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On the Development of New Poly(styrene−oxyethylene) Graft Copolymer Resin Supports for Solid-Phase Organic Synthesis

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With the aim of creating new, improved solid supports for organic synthesis, a series of poly(styrene−oxyethylene) graft copolymers **6a**−**d** was synthesized by anionic polymerization of ethylene oxide from a polystyrene-supported 1,3-diol **5b**. Graft lengths were varied from 29 to 58 repeat units (67−82 wt % polyoxyethylene). The so-formed alcohols **6a**−**d** were further transformed into chlorides **7a**−**d**, amines **8a**−**d**, and two commonly used linkers, Wang **9a**−**d** and HMPB **10a**−**d**. These functional group interconversions were efficiently monitored using gel-phase ^{13}C NMR, and the solid-state properties of all copolymers were characterized by differential scanning calorimetry. Thermal properties of these materials were found to be dominated by the polyoxyethylene composition. A correlation between the melting point associated with the graft lengths and the physical properties of the resins was observed. The optimum graft copolymer composition, determined by balancing the degree of functional group loading with resin crystallinity and swelling, was found to be in the 0.4−0.5 mmol g^{-1} range.

Introduction

Solid-phase organic synthesis (SPOS) has historically been the primary method for production of polypeptides, oligonucleotides, and other modified oligomers based on these structures. The extension of SPOS and automation to the broader arena of small, drug-like organic molecules has more recently become a major focus of the pharmaceutical and specialty chemical industries.[2] The potential for rapid and cost-effective identification and optimization of drug candidates, catalysts, and other materials through the use of combinatorial methods and automation is evident.

The most commonly used resin supports for SPOS include spherical beads of lightly cross-linked gel-type polystyrene (1−2% divinylbenzene) and poly(styrene−oxyethylene) graft copolymers which are functionalized to allow attachment of linkers and substrate molecules. Each of these materials has advantages and disadvantages depending on the particular application.[3] Commercially available supports and linkers were originally developed primarily for biopolymer synthesis and may not be ideal for the broader range of conditions required for small molecule synthesis. The continued adaptation of chemistry to the solid phase requires new supports and linkers which will tolerate the full spectrum of reaction conditions and reagents developed for chemistry in solution over the last century.

Lightly cross-linked gel-type polystyrene (GPS) has been most widely used due to its common availability and inexpensive cost. GPS beads which are functionalized with chloromethyl-, aminomethyl-, and a variety of linkers are commercially available from a variety of sources. A prominent characteristic of GPS beads is their ability to absorb large relative volumes of certain organic solvents (swelling). This swelling causes a phase change of the bead from a solid to a solvent-swollen gel, and therefore, the reactive sites are accessed by diffusion of reactants through a solvent-swollen gel network. In solvents which swell the polymer well, the gel network consists of mostly solvent with only a small fraction of the total mass being polymer backbone. This allows relatively rapid diffusional access of reagents to reactive sites within the swollen bead. In solvents which do not swell the polymer, the cross-linked network does not expand and the diffusion of reagents into the interior of the bead is impeded.[4] GPS has good swelling characteristics in solvents of low to medium polarity ranging from aliphatic hydrocarbons to dichloromethane. Polar, protic solvents, such as alcohols and water, do not swell GPS resins, and accessibility to all reaction sites may be compromised. Hence, GPS supports are most suitable for chemistry performed in solvents of low to medium polarity.

Poly(styrene−oxyethylene) graft copolymers (PS−PEG), first reported by Bayer and Rapp,[5] are another class of widely used supports for organic synthesis.[6,7] PS−PEG beads display relatively uniform swelling in a variety of solvents from medium to high polarity ranging from toluene to water. The polymers are produced by grafting ethylene oxide from the polystyrene backbone creating long flexible chains that terminate with a reactive site spatially separated from the more rigid polystyrene backbone. Accordingly, it has been postulated that molecules bonded to the ends of the PEG chains are in a "solution-like" environment relative to the sites near the rigid polystyrene backbone present in GPS. This environment can favorably impact reaction kinetics by allowing rapid diffusion of reagents through the swollen gel to sites that are removed from the backbone and more equivalent. For example, Rapp et al. have demonstrated that rate constants for the coupling of the active ester Boc-Gly-ONp to PS−PEG beads were of the same order of magnitude as in those solution.[8] This high degree of flexibility of the

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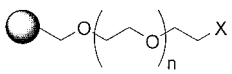
PEG chains was further demonstrated by successful application of gel-phase ^{13}C NMR to gain structural information on compounds while attached to the beads.[9] When swollen, good chain mobility results in high T_1 values and narrow line widths comparable to those observed for small molecules in solution. Large biomolecules, such as the 23.5 kDa enzyme trypsin, have been shown to penetrate PS−PEG beads, providing further evidence of the mobile and biocompatible environment of these materials.[10] Some disadvantages of PS−PEG supports[11,12] include (1) relatively low functional group loading compared with GPS; (2) the potential for the PEG chains to complex Lewis acids; (3) the potential instability of PEG; (4) the presence of linear PEG impurities found in the small molecule products after cleavage from the resin; (5) the tendency for resins to become sticky and difficult to handle as the syntheses progress.

To address some of the shortcomings of both GPS and PS−PEG, we have initiated a program to discover and develop new polymeric materials that have improved performance characteristics for more general applications.[13] We anticipate that this will permit more expedient adaptation of the rich heritage of solution chemistry to the solid-phase arena. The new PS−PEG resins described in this paper have been available commercially since early 1996 and have been successfully utilized in the preparation of substituted imidazoles,[14] *N*-alkyl sulfonamides,[15]acylamines,[16] 4-arylazetidin-2-ones,[17] and benzofurans.[18] Herein we report a full account of the development of ArgoGel, a new family of PS−PEG graft copolymers with high loading, good acid stability, and low linear PEG impurities. The effects of PEG graft length and end-group substitution on the solid-state characteristics of the graft copolymers are also presented. The high yield conversion of graft copolymers to supports containing two commonly used linkers and the rationale used to define the optimum loading range are also described.

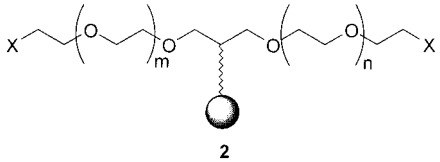
Results and Discussion

Our approach to novel PS−PEG graft copolymers centered around improving the acid stability of the polystyrene-graft linkage and increasing the functional group loading per unit weight of resin (mmol functional group/g resin). The existing commercial product, TentaGel **(1)**, is reported[8,19] to have a



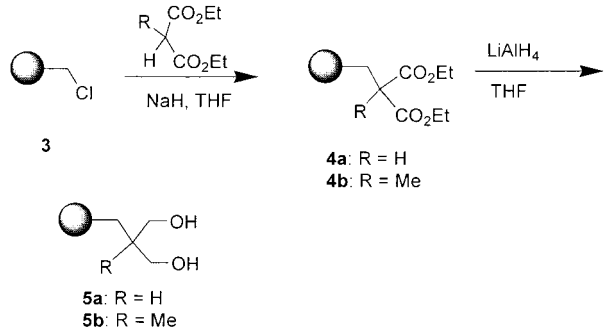
1 TentaGel

benzylic ether PS-graft linkage, which is well-known to be unstable to strongly acidic reagents, and average graft lengths of 68 units (3000 Da) to afford a PEG composition of ∼65 wt %. We envisioned improved stability could be obtained by replacing the benzylic ether linkage with an aliphatic linkage and increased loading through bifurcation prior to ethylene oxide grafting as indicated in structure **2**. In effect,



2

Scheme 1

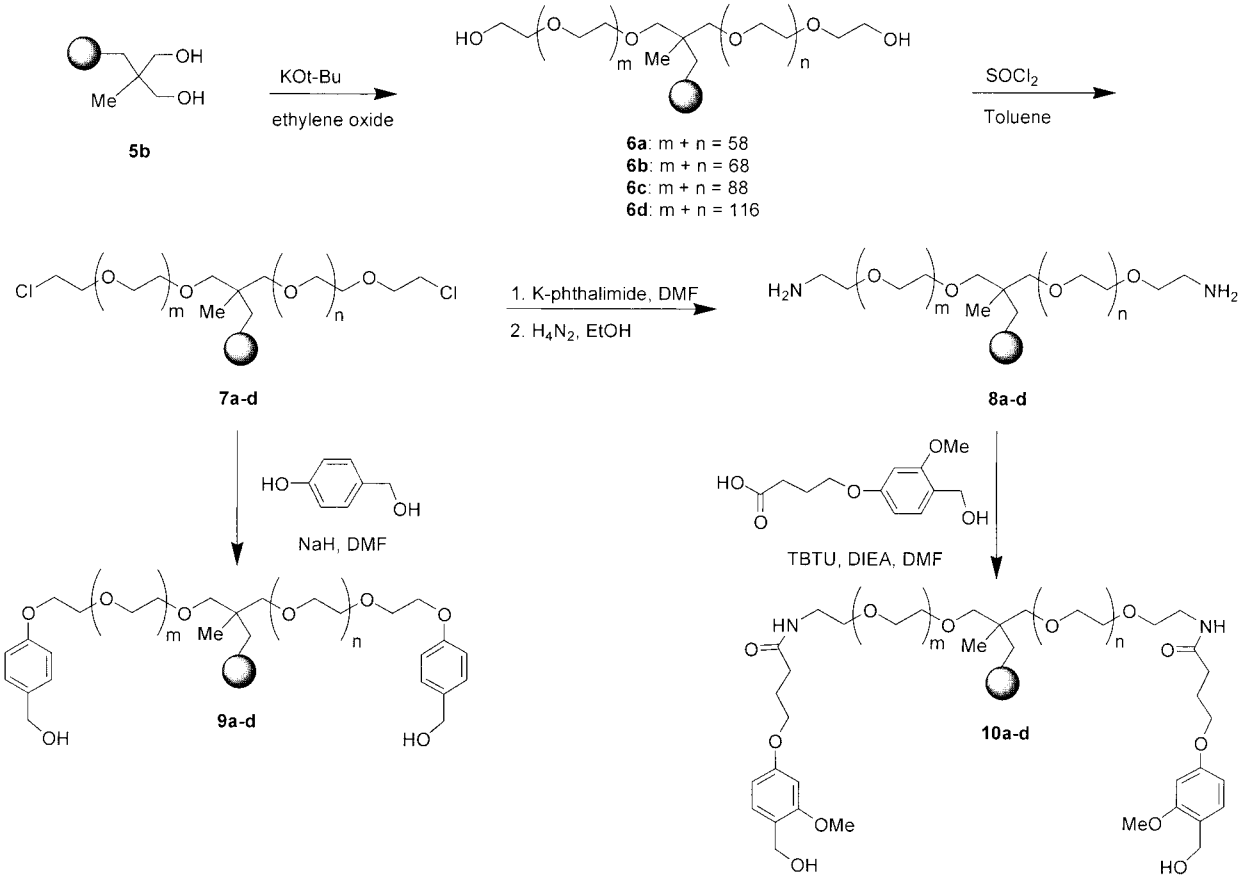


ethylene oxide grafting to a bifurcated intermediate affords a bifunctional PEG chain that is attached to the PS backbone at its center. This approach allows the preparation of new PS−PEG graft copolymers with twice the loading capacity relative to conventional monofunctional PS−PEG graft copolymers, while maintaining equivalent PEG molecular weights and thus levels of crystallinity (vide infra).

To realize this, two 1,3-diol functionalized polystyrene intermediates **5a**−**b** were prepared as shown in Scheme 1. Treatment of chloromethylpolystyrene **(3)** (1 mmol Cl g^{-1}) with the sodium derivative of diethylmalonate[20] or methyl diethylmalonate (60 °C, 21 h) afforded the diester intermediates **4a**−**b** as judged by IR spectroscopy and elemental analysis. Reactions typically proceeded to ∼85−90% conversion as determined by elemental analysis and/or Volhard[21] titration for residual chlorine. Subsequent treatment with lithium aluminum hydride (60 °C, 4 h) gave complete ester reduction as judged by IR spectroscopy. The 1,3-diols **5a**−**b** were isolated following a rigorous purification protocol to remove residual aluminum salts. The unreacted chlorine atoms from the first step were found to be reduced under these conditions. The total hydroxyl loading for **5a**−**b** was determined by coupling with Fmoc-glycine followed by release and quantitative analysis of the dibenzofulvene chromophore by UV spectroscopy.[22] Good agreement with theory was observed for the Me-substituted diol **5b** (1.73 mmol −OH/g resin) while low values were obtained for the H-substituted diol **5a** (0.93 mmol/g). A plausible explanation is that the acidic hydrogen present in **4a** was abstracted under the basic displacement reaction conditions leading to dialkylation (cross-linking) by adjacent chloromethyl sites. For this reason, the methyl-substituted derivative **5b** was ultimately selected for further development.

Graft copolymers were prepared by anionic polymerization of ethylene oxide initiated by the alkoxide formed from diol **5b** as shown in Scheme 2. It is well documented that the rate for anionic polymerization of ethylene oxide is strongly dependent on ion-pairing effects, which in turn is dependent on counterion and solvent.[23] Detailed studies by Price and Carmelite concluded that maximum rates were achieved with potassium counterion and DMSO solvent.[22f] Cyclic ethers, such as tetrahydrofuran (THF) and dioxane, are effective solvents when both alcohol and alkoxide forms of the propagating chain are present because ion-pairing is minimized by hydrogen bonding.[24] Minimal ion-pairing leads to facile proton exchange, and equilibration between initiation

Scheme 2



sites and gives, more or less, equivalent chain growth from every initiator site present.

We chose to use potassium *tert*-butoxide as the base and THF as the solvent because these conditions appeared to offer several advantages. In theory, only partial deprotonation of **5b** was required prior to the addition of ethylene oxide because the rapid alkoxide−alcohol equilibrium between propagating chain ends would ensure uniform grafting. A further advantage of this system was that the presence of adventitious water in the system would not terminate grafting prematurely, but rather enter into the polymerization and result in the production of linear PEG. A disadvantage of this method is the concomitant formation of linear PEG through initiation by *tert*-butoxide.

Ethoxylation of **5b** was accomplished by deprotonation with excess potassium *tert*-butoxide (1.1−1.5 equiv, 25 °C, 1 h) followed by addition of a prescribed amount of ethylene oxide (EO) solution in THF (8.6 M, 25 °C, 43 h). This led to facile polymerization as determined by weight gain of the isolated polymers, FTIR, and ^{13}C NMR spectroscopy (Chart 1, spectrum A). The graft copolymers were isolated following treatment with 1 M HCl in MeOH (50:50) to neutralize the mixture and destroy any unreacted EO by conversion to chloroethanol. Because the presence of residual linear PEG impurities was a major concern from the outset, a protocol for measuring the levels by extraction with TFA/water (95:5) was developed.[25] The crude materials were found to be contaminated by up to 25 wt % of linear PEG, formed by the solution-phase polymerization initiated by *t*-BuO^- or adventitious water (HO^-) present in the reaction mixture. Complete removal of this byproduct proved to be nontrivial. Extraction with various solvents known to dissolve linear PEG was unsuccessful even with prolonged times, elevated temperatures, and multiple cycles. Ultimately, the TFA protocol was applied to the preparative purification of entire batches in order to obtain material of required purity for further studies.

A series of graft copolymers, **6a**−**d**, with varying PEG chain lengths, was synthesized by adjusting the EO/initiator ratio to determine if graft molecular weight could be well-controlled by stoichiometry and to evaluate the effect of graft length on physical properties of the resins. The resulting copolymers were predominantly PEG in composition (67−82 wt %) which resulted in a proportionate reduction in hydroxyl loading (measured in mmol OH/g resin). The polymerizations were conducted by varying the monomer/initiator ratio from 27 to 57 as presented in Table 1. The results show that the graft lengths for copolymers **6a**−**d**, as determined by weight gain, agreed well with the theoretical values calculated from the charged monomer/initiator ratios, indicating that the polymerization reactions were equilibrium controlled. Theoretical hydroxyl loading was determined gravimetrically,[26] and the actual loading was measured by coupling with Fmoc-Gly followed by release and quantitation of the fluorenyl chromophore by UV spectroscopy.[21] The measured hydroxyl loading ranged from 0.32 to 0.50 as presented in Table 1. Good agreement between the calculated and measured loading was observed.

With the series of hydroxyl-substituted copolymers in hand, attention was focused on performing end-group

Chart 1 ^{13}C NMR Spectra Gathered from Copolymer Series b at 300 MHz in Benzene-d_6

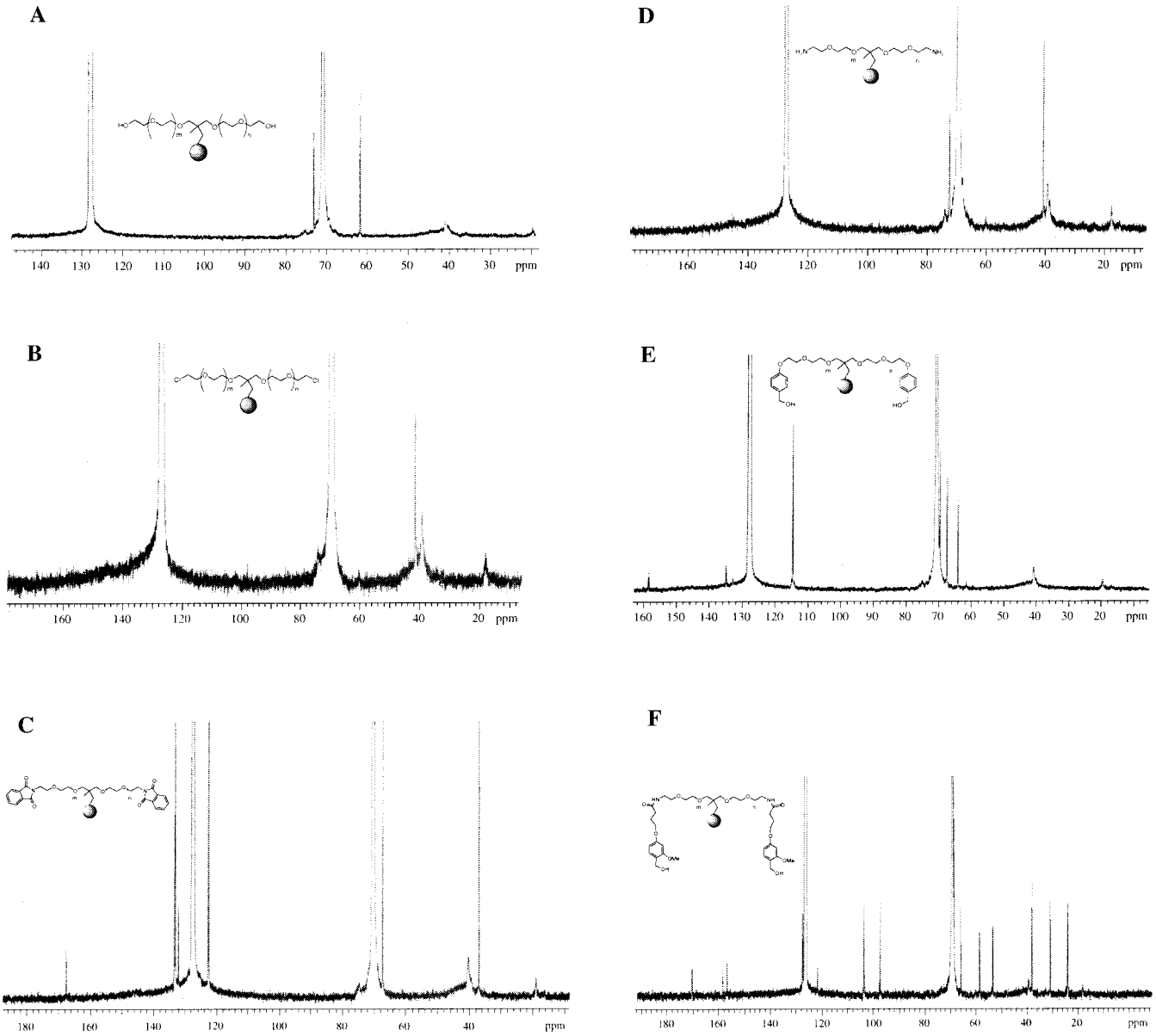


Table 1. Properties of Copolymers **6d**−**d**

polymer	EO/initiator[a]	graft length[b,c]	loading (mmol g^{-1}) calcd[c]	loading (mmol g^{-1}) measd[d]
6a	27	29	0.55	0.50
6b	36	34	0.46	0.47
6c	43	44	0.38	0.40
6d	57	58	0.30	0.32

[a] Moles of EO/(moles of polymer-OH + moles of *t*-BuOK). [b] Average number of ethylene glycol units per graft arm. [c] Based on weight gain. [d] Determined by quantitative Fmoc protocol.

modification and the analysis of the corresponding effect on physical properties. The Gabriel amine synthesis has been reported to be effective on monofunctional PS−PEG copolymers[27] and was applied to the present series as shown in Scheme 2. Treatment of alcohols **6a**−**d** with thionyl chloride in toluene (75 °C, 16 h) followed by washing, isolation, and drying gave quantitative conversion to the chlorides **7a**−**d** as determined by ^{13}C NMR (Chart 1, spectrum B) and elemental chlorine analysis. Halogenation with thionyl chloride was found to be more efficient and cost-effective than bromination with the toxic and expensive CBr_4/PPh_3 system as previously described.[26] Subsequent treatment with potassium phthalimide in DMF (70 °C, 22 h) gave phthalimide substitution as determined by ^{13}C NMR (Chart 1, spectrum C) and IR spectroscopy. The DMF was exchanged for EtOH, and the Ing-Manski procedure[28] was applied to effect hydrazineolysis affording the primary amines **8a**−**d** in a single-pot operation as determined by IR and ^{13}C NMR (Chart 1, spectrum D). Amine loading was determined by picrate salt formation followed by release and quantitative analysis via UV spectroscopy[29] or by elemental analysis for nitrogen. Good correlation between initial hydroxyl loading, intermediate chloride, and final amine loading indicated that all reactions were high-yielding and that the end-group functionality could be efficiently manipulated (Table 2). Alcohols **6a**−**d** and amines **8a**−**d** displayed excellent chemical stability to the strong acid cleavage conditions often employed in SPOS (TFA cleav-

Table 2. Functional Group Loading (mmol g^{-1}) of End-Group Modified Polymers

starting alcohol	amine loading **8a−d**		Wang loading **9a−d**		HMBP loading **10a−d**	
	calcd[a]	found[b]	calcd[a]	found[c]	calcd[d]	found[c]
6a	0.50	0.50	0.47	0.47	0.43	0.41
6b	0.47	0.47	0.44	0.39	0.41	0.33
6c	0.40	0.38	0.38	0.39	0.35	0.30
6d	0.32	0.33	0.30	0.27	0.29	0.26

[a] Based on the measured loading of alcohols **6a−d**. [b] Measured by elemental nitrogen analysis. [c] Measured by quantitative Fmoc protocol. [d] Based on the measured loading of amines **8a−d**.

Table 3. Swelling Volume (mL/g) for Polystyrene and Various PS−PEG Graft Copolymers at 25 °C (mL/g)

solvent	toluene	THF	DCM	DMF	MeOH	water
PS−NH_2[a]		8.0	8.9	8.0	2.8	2.1
TentaGel-OH[b]		4.5	5.8	4.5	3.8	3.8
ArgoGel-OH[c]	5.2	5.8	7.5	6.0	4.7	3.9
TentaGel-NH_2[b]		3.9	5.5	4.0	3.0	3.0
ArgoGel-NH_2[c]	6.2	6.4	8.6	5.0	4.9	4.0

[a] Obtained from Bachem. [b] Obtained from Rapp Polymere. [c] Obtained from Argonaut Technologies.

age). The level of linear PEG (produced as a byproduct during grafting) was measured by extraction with 95:5 TFA/water for 4 h followed by concentration of the filtrate. Linear PEG levels of <0.5 wt % were routinely obtained. The resins also displayed good swelling in a panel of solvents ranging from toluene to water as shown in Table 3. Swelling values exceeded those observed for the corresponding TentaGel resins in all cases.

End-group modification was also evaluated by preparation of copolymers containing the 4-hydroxmethylphenyl ether (Wang)[30] and the related analogue (HMPB)[31] **10a−d** linker groups. Treatment of the chlorides **7a−d** with the sodium salt of 4-hydroxymethylphenol in DMF (80 °C, 2 h) afforded the desired 4-hydroxmethylphenyl ethers **9a−d** in quantitative yield as determined by ^{13}C NMR (Chart 1, spectrum E) and hydroxyl loading measurements (Table 2). Likewise the HMPB linker was coupled onto the amines **8a−d** using standard peptide coupling techniques (TBTU, DIEA, DMF) affording alcohols **10a−d**. The reaction was complete in 75 min as determined by the ninhydrin[28] colorimetric test and was complete as determined by ^{13}C NMR (Chart 1, spectrum F) and hydroxyl loading measurements (Table 2).

Copolymer Analysis. In addition to the standard methods of FTIR[32] and elemental microanalysis[33], PS−PEG graft copolymers are amenable to qualitative analysis using gel-phase ^{13}C NMR. The relatively mobile environment created by grafting PEG chains on to the more rigid PS backbone allowed the easy application of gel-phase ^{13}C NMR in a standard spectrometer.[8,34] The advent of the magic angle spinning technology has also allowed high-quality ^1H NMR data to be collected; however, specialized equipment is required.[35] The present work routinely employed ^{13}C NMR to efficiently monitor all end-group transformations after the grafting reaction. Chart 1 shows typical spectra gathered on a 300 MHz instrument (4096 scans) in benzene-d_6. All spectra contain signals in the 127−128 ppm range from the solvent, a sharp resonance at 70.5 ppm due to the nonterminal oxyethylene carbons of the PEG chains, and broad signals at 40.5 and 19.0 ppm due to the neopentyl graft-to-PS spacer methylene carbons and the quaternary methyl group, respectively. Signals arising from the aromatic and alkyl carbons of the PS backbone were broadened to the point where they were lost in the noise and so did not interfere with spectral interpretation. The diagnostic resonances were those originating from the terminal oxyethylene unit and any appended linker or molecule. Spectrum **A**, derived from the unsubstituted alcohol **6**, showed the α and β carbons of the terminal hydroxyl shifted to 61 and 72 ppm, respectively. Upon conversion of the alcohol **6** to the chloride **7**, the α and β carbons were shifted upfield to 42 and 70 ppm, respectively (spectrum B). Corresponding shifts were observed upon conversion to the amine **8** (spectrum D). This illustrated that resonances arising from the terminal PEG unit could be used to monitor fundamental functional group conversions on the base resins in the absence of linkers or substrate molecules. The spectrum of the intermediate phthalimide is represented in spectrum C. In this case, signals from the additional carbon atoms of the phthalimide moiety were clearly recognized at 168, 133, 132, and 127 ppm. There was also the usual upfield shift of the α and β carbons from the terminal oxyethylene unit to 67 and 37 ppm, respectively. Spectra E and F showed signals from the additional carbon atoms of the linker modified materials. These spectra were very similar to those obtained from the non resin bound counterparts in solution.

Table 4. Graft Copolymer Thermal Characterization

series	graft M_n	**6** $T_g/T_m/\Delta H_f$	**8** $T_g/T_m/\Delta H_f$	**9** $T_g/T_m/\Delta H_f$	**10** $T_g/T_m/\Delta H_f$
a	2500	−/42/76	−/43/70	−50/21,34/44	−49/−/−
b	3200	−/49/101	−/44/92	−/32/57	−48/24,32/44
c	3800	−/51/111	−/49/109	−/43/64	−45/40/69
d	5000	−/53/123	−/52/117	−/47/94	−/43/80

Important features of any resin used for SPOS are the physical properties in the dry state. Conventional GPS beads are free-flowing powders because polystyrene-*co*-divinylbenzene is a glassy polymer with a glass transition temperature (T_g) = 110 °C. In contrast, the physical properties of PS−PEG graft copolymers are highly dependent on the percentage of PEG and the length of the grafts. Differential scanning calorimetry (DSC) was used for determination of the thermal transitions of this series of eight copolymers (Table 4). The alcohol series **6a−d** were crystalline, free-flowing powders with melting point transition temperatures (T_m's) ranging from 42 to 53 °C which increased with molecular weight. These values were comparable to those reported for unbound linear PEG's of corresponding length. No T_g's associated with glassy PEG or polystyrene domains (T_g = 110 °C) were observed. Hence, for **6a−d** the crystalline PEG dominated the solid-state properties of the copolymer. This trend was consistent for copolymers with PEG compositions in the range of 70−82 wt %.

The best correlation of melting point and molecular weight between the copolymers and unbound linear PEG was obtained if the two arms of the grafted diol were considered to be a single PEG chain with a defect at its center (point of attachment to PS backbone). This defect accounts for a slight depression in T_m relative to linear PEG of comparable molecular weight (∼5 °C) due to the substituted 1,3-diol linkage to the polystyrene-*co*-divinylbenzene backbone. The

thermal behavior of the amine series **8a**−**d** was completely analogous. Modification of the PEG chain ends with the Wang **9a**−**d** or the HMPB **10a**−**b** linkers led to a substantial decrease in melting point. In the case of **9a** and **10a**−**c**, the appearance of a glass transition associated with glassy PEG domains was observed. This is consistent with a disruption of crystallinity by the covalently bonded small molecules. The effect is greatest for the higher loading, shorter graft length resins and is exacerbated by bulky end groups. For example, in the HMPB series **10a**−**d**, only **10d** was a powder; increased resin clumping and stickiness was observed as graft length decreased. Resins with T_m's and/or T_g's at or near room temperature were not free-flowing powders. Unbound linear PEG's of comparable molecular weight and phase behavior are waxy solids, again demonstrating the good correlation between physical characteristics of these graft copolymers and unbound linear PEG's of similar molecular weight. It is important to note that this bead clumping phenomenon is related only to the solid state, and that once solvent-swollen all the samples dispersed well and were indistinguishable. These results showed that optimum loading for these resins is in the range of 0.4−0.5 mmol/g when free-flowing dry beads are required.

Conclusion

A series of novel poly(styrene−oxyethylene) graft copolymers has been synthesized, characterized, and subjected to end-group modification. Graft copolymerization of ethylene oxide onto a bifurcated 1,3-diol modified polystyrene backbone afforded PS−PEG resin beads with high loading and good acid stability. Hydroxyl, chloro, amino, and two linker-modified materials were obtained by high-yielding transformation of end-group functionality. Gel-phase ^{13}C NMR was routinely used to monitor end-group reactions of the graft copolymers. DSC was used to evaluate the thermal properties of the resins. A correlation between the melting point associated with the PEG graft lengths and the physical properties of the resins was observed. The optimum graft copolymer composition, determined by balancing the degree of functional group loading with resin crystallinity, was found to be 0.4−0.5 mmol g^{-1}. This loading range has since been adopted for ArgoGel base resin products.

Experimental Section

Elemental analyses were obtained form Galbraith Laboratories, Knoxville, TN. Gel-phase ^{13}C NMR were taken on a Varian 300 spectrometer in benzene-d_6 (4000−28000 scans) and are reported in ppm. Infrared spectra were recorded on a Nicholet Impact 410 spectrometer equipped with an InspectIR microscope on a random sampling of single beads and are reported in cm^{-1}. Differential scanning calorimetry experiments were conducted by the EPIC Applied Polymer Research Laboratory, University of Akron, Akron, Ohio. Tetrahydrofuran used in the ethoxylation reactions was distilled from sodium benzophenone ketyl just prior to use. Potassium *tert*-butoxide (20 wt % in THF) was purchased from Callery Chemical, PA. Merrifield resin (1−2% cross-linked, 1 mmol Cl g^{-1}, 200−400 mesh) was obtained from Bachem. DMF was Merck Omnisolv grade obtained from EM Science). Solvents used for UV measurements were as follows: dichloromethane, Fisher HPLC grade/UV cutoff 235 nm; methanol, Fisher HPLC grade/UV cutoff 202 nm; ethanol, Spectrum Chemicals 190 proof. Loading values are reported in mmol g^{-1}.

Prior to isolation all resins were washed sequentially by using a vacuum reservoir connected to a sintered glass gas dispersion tube via Teflon tubing. The gas dispersion tube was submersed to the lowest point in the flask during the vacuum-assisted solvent removal. In this way, resin transfer to and from filter funnels was minimized and washing could be conducted at elevated temperatures. This apparatus is referred to as a "vacuum filtration tube".

Poly(styrene-*co*-divinylbenzene) Diethylester (4b). A 3 L, three-necked, round-bottom flask was fitted with a mechanical stirrer, reflux condenser, thermocouple, and addition funnel. The assembled apparatus was dried by heating to 100 °C under a N_2 sweep followed by cooling to 25 °C. The flask was charged with Merrifield resin (60.0 g, 1 equiv) followed by THF (900 mL). A second 500 mL pear-shaped flask containing a magnetic stirring bar was oven-dried, fitted with a thermocouple, vacuum-purged with N_2, and charged with sodium hydride (7.20 g, 3.0 equiv, 60% in oil) followed by THF (300 mL). The addition funnel was charged with methyl diethylmalonate (32.40 g, 3.1 equiv). The flask was placed in a 15 °C water bath, and the malonate was added dropwise over 20 min during which time the temperature was allowed to rise to 30 °C. *Caution: Hydrogen gas evolution!* After the mixture was stirred for an additional 10 min, the resulting pale-yellow solution was transferred to the addition funnel fitted to the other flask. The solution of the sodium salt of the malonate was added dropwise to the resin over a 10 min period with stirring at 45 rpm. The suspension was then heated to 60 °C and held for 21 h with agitation. The flask was cooled to 40 °C and quenched with glacial acetic acid (10.3 mL, 3.0 equiv). The solvent was removed by vacuum filtration tube, and the resin was washed sequentially with 600 mL portions of the following solvents while maintaining a temperature of 40 °C for 10 min during each cycle: 1 × THF, 1 × water/MeOH (50:50), 2 × MeOH. The product was isolated by filtration in a sintered glass funnel and vacuum-dried to constant weight (65 °C, 27 inHg, air bleed). The isolated yield was 67.91 g (99.5%) as white, free-flowing beads. IR: 1730 (C═O), 1225 (C−O).

Poly(styrene-*co*-divinylbenzene) Diol (5b). A 3 L, three-necked, round-bottom flask was fitted with a mechanical stirrer, reflux condenser, thermocouple, and addition funnel. The assembled apparatus was dried by heating to 100 °C under a N_2 sweep followed by cooling to 25 °C. The flask was charged with diester **4b** (67.9 g, 1 equiv) followed by THF (1200 mL). The addition funnel was charged with $LiAlH_4$ (126 mL, 2.1 equiv, 1 min in THF). Stirring at 45 rpm was initiated, and the $LiAlH_4$ solution was added dropwise at such a rate that the internal temperature remained below 30 °C. The temperature was raised to 60 °C and held for 4 h. The suspension was cooled to 50 °C and quenched with a solution of *t*-BuOH (60 mL, 10.5 equiv) in THF (540 mL). The solvent was removed by vacuum filtration tube,

and the resin was washed sequentially with 600 mL portions and agitation at 40 °C for 10 min during each cycle: 1 × THF, 1 × 2 min HCl/THF (25:75), 1 × water/THF (50:50), 1 × water/THF (50:50), 1 × water/THF (75:25), 2 × MeOH. The product was isolated by filtration in a sintered glass funnel and vacuum-dried to constant weight (65 °C, 27 inHg, air bleed) affording 62.23 g (99.7%) as white, free-flowing beads. Hydroxyl loading: 1.7 as determined by Fmoc-Gly coupling. IR: 3150−3700 (O−H). Anal. Found: C, 83.34; H, 7.22.

General Procedure for Preparation of Graft Copolymers 6a−d. A 250 mL oven-dried, cylindrical, peptide-type vessel equipped with a bottom drain below a sintered glass frit, a sidearm addition port, and a wide-mouth threaded top port was oven-dried and flushed with N_2. The vessel was charged with diol **5b** (1 equiv) and dry THF (2.8 mL/g resin). The THF was removed through the bottom drain using N_2 pressure, and the rinsing operation was repeated. The vessel was charged with THF (14 mL/g resin) followed by a solution of *t*-BuOK (1.1 equiv, 1.65 M in THF) and allowed to stand for 1 h. The pale-yellow resin was treated with the specified amount of ethylene oxide solution[36] in THF. *Caution: Ethylene oxide is a highly toxic, highly flammable gas. Extreme precautions must be exercised when handling this material.* The vessel was placed on a wrist action shaker behind a blast shield, and agitation was continued for 43 h. During this time, the resin bed volume increased to nearly the top of the solvent level. The suspension was treated with MeOH (2 mL/g **5b**), and the solvent was removed via N_2 pressure into a flask containing enough 1 M HCl to acidify the mixture. *Caution: Residual ethylene oxide may be present!* The resin was washed sequentially with the following solvents (25 mL/g **5b**) using a 15 min agitation period during each cycle: 2 × MeOH, 1 × MeOH/1 M HCl (50:50), 1 × water, 2 × MeOH. The resin was suction-dried for 1 h, transferred to a vacuum oven, and dried to constant weight (25 °C, 27 inHg, air bleed) or taken directly in to the purification step.

Purification of Graft Copolymers 6a−d. The crude resin was placed in a 500 mL cylindrical, peptide-type vessel equipped with a bottom drain below a sintered glass frit, a sidearm addition port, and a wide-mouth threaded top port and treated with 350 mL of a mixture of TFA and water (95:5). The vessel was allowed to stand at ambient temperature with occasional shaking for 6 h. The liquid was removed with nitrogen pressure and the resin was washed with 3 × 250 mL of MeOH. The resin was treated with 200 mL of MeOH/water (90:10) followed by the portionwise addition of NH_4OH (7.4 M) until the mixture maintained a pH = 9 for a 3 h period. The solvent was removed using nitrogen pressure the resin was washed sequentially with the following solvents: 150 mL water, 150 mL MeOH/water (90:10), 150 mL MeOH, 2 × 150 mL THF. The product was suction dried for 1 h, transferred to a vacuum oven, and dried to constant weight (25 °C, 27 inHg, air bleed).

Graft Copolymer 6a was prepared from 8.82 g of **5b,** 13.6 mL of *t*-BuOK (22.4 mmol), and 170 mL of EO solution (5.85 M, 995 mmol). The crude product was taken directly on to the purification step affording 27.2 g of slightly tacky white beads. Loading: 0.50 by Fmoc-Gly coupling. IR: 3200−3700 (O−H). ^{13}C NMR: 61.0 (−O−CH_2−CH_2−OH), 70.1 [(−O-CH_2-CH_2−O−)$_n$], 72.3 (−O−CH_2−CH_2−OH).

Graft Copolymer 6b was prepared from 6.00 g of **5b,** 7.2 mL of *t*-BuOK (11.9 mmol), and 75 mL of EO solution (8.65 M, 810 mmol). A crude yield of 26.5 g was isolated along with 17.1 g of linear PEG from the liquors. Following the purification protocol, a yield of 22.2 g of free-flowing white beads was obtained. Loading: 0.47. IR and ^{13}C NMR were identical to **6a**.

Graft Copolymer 6c was prepared from 6.00 g of **5b** and 7.2 mL of t-BuOK (11.9 mmol), and 112 mL of EO solution-(8.65 M, 972 mmol). A crude yield of 30.0 g was isolated. Following the purification protocol a yield of 27.0 g of free-flowing white beads was obtained. Loading: 0.40. IR and ^{13}CNMR were identical to **6a**.

Graft Copolymer 6d was prepared from 5.00 g of **5b,** 6.0 mL of *t*-BuOK (9.9 mmol), and 125 mL of EO solution (8.65 M, 1081 mmol). The crude product was taken directly on to the purification step affording 27.9 g of free-flowing white beads. Loading: 0.32. IR and ^{13}C NMR were identical to **6a**.

General Procedure for Preparation of Chlorides 7a−d. A suitably sized three-necked, round-bottom flask was fitted with a mechanical stirrer, reflux condenser, and thermocouple. The assembled apparatus was dried by heating to 100 °C under a N_2 sweep followed by cooling to 25 °C. The flask was charged with the appropriate alcohol **6a−d** (1 equiv) followed by toluene (8 mL/g resin) and thionyl chloride (7.0 equiv). Stirring was initiated at 45 rpm and the suspension was heated to 75 °C and held for 16 h. After cooling to 55 °C the solvent was removed using a vacuum filtration tube, and the resin was washed sequentially with the solvents listed below. Each wash volume was 8 mL/g resin, and agitation at 55 °C was maintained for 10 min during each cycle: 2 × toluene. The flask was cooled to 25 °C, and the resin was washed with 5 × MeOH. The product was isolated by filtration and vacuum-dried to constant weight (25 °C, 27 inHg, air bleed).

7a was prepared from 18.0 g of alcohol **6a** and 18 mL of thionyl chloride, affording 16.8 g of pale-yellow beads. ^{13}C NMR: 42.1 (−O−CH_2-CH_2−Cl), 70.1 [(−O−CH_2−CH_2−O−)$_n$ and (−O−CH_2−CH_2−Cl)]. Loading: 1.98% Cl or 0.56 mmol Cl/g resin.

7b was prepared from 16.0 g of alcohol **6b** and 4 mL of thionyl chloride, affording 15.1 g of pale-yellow beads. Loading: 1.56% Cl or 0.44 mmol Cl/g resin. ^{13}C NMR was identical with **7a** above.

7c was prepared from 20.0 g of alcohol **6a** and 5.1 mL of thionyl chloride, affording 16.8 g of pale-yellow beads. Loading: 1.38% Cl or 0.39 mmol Cl/g resin. ^{13}C NMR was identical with **7a** above.

7d was prepared from 15.0 g of alcohol **6a** and 2.5 mL of thionyl chloride, affording 15.2 g of pale-yellow beads. Loading: 0.96% Cl or 0.27 mmol Cl/g resin. ^{13}C NMR was identical with **7a** above.

General Procedure for the Preparation of Amines 8a−d. A suitably sized three-necked, round-bottom flask was fitted with a mechanical stirrer and thermocouple. The

assembled apparatus was dried by heating to 100 °C under a N_2 sweep followed by cooling to 25 °C. The flask was charged with the appropriate chloride **7a**−**d** (1 equiv) followed by potassium phthalimide (5 equiv) and DMF (8 mL/g resin). Stirring was initiated at 45 rpm, and the suspension was heated to 75 °C and held for 16 h. After the mixture cooled to 55 °C, the reaction was quenched by adding water (2.5 mL/g **7a**−**d**), the solvent was removed by vacuum filtration tube, and the resin was washed sequentially with the solvents listed below. Each wash volume was 8 mL/g resin, and agitation at 50 °C was maintained for 10 min during each cycle: 1 × DMF/water (50:50), 1 × EtOH/water (50:50), 2 × EtOH. The flask was charged with EtOH (9 mL/g **7a**−**d**) followed by hydrazine hydrate (10 equiv, 55% in water). Stirring was initiated at 45 rpm, and the suspension was heated to 70 °C and held for 22 h. After cooling to 55 °C, the solvent was removed by vacuum filtration through a gas dispersion tube submersed to the lowest point in the flask. The resin was washed sequentially with the solvents listed below via vacuum filtration tube. Each wash volume was 12.5 mL/g resin, and at agitation at 50 °C was maintained for 10 min during each cycle: 1 × MeOH/water (50:50), 1 × water, 2 × MeOH. The product was isolated by filtration and vacuum-dried to constant weight (25 °C, 27 inHg, N_2 bleed).

8a was prepared from 8.00 g of chloride **7a**, affording 6.97 g of slightly tacky white beads. Loading: 0.51 by picric acid analysis and 0.50 by N analysis. IR: 3400−3600 (N−H). ^{13}C NMR: 41.5 (−O−CH_2−*C*H_2−NH_2), 70.1 [(−O−*C*H_2−*C*H_2−O-)$_n$], 73.1 (−O−*C*H_2−CH_2- NH_2). Anal. Found: C, 63.78; H, 9.06; N, 0.70; O, 26.68.

8b was prepared from 8.00 g of chloride **7b**, affording 7.81 g of free-flowing, white beads. Loading: 0.51 by picrate analysis and 0.47 by N analysis. IR and NMR were identical to those of **8a**. Anal. Found: C, 62.72; H, 9.24; N, 0.66; O, 28.88.

8c was prepared from 10.0 g of chloride **7c** affording 9.66 g of free-flowing, white beads. Loading: 0.38 by N analysis. IR and ^{13}C NMR were identical to those of **8a**. Anal. Found: C, 61.26; H, 9.34; N, 0.54; O, 30.60.

8d was prepared from 15.0 g of chloride **7d**, affording 7.23 g of free-flowing, white beads. Loading: 0.33 by N analysis. IR and ^{13}C NMR were identical to those of **8a**. Anal. Found: C, 60.11; H, 9.40; N, 0.46; O, 31.70.

General Procedure for Attachment of Wang Linker to Chlorides 7a−d. A suitably sized three-necked, round-bottom flask was fitted with a mechanical stirrer and thermocouple. The assembled apparatus was dried by heating to 100 °C under a N_2 sweep followed by cooling to 25 °C. The flask was charged with sodium hydride (5 equiv) followed by DMF (5 mL/g resin). The suspension was stirred at 45 rpm for 30 m. To the resulting solution was added the appropriate chloride **7a**−**d** and the suspension was heated in an 80 °C oil bath for 15 h. After the mixture was cooled to 25 °C, the solvent was removed by vacuum filtration through a gas dispersion tube submersed to the lowest point in the flask. The resin was washed sequentially with the solvents listed below by employing the method described above to remove solvents between washes. Each wash volume was 8 mL/g resin at agitation maintained for 10 min during each cycle: 1 × DMF, 1 × DMF/water (50:50), 1 × THF/water (50:50), 1 × MeOH/water (50:50), 3 × MeOH. The product was isolated by filtration and vacuum-dried to constant weight (25 °C, 27 inHg, N_2 bleed).

9a was prepared from 2.00 g of chloride **7a** affording 2.05 g as tacky tan beads. Loading: 0.47 by Fmoc-Gly coupling. IR 3550 (O−H). ^{13}C NMR: 63.5 (Ar−*C*H_2−OH), 66.8 (−O−CH_2−*C*H_2−O−Ar), 69.1 (−O−*C*H_2−CH_2−O−Ar), 113.9, 134.3, 157.9 (−O−*Ar*−CH_2−).

9b was prepared from 2.70 g of chloride **7b**, affording 2.8 g as free-flowing tan beads. Loading: 0.39 by Fmoc-Gly coupling. IR and ^{13}C NMR were identical to **9a**.

9c was prepared from 2.00 g of chloride **7c**, affording 2.03 g as free-flowing tan beads. Loading: 0.39 by Fmoc-Gly coupling. IR and ^{13}C NMR were identical to **9a**.

9d was prepared from 3.00 g of chloride **7c**, affording 3.10 g as free-flowing tan beads. Loading: 0.27 by Fmoc-Gly coupling. IR and ^{13}C NMR were identical to **9a**.

General Procedure for Attachment of HMPB Linker to Amines 8a−d. A suitably sized three-necked, round-bottom flask was fitted with a mechanical stirrer. The assembled apparatus was dried by heating to 100 °C under a N_2 sweep followed by cooling to 25 °C. The flask was charged with HMPB linker (1.2 equiv) followed by DMF (3.5 mL/g resin), 2-(1*H*-benzotriazole-1-yl)1,1,3,3-tetramethyluronium tetrafluoroborate (1.2 equiv), and DIEA (3.6 equiv). The mixture was stirred at 45 rpm for 10 min. To the resulting solution was added the appropriate amine **8a**−**d**, and the suspension was stirred at 25 °C for 75 min, at which point a ninhydrin test on a small aliquot was negative. The solvent was removed by vacuum filtration tube, and the resin was washed sequentially with the solvents listed below. Each wash volume was 8 mL/g resin at agitation maintained for 10 min during each cycle: 2 × DMF, 1 × DMF/piperidine (80:20), 1 × DMF, 1 × THF, 3 × MeOH. The product was isolated by filtration and vacuum-dried to constant weight (25 C, 27 inHg, N_2 bleed).

10a was prepared from 0.500 g of amine **8a**, affording 0.562 g as tacky white beads. Loading: 0.41 by coupling Fmoc-Gly. IR 3250−3700 (O−H), 1664 (C═O). ^{13}C NMR: 28.1, 35.0, 42.1, 57.6, 62.7, 70.1, 101.7, 107.9, 125.9, 131.8, 161.0, 162.7, 175.0.

10b was prepared from 2.099 g of amine **8b**, affording 2.282 g as tacky white beads. Loading: 0.33 by coupling Fmoc-Gly. IR and ^{13}C NMR were identical to **10a**.

10c was prepared from 2.035 g of amine **8c**, affording 2.156 g as tacky white beads. Loading: 0.30 by coupling Fmoc-Gly. IR and ^{13}C NMR were identical to **10a**.

10d was prepared from 2.07 g of amine **8d**, affording 2.13 g as free-flowing white beads. Loading: 0.26 by coupling Fmoc-Gly. IR and ^{13}C NMR were identical to **10a**.

General Method for Determination of Amine Loading via Picric Acid Salt. Binding Picric Acid. Approximately 25 mg of resin was weighed into a tared 3 mL polypropylene cartridge (20 μm frit, Applied Separations). The resin was washed with 3 mL portions of the following solvents and reagents: 2 × DCM, 3 × DIEA/DCM (5:95, freshly prepared), DCM, 2 × MeOH, 2 × DCM, 0.1M picric acid/

DCM for 5 min, DCM until filtrate has an absorbance ≤0.05 at 340 nm after zeroing spectrophotometer with DCM (usually ≥ 20 washes).

DIEA−Picrate Formation. The resin was washed with 2 × 1.5 mL DIEA/DCM (5:95) for 2 min, each time collecting the filtrate in a 25 mL volumetric flask. The resin was further washed with EtOH (95%) to bring the volume up to exactly 25 mL.

DIEA−Picrate Analysis. A blank was prepared by dilution of 1.2 mL of DCM with EtOH (95%) up to volume in a 10 mL volumetric flask. This solution was used to zero the spectrophotometer at 358 nm. Samples were prepared similarly by diluting 1 mL of the filtrate solution with EtOH (95%) into a 10 mL volumetric flask. Absorbance measurements were taken at 358 nm, and the substitution level was calculated according to eq 1 where A_{358} is the absorbance and M is the mass of the resin in milligrams.

$$\text{amine loading (mmol/g)} = 0.172A_{358}/0.001M \qquad (1)$$

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