, 200–500 μm, (iii) Polymer Laboratories GPC Resin, PL, particle size ~10 μm. All of these were used as supplied except for XAD-4, which was extracted overnight with acetone and then vaccum dried at 50°C for 24 h.

Monomers

***N,N*-Dimethylacrylamide (DMA).** An ether solution (510 mL) of dimethylamine (128 mL, 25% MeOH solution, 1.94 mol) was stirred at −70°C while a solution of acryloyl chloride (79 mL, 0.95 mol) in ether (500 mL) was added dropwise over a 4-h period. This was then allowed to warm to room temperature overnight. The mixture was filtered and hydroquinone (0.5 g) was added before removal of the solvents on a rotatory evaporator. The resultant reddish oil was distilled *in vacuo* to yield a colorless liquid, which was again inhibited with a little hydroquinone and then stored at 0°C. ^{1}H NMR ($CDCl_3$): δ = 3.0–3.1, d, 6 protons, —$N(CH_3)_2$; δ = 5.5–6.9, m, 3 vinyl protons. Recently, supplies of this monomer were obtained from Polysciences, Ltd.

Acryloyl Sarcosine Methyl Ester (ASME). Methanol (200 mL) was stirred at −10°C and thionyl chloride (16.1 mL, 0.22 mol) was added over a period of 10 min. Sarcosine (15 g, 0.2 mol) was then added in 1- to 2-g portions over a 15-min period. The mixture was allowed to warm to room temperature, stirred for 2 h, and finally refluxed on an oil bath for a further 2 h. Methanol was removed on a rotary evaporator, and anhydrous ethyl acetate (200 mL) was added. The resulting suspension, isolated from the atmosphere by a drying tube, was stirred at room temperature while triethylamine (70 mL, 0.46 mol) was added over a 10-min period. A solution of acryloyl chloride (19 mL, 0.2 mol) in ethyl acetate (100 mL) was then added cautiously over 1.5 hr, and the mixture was stirred overnight at room temperature. After filtering the filtrate was diluted to ~500 mL with ethyl acetate and then washed with citric acid solution (10%, 3 × 30 mL) aqueous sodium bicarbonate (5%, 3 × 30 mL) and water (3 × 30 mL). To the separated ethyl acetate layer was added hydroquinone (0.2 g) and the solution dried over sodium sulfate, before removing the solvent on a rotary evaporator. The yield of the viscous liquid product was 22.5 g (~73%). Samples of ASME were fractionally vacuum-distilled immediately prior to use in grafting experiments. ^{1}H NMR ($CDCl_3$): δ = 3.15, s, 3 protons, $>NCH_3$; δ = 3.75, s, 3 protons, —CO_2CH_3; δ = 4.2s, 2 protons $>NCH_2CO_2$—; δ = 5.5–6.9, m, 3 vinyl protons.

Ethylenebisacrylamide (EBA). Sodium acetate (43.4 g) and ethylenediamine (16.0 mL) were dissolved in chloroform (240 mL) and the mixture was cooled to 0°C. Acryloyl chloride (39.1 mL) was added dropwise over 1 h, and the temperature was not allowed to rise above +10°C. After complete addition the

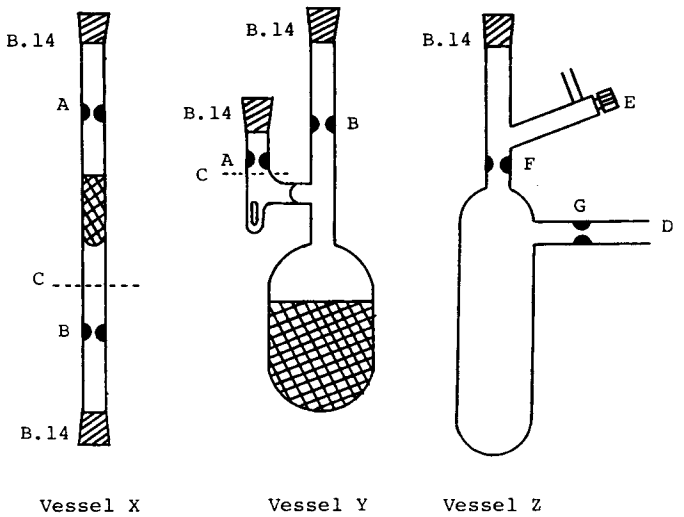

Fig. 1. Vacuum reaction vessels used in γ-radiation grafting experiments (B.14 cones indicate the approximate scale).

mixture was allowed to come to room temperature and hydroquinone (0.4 g) was added before refluxing for 1 h. The mixture was filtered while hot, and, on allowing the filtrate to cool, off-white crystals formed. These were collected and recrystallized from chloroform (~400 mL). Finally after drying over calcium chloride they were stored at 0°C. ^{1}H NMR (CD_3OD): δ = 3.45, s, 4 protons $>NCH_2CH_2N<$; δ = 5.5–6.4, m, 6 vinyl protons.

Methylenebisacrylamide (MBA). This was used as supplied by British Drug House.

γ-Ray Radiation Grafting

In the small test scale experiment, (see Fig. 1) polymer particles (~1 g) were introduced into vessel X, which after evacuation at $\sim 10^{-5}$ mm Hg was sealed off at both constrictions A and B. Each such ampule was then exposed to γ-radiation from a ^{60}Co source located at the Scottish Universities Research and Reactor Centre, National Engineering Laboratory, East Kilbride, Scotland. The dose rate was ~0.25 Mrads/h, and after preliminary experiments an irradiation time of 6 h was adopted as the norm. After this period, ampoules were immersed in liquid nitrogen for transport back to the University laboratories, and were maintained at this temperature until graft polymerization was carried out. With the larger scale samples (~10–12 g) vessel Y replaced X, but the procedure remained essentially unchanged. The irradiation ampoule still at liquid N_2 temperature was broken open at C, a small magnetic breaker inserted, and then the ampoule glass blown onto vessel Z at D. Sufficient ASME monomer (freshly vacuum distilled) to cover the irradiated polymer sample was introduced into Z via the teflon stopcock E. This was closed and the monomer outgassed in the usual way. The vessel was sealed off at F and the break seal on the irradiation vessel was crushed. ASME monomer was then tipped onto the irradiated polymer sample retained at liquid N_2 temperature. Vessel Z was then removed

by sealing off at G. The irradiation ampoule was gently thawed and finally immersed in a water bath at 80°C for 1 h before being left overnight at room temperature. After breaking open the ampule, the grafted sample was removed and extracted with 1,2-dichloroethane in a Soxhlet for 24 h before vacuum drying at ~40°C.

Polystyrene Resin Impregnations

Polystyrene beads (XAD-4, 10 g) were imbibed with a dimethylformamide/water solution (25 mL, 2/1) containing DMA (2.9 g), ASME (0.42 g), EBA (0.32 g), and ammonium persulfate (0.38 g). These were placed in a flanged flask (100 mL) and then rotated for 1 h at 80°C on a modified rotary evaporator device.[6] Some aggregation of particles occurred; but these were readily separated by gentle crushing, and the product was washed with water, tetrahydrofuran, and acetone. Finally it was extracted overnight in a Soxhlet using tetrahydrofuran.

With resin SM-2 the ASME was reduced to 0.21 g, and EBA was replaced with MBA (0.29 g). With the partially cured Polymer Laboratories GPC resin, ASME monomer alone was used (weight ratio 1/1 with resin) and the solvent employed was 1,2-dichloroethane (50 mL) with the initiator azobisisobutyronitrile (AIBN, 0.05 g).

Solvent Imbibitions

These were determined by a simple centrifugation technique, adapted from that described by Pepper et al.[7]

Sarcosine Contents

These were determined at the Medical Research Council Laboratories, University Medical School, Cambridge using a standard digestion and high performance liquid chromatographic procedure as previously reported.[5]

RESULTS AND DISCUSSION

The initial grafting experiments were carried out using PTFE on a 1-g scale in the presence of DMA monomer in aqueous solution (5–50%). Even using substantial amounts of metal salts to inhibit nongrafting solution polymerization,[8] considerable waste of monomer resulted, and the level of grafting achieved was poor. Infrared analysis of irradiated samples showed no evidence of a carbonyl peak, indicative of grafted polyamide. As a result of this, the alternative technique described previously was adopted. Polymers were irradiated in the absence of monomer to produce trapped radicals and then stored at liquid nitrogen temperature prior to introduction of the monomer and subsequent graft polymerization. In addition, the level of sarcosine incorporation was found to be very low, using a comonomer mixture of DMA and ASME, and so in the routine grafting procedure ASME only was employed. It was anticipated that the level of activation of ASME residues for use in solid phase synthesis might be controlled by use of appropriate amounts of ethylene diamine and that the re-

TABLE I
Grafting of Poly(acryloyl Sarcosine Methyl Ester) onto Inert Hydrocarbon Polymers[a]

Polymer	Grafted	Scale (g)	% N microanalysis	Sarcosine content (mmol·g^{-1})	Solvent imbibition (g/g) Water	Toluene
PTFE	no	—	—	—	—	—
	yes	1	0.76	0.30	—	—
	yes	12	~0	0.01	—	—
HDPE	no	—	—	—	0.09	0.01
	yes	1	0.97	0.25	—	—
	yes	12	3.08	2.07	0.25	0.09
LDPE	no	—	—	—	0.09	0.38
	yes	1	1.94	1.02	1.25	0.16
	yes	12	1.74	1.24	0.93	0.20
PP–gas	no	—	—	—	0.04	0.10
	yes	1	0.58	0.23	0.74	0.15
PP–diluent	no	—	—	—	0.02	0.27
	yes	1	2.96	2.08	0.35	0.15
	yes	12	1.14	0.70	0.08	0.21
PP/PE–gas	no	—	—	—	0.05	0.18
	yes	1	0.86	0.59	0.20	0.24
PP/PE–diluent	no	—	—	—	0.07	0.18
	yes	1	3.52	2.63	0.40	0.27
	yes	10	2.42	1.93	0.20	0.28

[a] See under Experimental for reaction conditions.

sidual residues might be effectively deactivated by reaction with dimethylamine.

The results of the various grafting experiments are shown in Table I. With PTFE, despite a satisfactory level of grafting on a 1-g scale, as shown by the nitrogen microanalysis and the sarcosine content, all attempts to achieve similar results on a 12-g scale failed completely, the entry in Table I representing only one of many attempts. As a result of this, no further experiments were carried out with this material. The remaining hydrocarbon polymers also grafted satisfactorily on a 1-g scale. With PP–gas and PP/PE–gas the level achieved was only ~25% of the results with the corresponding materials prepared in the presence of a diluent, i.e., PP–diluent and PP/PE–diluent (these are believed to have larger surface areas), and, consequently, the latter two were selected for scale-up. In both cases, the level of grafting fell, but was, nevertheless, more than adequate giving sarcosine contents of 0.70 and 1.93 mmol·g^{-1}, respectively. LDPE appeared to graft as well on the larger scale as it did on the small test scale, and HDPE gave even higher levels on scaling up. These results eliminate the possibility that the geometry of the larger scale irradiation tube gives rise to poor γ-ray exposure, and suggest that the variations obtained on scale-up are a function of the free radical chemistry of each irradiated polymer.

In all cases there is a rewarding correlation between the level of grafting as measured by elemental microanalysis of nitrogen and the level of sarcosine incorporated (also qualitatively with the infrared carbonyl band as 1745 cm^{-1}). As a basis for solid phase synthesis, a reasonable value for the latter would be

~0.2 mmol g^{-1}, and all of the scaled reactions, except that using PTFE, gave grafted products with more than sufficient sarcosine residues present. In addition, all of the materials retained their particulate form and would be suitable for packing into columns. However, it must be emphasized that even the starting materials were not spherically symmetric, nor were their grafted products.

A very crude estimate of the dimensions of the grafted layers can be made from the elemental nitrogen analyses. These lie typically in the range 0.5–3.0%. Hence 1 g of composite contains ~0.05–0.30 g of grafted polymer. Assuming a polymer density of unity, this corresponds to a volume of ~0.05–0.3 cm^3. Thus, if the surface area of the original polymer is x $m^2 \cdot g^{-1}$ and uniform coverage is achieved, the thickness of the grafted layers is the range $(1/x) \times (5 \times 10^{-6}$–$3 \times 10^{-5})$ cm. Hence for $x \sim 100$ $m^2 \cdot g^{-1}$, thicknesses of 0.05–0.30 μ result, and for $x \sim 1$ $m^2 \cdot g^{-1}$ thicknesses are 5–30 μ. Unfortunately, details of surface areas are not available, but certainly PP–diluent and PP/PE–diluent are likely to be of high surface area whereas LDPE, PP–gas, and PP/PE–gas are likely to be much lower.

The favorable change in the polarity of the grafted materials is evidenced by the solvent imbibition behavior. Typically, the starting hydrocarbon polymers take up ~0.02–0.09 g water/g each dry matrix. On grafting ASME polymer, this rises to ~0.1–1.25 g and in general for a given matrix there is a rough correlation of water imbibition with the level of grafting. In contrast, the uptake of toluene is less strongly influenced in some instances, rising a little while in others falling somewhat. Polar solvents like acetonitrile and 1,2-dichloroethane were examined in a few cases only, but generally the grafted species responded to these at least as well as they did to water. Thus it would appear that polyethylene- and polypropylene-based materials can be suitably grafted to yield composite species with features attractive for application as "solid phase" supports.

Impregnated Polystyrene Resins

Macroporous polystyrene resins are attractive starting materials for the production of composite support species because of their spherical rigid particulate form. Providing this can be retained during the introduction of a secondary polar matrix into the macropores, then the final product should be admirably suitable for packing into columns and use in a continuous automated solid phase process.

Our first attempts employed a porous resin from a polymerization which had been prematurely stopped. The initial divinylbenzene content was high, and the residual double-bond content of the resin was estimated (by ICl/thiosulfate back-titration) as ~1.0 mmol·g^{-1}. In this approach linear poly(acryoylsarcosine methyl ester) was to be formed within the resin macropores with simultaneous grafting via the pendant styryl functions. The first entry in Table II confirms that substantial incorporation of linear polymer did occur, and, since the resin was exhaustively extracted, it would seem that this was substantially chemically grafted. The initial resin swelled significantly in toluene because the prematurely terminated reaction had restricted the level of crosslinking. The latter appeared to be effectively completed during the grafting of ASME polymer, and the toluene imbibition dropped remarkably. At the same time, the improved polar character of the composite was shown by the substantial increase in water

TABLE II
Polystyrene Resins Impregnated with Polyamide Secondary Networks[a]

Resin	Size (μm)	Impregnated	Wt ratio Ps/DMA/ ASME	% Micro-analysis	Sarcosine content (mmol·g^{-1})	Solvent imbibition (g/g)	
						Water	Toluene
PL	~10	no	—	—	—	0.28	1.89
		yes	1/0/1	4.89	3.48	0.74	0.16
XAD-4	200–2000	no	—	—	—	0.06	1.24
		yes	10/2.9/0.42	3.82	~0.20[b]	2.30	0.87
SM-2	200–500	no	—	—	—	0.07	0.87
		yes	10/2.5/0.21	3.71	0.06	1.79	0.69

[a] See under Experimental for reaction conditions.
[b] Some contamination in amino acid analysis.

imbibition. The spherical nature of the resin was maintained, but on contact with solvents like dichloromethane the particles became swollen and relatively soft and thus do not appear to be good candidates for use under pressure.

The idea of using partially polymerized polystyrene resins for impregnation was therefore abandoned in favor of fully polymerized commercially available materials. In addition, in the likely absence of substantial pendant vinyl groups, it was decided to lightly crosslink the secondary matrix in order to retain it effectively within the primary resin macropores. The secondary network was chosen to have a similar composition to that of the polyamide resins, as reported by Sheppard and his co-workers,[1,2] and were essentially lightly crosslinked DMA–ASME copolymers. The first fully cured polystyrene resin examined was one of small particle size, ~10 μm, used as a column packing for gel permeation chromatography. Each attempt to introduce a secondary crosslinked network into this while retaining the individual identity of each resin bead met with aggregation problems. Even when the secondary polymerizing solution was limited in volume so that it just wet the primary resin beads, during polymerization soft gel exuded from each particle eventually causing aggregation. All adjustments to the rotating flask to eliminate this met with failure.

The use of larger particle size resins, however, was much more successful presumably because of the much higher internal volume-to-surface area ratio. By keeping the polymerization flask in constant rotation, the individuality of polymer resin beads was maintained during secondary network formation. Both XAD-4 and Bio-Beads SM-2 (Table II) proved to be very suitable host matrices, with both final products maintaining their rigidity and spherical form. Elemental nitrogen microanalysis confirmed the incorporation of the secondary polyamide network, and the presence of the ASME comonomer residue was shown by positive sarcosine analyses. The amino acid content correlated qualitatively with the comonomer mixtures employed.

The toluene uptake of both composite materials was reduced relative to that of each primary matrix (Table II) but simultaneously the presence of the secondary polyamide network caused a substantial rise in the water compatibility. Thus, once again, the composite products display enhanced polar character attractive for application in the solid phase method. The material based on SM-2 looked particularly attractive and 1 g of this (~2.8 mL) took up ~2 mL of di-

methylformamide before appearing wet, and its volume did not change significantly. The measured sarcosine content of this was somewhat lower than predicted by the comonomer feed employed, but in a preliminary solid phase experiment, carried out at the MRC Laboratories, Cambridge, U.K. ~0.025 mmol/g of these residues was activated and two successive amino acid residues were coupled with ~100% yield.

The various composite materials described all seem to possess physical and chemical characteristics suitable for solid phase supports and for application in continuous flow oligomer synthesis, and are worthy of further examination. The latter impregnates, in particular, are easy to prepare and appear to be the most optimistic candidates. Although the preliminary activation and coupling experiments using the SM-2-based species look encouraging, further work is required to optimize the structure of the primary network employed. Judicious choice of pore size and pore size distribution, crosslink ratio, and overall morphology looks very likely to produce composite materials with optimum characteristics for technical application.

We are grateful for the receipt of a research fellowship for S.B.K. from the Medical Research Council and a CASE studentship for J. G. H. from the Science and Engineering Research Council in collaboration with Polymer Laboratories, Ltd., Church Stretton, U.K. We also acknowledge warmly the help of Dr. R. C. Sheppard and his colleagues, MRC Laboratories, Cambridge, U.K., and Mr. J. Izatt, Scottish Universities Research and Reactor Centre, National Engineering Laboratory, East Kilbride, U.K.

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Received February 1, 1983
Accepted May 13, 1983