JOC Article

Synthesis and Evaluation of Poly(oxyethylene glycol) Polymer (POP) Supports

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Mono- and α,ω-bis-styryl-oligo(oxyethylene glycol) ethers have been constructed in an efficient two-step synthesis. From these precursors, poly(oxyethylene glycol) polymer (POP) supports of varying monomer and cross-linker composition have been produced. The swelling properties and mass-solvent uptake of these novel materials have been evaluated in a variety of solvents, demonstrating that POP supports exhibit enhanced solvent compatibilities over the commercial resins TENTA-GEL, ARGO-GEL, and Merrifield's resin. The utility of POP supports in solid-phase organic chemistry has also been demonstrated successfully. It is anticipated that these high-loading polymeric supports will have generic application in the solid-phase synthesis of combinatorial libraries and the in situ screening of these libraries in the aqueous environment of a bioassay.

Introduction

Merrifield first introduced the concept of solid-phase organic chemistry (SPOC) by utilizing a chloromethylstyrene solid support for peptide synthesis.[1] Predominantly, SPOC has favored the use of styrene-based resins because of their thermal, chemical, and mechanical stability.[2] Despite their widespread use, styrene-divinylbenzene polymer supports (PS-DVB) exhibit limited swelling in highly polar solvents such as water.[3] Reduced accessibility of polar reagents into the polymer matrix often gives low-yielding on-bead reactions and, in addition, severely restricts the usage of these polymer supports in aqueous bioassays.[3] In attempts to circumvent these limitations, a variety of linkers have been attached to PS-DVB supports to optimize their properties for specific applications.[4] While linkers modify the local chemical environment around the reactive sites of these resins, they do not have a significant effect upon the intrinsic hydrophobicity of polystyrene-based resins. An alternative approach to impart polar solvent/aqueous compatibility is to graft larger linker units such as poly(ethylene glycol) (PEG), directly onto the polystyrene support.[5] PEG-containing supports of this type are available commercially as TENTA-GEL and ARGO-GEL and have been used successfully for SPOC. A disadvantage of the grafting process is that, while the number of chemically reactive sites within the resin remains constant, the resin mass increases dramatically. This reduces the polymer loading significantly. As an alternative to grafting long-chain PEG molecules, a recent patent describes the grafting of short-chain PEG-based molecules onto polystyrene-based supports.[6] The resultant materials can be constructed with higher loadings of resin than either TENTA-GEL or ARGO-GEL and, in some instances, swell in water or alcohols.

Until recently, however, little effort has been put into modification of the polymer matrix.[3,7] Most notably, Kurth has reported the polymerization of styrene with a number of oligo(oxyethylene glycol) ether cross-linking agents to generate a set of resins that swell significantly in a range of aprotic organic solvents but are not compatible with water.[3] In addition, although the PEG-based cross-linked resins swell more than the corresponding divinylbenzene cross-linked resins, these resins are not good supports for organic synthesis since they possess labile benzylic ether linkages. In related work, Janda has synthesized "organic solvent-like" polystyrene resins by polymerizing styrene, 4-vinylbenzyl chloride, and a tetrahydrofuran derived cross-linker.[7g] These resins also exhibit excellent swelling properties in a wide range of aprotic organic solvents. However, in contrast to the cross-linkers utilized by Kurth, Janda's tetrahydrofuran derived cross-linking agents contain only phenolic ether bonds, and thus the resultant resins are chemically robust. The Janda resins are, however, pre-

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dominantly polystyrene-based and thus not suitable for use in aqueous environments.

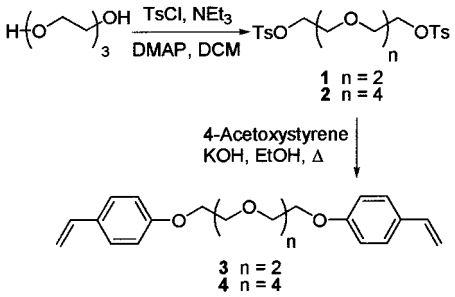
We wished to develop a set of high-loading polymeric supports that lacked reactive chemical linkages such as benzylic ethers and that would swell significantly in both aqueous *and* organic solvents. These supports are intended for use in SPOC and subsequent in situ on-support assay in aqueous media. PEG is chemically robust and can impart both organic and aqueous compatibility onto polymers.[3,5−7] Consequently, a series of PEG-based polymeric supports that contained uniformly distributed functional groups within a chemically inert polymer matrix were required for evaluation purposes. Herein is reported a facile two-step synthesis of mono- and bis-styrene-functionalized oligo(oxyethylene glycol) ethers. The polymerization of these monomers to produce a series of polymers of varying monomer composition, molar percentage cross-linking (%XL), and ethylene oxide chain length is described. In addition, the swelling properties and mass-solvent uptake versus time of these novel POP supports in DCM, DMF, THF, toluene, and water are compared with those of the commercial resins, Merrifield's resin, TENTA-GEL, and ARGO-GEL.

Results and Discussion

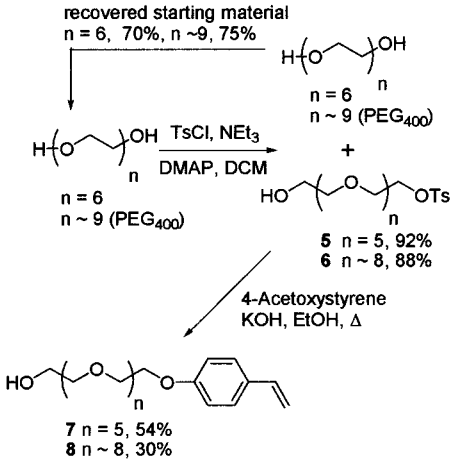
Synthesis of PEG-Based Monomers and Cross-Linkers. To enable construction of the PEG-based polymeric supports, a number of mono- and bis-polymerizable oligo(oxyethylene glycol) ethers were required. Styrene was chosen as the desired polymerizable unit for its compatibility with the scintillant-containing monomers used routinely in our laboratories.[8] In a synthesis of crown ethers, Nishimura utilized bis-tosyl PEG derivatives in a three-step synthesis of two bis-styrene-functionalized oligo(oxyethylene glycol) ethers.[9] Since these styrene-containing ethers did not contain benzylic ether linkages, we elected to use one of them, α,ω-bis-styryl-pentaethylene glycol **4**, as a cross-linking agent for our polymer supports. A novel one-step route to this target was devised on the basis of methodology previously described by Janda.[7g] Commercial 4-acetoxystyrene was treated with potassium hydroxide in the presence of commercial penta(ethylene glycol) di-*p*-toluenesulfonate **2**. This one-pot hydrolysis and subsequent in situ coupling reaction proceeded smoothly, giving the desired target **4** in good yield. Tri(ethylene glycol) di-*p*-toluenesulfonate **1**, readily synthesized from toluenesulfonyl chloride and tri(ethylene glycol), also underwent this one-step hydrolysis−coupling procedure giving cross-linking agent **3** (Scheme 1).

PEG-based monomers containing both a polymerizable styrene unit and chemical functionality to enable the generation of chemically reactive supports were also required. While bis-functionalized PEG is available or else readily accessible, commercial heterofunctionalized PEG is prohibitively expensive for routine large-scale production of monomers.[10] In addition, the synthetic methodology used to construct such molecules is non-trivial.[11] Consequently, a facile and cost-effective route to monostyrene-functionalized oligo(oxyethylene glycol) ethers was required.

SCHEME 1



SCHEME 2



The synthesis of oligo(oxyethylene glycol) mono-*p*-toluenesulfonates is well documented.[12] Specifically, hexaethylene glycol was reacted with toluenesulfonyl chloride utilizing the methodology described by Brjesson and Welch.[12b] However, the workup procedure was modified to preclude the need for purification by column chromatography. A simple extraction procedure gave pure samples (as assessed by NMR) of both hexaethylene glycol mono-*p*-toluenesulfonate (**5**) and excess, unreacted hexaethylene glycol in excellent yields. This workup procedure also proved to be extremely effective in the synthesis of poly(oxyethylene glycol)$_{400}$ mono-*p*-toluenesulfonate **6**. With multigram quantities of monotosylates **5** and **6** readily and cheaply available, we wished to investigate if the one-pot hydrolysis−coupling procedure utilized in the construction of the cross-linkers could be extended to the generation of monostyrenic-PEG despite the presence of an unprotected primary hydroxyl group. Again, the reaction with 4-acetoxystyrene proceeded smoothly giving both monostyryl-hexaethylene glycol **7** and monostyryl-poly(oxyethylene glycol)$_{400}$ **8** (Scheme 2).

Polymerization of PEG-Based Monomers and Cross-Linkers. Microscale suspension polymerization of

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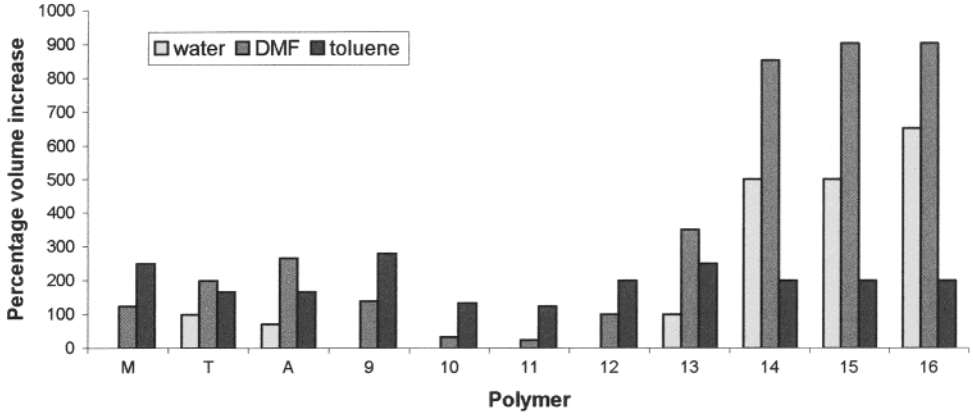


FIGURE 1. Graph showing the percentage of volume change of polymers **9**−**16**, Merrifield's resin (**M**), TENTA-GEL (**T**), and ARGO-GEL (**A**) upon exposure to water, DMF, and toluene.

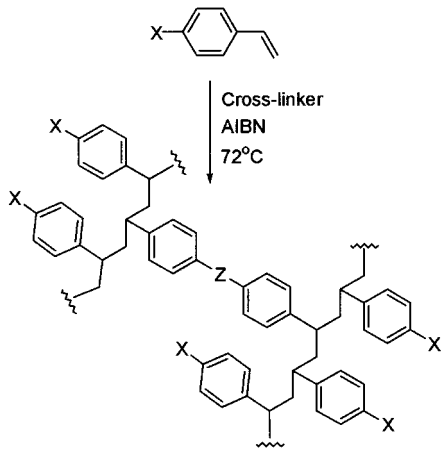
styrene cross-linked with 2, 14, and 20 mol % bis-styryl-penta(oxyethylene glycol) ether **4** gave beaded products **9**−**11**, respectively. These materials were required to indicate what extent of cross-linking by a PEG-based cross-linking agent would be preferable for good solvent compatibility. To enable direct comparison of these resins, no porogen was employed in the construction of the more highly cross-linked resins **10** and **11**. Microscale suspension polymerization of styrene cross-linked with 2 mol % bis-styryl-tri(oxyethylene glycol) ether **3** gave resin **12**. This resin was required for comparison with resin **9** to enable the effect of the PEG chain length of the cross-linking agent upon solvent compatibility to be evaluated. In all cases, a monomer to bulk-phase ratio of 1:10 and a mole percent fraction of AIBN of 0.8% was used as related work had shown that these amounts give good yields of beaded product.[8a]

The miscibility of monostyryl-oligo(oxyethylene glycol) monomers **7** and **8** with 1% PVA solution prompted their bulk polymerization with 2 mol % of either PEG-based cross-linking agent **4** or DVB to give gel-like polymers **13**−**16** (Scheme 3). These materials were required to establish whether it was preferable, in terms of general solvent compatibility, to combine a PEG-based monomer and cross-linker or a PEG-based monomer and a styryl-based cross-linker.

Solvent Swelling Assay of Polymers. Polymers **9**−**16**, constructed from the PEG-containing monomers and cross-linkers, were evaluated for their swelling properties in a range of solvents. A syringe-based solvent swelling assay with considerable literature precedent was employed.[3,7e] In this manner, the percentage of volume increase of each polymer was measured in water, DMF, and toluene. For comparative purposes, commercial samples of Merrifield's resin, TENTA-GEL, and ARGO-GEL were evaluated in an identical fashion.

Figure 1 clearly shows that polymers **14**−**16**, containing a PEG-based monomer, swell far more in water than all of the other polymer supports, most notably TENTA-GEL and ARGO-GEL, which are sold commercially as aqueous compatible supports. The predominantly styrene-based polymers, Merrifield's resin, and styrene-PEG-cross-linked resins **9**−**12** fail to show any significant swelling. A similar trend is observed for DMF, but interestingly, the swelling properties of **14**−**16** in toluene are very similar to those observed for all of the other

SCHEME 3



9 (Styrene X=H, **4** Z= O-$(C_2H_4O)_5$ 2%XL)
10 (Styrene X=H, **4** Z= O-$(C_2H_4O)_5$ 14%XL)
11 (Styrene X=H, **4** Z= O-$(C_2H_4O)_5$ 20%XL)
12 (Styrene X=H, **3** Z= O-$(C_2H_4O)_3$ 2%XL)
13 (**7** X=$(C_2H_4O)_6$OH, DVB 2%XL)
14 (**8** X=$(C_2H_4O)_9$OH, DVB 2%XL)
15 (**7** X=$(C_2H_4O)_6$OH, **4** Z=O-$(C_2H_4O)_5$ 2%XL)
16 (**8** X=$(C_2H_4O)_9$OH, **4** Z=O-$(C_2H_4O)_5$ 2%XL)

polymers. As expected and in agreement with another similar study,[3] resins **9**−**11** exhibit decreasing swelling characteristics with increasing degrees of cross-linking in DMF and toluene (Figure 1). Similarly, a comparison of the degree of swelling of resins **9** and **12** indicates that increasing the length of the PEG-based cross-linker, from triethylene glycol to pentaethylene glycol, results in increased swelling of the resin in DMF and toluene.

Polymers **14**−**16** had the best swelling characteristics in water and thus seemed the most likely candidates for use in on-support aqueous-based assays. Consequently, these polymers were further evaluated for their compatibility with DCM and THF for application in solid-phase peptide chemistry (SPPC). For comparative purposes, Merrifield's resin, TENTA-GEL, and ARGO-GEL were also evaluated in these solvents. Again, polymers **14**−**16** exhibited excellent compatibility with both solvents and swelled to far greater extents than the commercial controls (Figure 2).

Mass-Solvent Uptake Assay. The internal matrix of polymers **14**−**16** has been tailored with the specific intention of giving an increased surface energy in com-

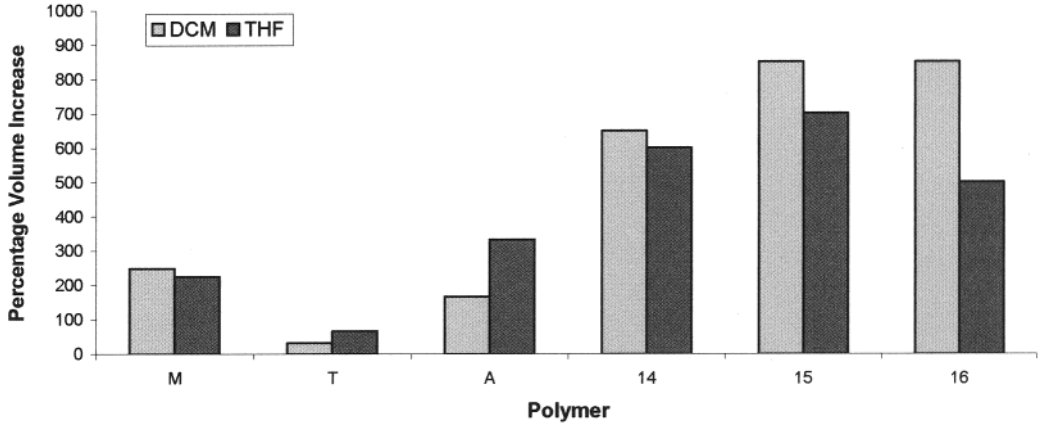


FIGURE 2. Graph showing the percentage of volume change of polymers **14**−**16**, Merrifield's resin (**M**), TENTA-GEL (**T**), and ARGO-GEL (**A**) upon exposure to DCM and THF.

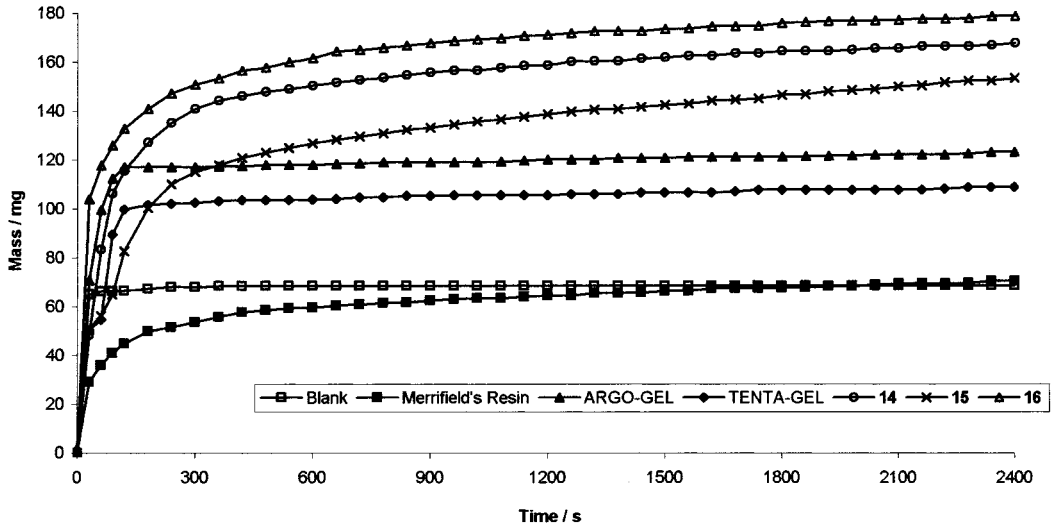


FIGURE 3. Mass-water uptake versus time of polymers **14**−**16** relative to that of commercial resins and a blank control.

parison to those of the commercial resins. The effect of increasing the surface energy of a polymer is to create a thermodynamically unfavorable solid/air interface, which causes rapid and complete wetting by spontaneous penetration of high surface energy solvents such as water into the polymer matrix.[13] Although solvent swelling assays give an insight into the site accessibility of a polymer, we were also interested in quantifying the amount of solvent penetrating the matrix of polymers **14**−**16**. Conventionally, the wetting of nonporous surfaces and porous solid powders by liquids can be quantified by contact angle measurements[13,14] and the Washburn technique,[14,15] respectively. Unfortunately, neither technique can be used to study gel-type polymers since swelling of the polymer necessarily causes the contact surface between the liquid and solid to vary. Consequently, we elected to study the PEG-based polymers **14**−**16** using a mass-solvent uptake assay. The assay involved bringing a solvent just into contact with the surface of a polymer sample so that the solvent penetrates the polymer matrix through capillary action. The amount of solvent penetrating the polymer matrix can be quantified using a microbalance. Recording a mass reading at fixed time intervals allows a time-dependent solvation profile to be obtained for the polymer sample. In addition, the mass of solvent imbibed by the polymer sample can also be used to calculate the volume of solvent imbibed by the polymer at any time. To the best of our knowledge, this assay represents the first example whereby chemically functionalized gel-type polymers, specifically designed for use in SPOC, have had their solvent compatibilities and swell kinetics evaluated in this manner.

Mass-Water Uptake Assay of POP Supports. Equal aliquots of each of the PEG-based polymers **14**−**16** and the commercial resins TENTA-GEL, ARGO-GEL, and Merrifield's resin were analyzed for mass-water uptake (Figure 3). Figure 3 shows clearly that the final mass-solvent uptake values for each of the polymers **14**−**16** are about twice those of TENTA-GEL and ARGO-GEL resins. The mass-solvent uptake versus time profile also demonstrates that Merrifield's resin is completely hydrophobic. In addition, the profiles obtained for TENTA-GEL and ARGO-GEL resins plateau faster than those obtained for polymers **14**−**16**. A possible explanation for

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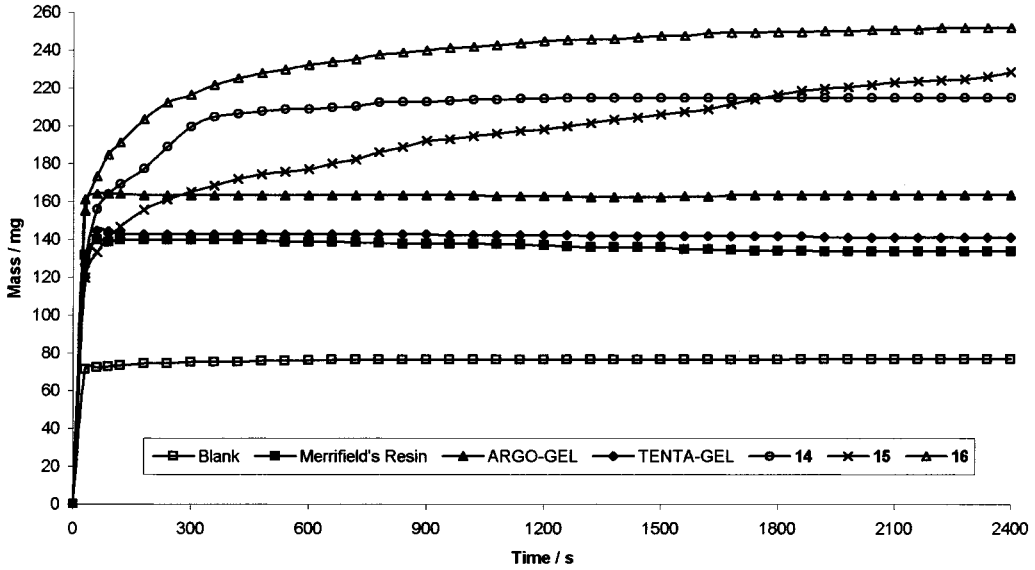

FIGURE 4. Mass-DMF uptake versus time of polymers **14**−**16** relative to that of commercial resins and a blank control.

this observation is that there is rapid solvation of the grafted PEG-containing regions of TENTA-GEL and ARGO-GEL and that, subsequently, there is little if any solvation of the hydrophobic polystyrene backbones of these resins. In contrast, after the peripheral PEG surfaces of polymers **14**−**16** have been solvated rapidly, it appears that more time is required for complete solvent penetration to the PEG-containing cores of these polymers.

Although polymer **13** takes up a mass of water similar to that taken up by TENTA-GEL and ARGO-GEL (data not shown), replacement of the DVB cross-linker in polymer **13** with α,ω-bis-styryl-pentaethylene glycol **4** gives polymer **15** and results in a polymer with a dramatically increased mass-water uptake that is far greater than those of both commercial resins. Similarly, replacement of the monostyryl-hexaethylene glycol monomer **7** in polymer **13** with monostyryl-poly(oxyethylene glycol)$_{400}$ **8** gives polymer **14**, which again exhibits a dramatically increased mass-water uptake. In summary, incorporating a PEG chain into the cross-linker or increasing the PEG chain length of the monomer results in polymers with a greater mass-water uptake. In addition, since polymer **14** (DVB cross-linker; monostyryl-poly(oxyethylene glycol)$_{400}$ monomer **8**) takes up a greater mass of water than polymer **15** (α,ω-bis-styryl-pentaethylene glycol **4** cross-linker; monostyryl-hexaethylene glycol **7**), the importance of the PEG length of the monomer appears to outweigh the effects of the small amount of cross-linker incorporated in gel-type supports such as these.

Mass-DMF Uptake Study of POP Supports. In a manner identical to that of the aqueous study, POP supports **14**−**16** and commercial resins TENTA-GEL, ARGO-GEL, and Merrifield's resin had their mass-solvent uptake versus time measured in DMF (Figure 4). The final mass-DMF uptake of polymers **14**−**16** is approximately double that of commercial Merrifield's resin, TENTA-GEL, and ARGO-GEL. This finding consolidates the solvent swelling assay results (Figure 1b), which showed that in DMF, polymers **14**−**16** swell to about three times the volume of the commercial polymer controls. Both of these results are presumably a consequence of the greater solvent accessibility toward a PEG cross-linked matrix compared with that of the DVB cross-linked styrene cores of ARGO-GEL and TENTA-GEL. As with the mass-solvent uptake results obtained using water, the profiles obtained for TENTA-GEL and ARGO-GEL resins plateau faster than those obtained for polymers **14**−**16**. In addition, and in complete contrast to the aqueous study, the mass-DMF uptake profile obtained for Merrifield's resin is very similar to that obtained for TENTA GEL in DMF.

Mass-Toluene Uptake Study of POP Supports. The profiles obtained from the rate−toluene uptake assay indicate that the mass-toluene uptake decreases in the order Merrifield's resin, TENTA-GEL/ARGO-GEL, **14**/**15**/**16** (Figure 5). This order reflects the hydrophobicity of each class of polymer studied and consolidates the view of Merrifield's resin behaving as a polystyrene resin, TENTAGEL and ARGO-GEL behaving as polystyrene resins with PEG grafts, and finally, the POP supports behaving predominantly as PEG-based supports with styryl grafts. Interestingly, such subtleties are less apparent in the solvent swelling assay where all of the polymers evaluated give relatively similar swelling volumes in toluene.

SPPC on POP Supports. Having established that POP supports **14**−**16** were compatible with a wide range of solvents of differing polarities, we wished to evaluate their utility as supports for SPOC. Accordingly, we elected to carry out two successive couplings of Fmoc-Gly-OH to the pendant hydroxyl functionalities within the POP supports. In each case, a standard Fmoc release assay[16] was used to monitor the extent of reaction. After the first round of couplings, the loadings of the three POP supports **14**−**16** were found to be 0.65, 0.68, and 0.57 mmol/g, respectively. While somewhat lower than the theoretical loadings calculated for these supports (Table 1), these experimentally determined values are still significantly higher than the theoretical loadings reported

(16) *NovaBiochem Catalog and Peptide Synthesis Handbook*; NovaBiochem: La Jolla, CA, 1998; p S37.

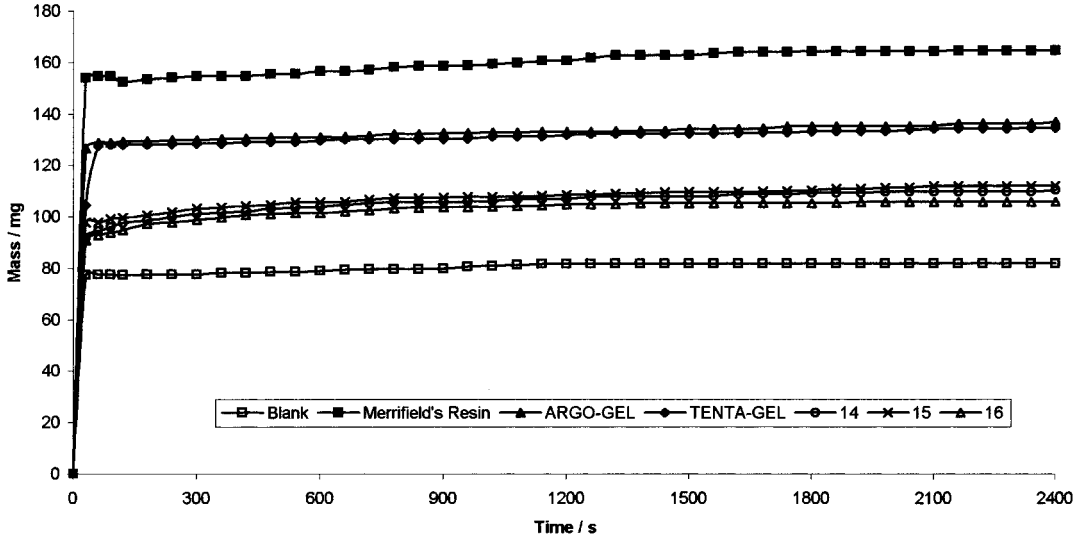

FIGURE 5. Mass-toluene uptake versus time of polymers **14**−**16** relative to that of commercial resins and a blank control.

TABLE 1. Theoretical and Experimentally Determined Loadings of POP Supports 14−16 after Two Successive Rounds of Fmoc-Gly-OH Coupling

	loading (mmol/g^{-1})[a]		
POP support	theoretical	coupling 1	coupling 2
14	1.92	0.65 (34%)	0.41 (63%)
15	2.53	0.68 (27%)	0.43 (63%)
16	1.90	0.57 (30%)	0.44 (77%)

[a] Each experimental loading was established using a standard Fmoc release assay.[16] The numbers in brackets refer to the yield of each coupling reaction. The yield for coupling 2 was calculated using the loading of the support established in coupling 1. Theoretical loadings were calculated from the monomer compositions used in the construction of the supports.

for the commercial samples of ARGO GEL and TENTA GEL used in this study, 0.47 and 0.28 mmol/g, respectively. In addition, the second round of Fmoc-Gly-OH couplings gave average yields of 68%. This encouraging result indicates that POP supports are well suited for use in SPOC.

Conclusions

In summary, a one-step synthetic procedure has been utilized to synthesize pure heterofunctionalized oligo(oxyethylene glycol) ethers. A simple extraction procedure was used to purify these compounds and also enabled the facile recovery of excess oligo(oxyethylene glycol) ether starting materials. The orthogonally functionalized materials together with doubly functionalized oligo(oxyethylene glycol) ethers were converted, in a one-pot reaction, into mono- and bis-styryl-oligo(oxyethylene glycol) ethers, respectively. Polymerization of these monomers and cross-linkers generated a range of novel polymeric materials. Initially, the swelling properties of these materials were evaluated, in a variety of solvents, by using a conventional solvent swelling assay. The actual mass of solvent imbibed by the polymers was then quantified using a novel mass-solvent uptake assay. These studies demonstrate successfully that POP supports are readily compatible with both water and a range of organic solvents with widely differing polarities. Finally, POP supports **14**−**16**, exhibiting superior aqueous compatibility relative to the commercial resins TENTA-GEL and ARGO-GEL, were utilized successfully as supports for SPPC.

We intend to exploit the exceptional compatibility of these polymeric supports with both organic and aqueous solvents in future work. Currently, we are attempting to construct POP supports that incorporate scintillant molecules covalently. These materials will then be used for the organic synthesis of polymer-supported libraries to be screened in situ and under aqueous conditions for biological activity.

Experimental Section

General Information. All reactions involving moisture-sensitive reagents were conducted in oven dried (120 °C) glassware. Dichloromethane (CH_2Cl_2), tri(ethylene glycol), and triethylamine were distilled from calcium hydride. Hexa(ethylene glycol) and poly(oxyethylene glycol)$_{400}$ were heated at 120 °C under high vacuum for 1 h. All other reagents were used as received from commercial suppliers. ARGO-GEL-OH (0.47 mmol/g), Merrifield's resin 2% DVB (100−200 mesh, 0.89 mmol/g), and TENTA-GEL-OH resin (0.27 mmol/g) were purchased commercially. An aqueous solution of PVA refers to a 1 wt %/wt aqueous solution of poly(vinyl alcohol) (87−89% hydrolyzed, average MW 85 000−146 000). All reaction mixtures were stirred magnetically unless otherwise stated. Where appropriate, reactions were monitored by thin-layer chromatography using silica gel 60 F_{254} precoated glass plates, which were visualized with UV light and then developed using either iodine, a solution of 10% phosphomolybdic acid in ethanol, or an aqueous solution of potassium permanganate. Flash column chromatography was carried out using silica gel 60 (0.035−0.070 μm, 220−440 mesh). The mass-solvent uptake assays (described in General Procedure 3) were performed using a conventional microbalance. For ^{1}H NMR and ^{13}C NMR spectra, deuterated chloroform was used as the solvent and chemical shift values (δ) are reported in parts per million relative to the residual signals of this solvent (δ 7.24 for ^{1}H and δ 77.0 for ^{13}C). Coupling constants are reported in hertz. ^{13}C NMR spectra were recorded using the PENDANT program.[17] Low-resolution mass spectra were recorded with an ion-trap spectrometer using atmospheric pressure chemical ionization (APCI). High-resolution mass spectra were recorded

by Mr. Peter Ashton (School of Chemistry, Birmingham University) using an electrospray mode with a mobile phase of methanol (200 μL/min) and a lock mass to correct the mass scale. Elemental analyses were performed by Medac, Ltd., Brunel Science Center, Cooper's Hill Lane, Engelfield Green, Egham, Surrey, UK. Infrared spectra were recorded as either a thin film/gel pressed between two sodium chloride plates or as a solid suspended in a potassium bromide disk. Melting points (mp) are uncorrected.

General Procedure 1 (GP1): Microscale Suspension Polymerization. A monomer and cross-linking monomer were stirred together for 15 min at room temperature. AIBN (0.76 equiv) was added and the resultant mixture stirred for an additional 10 min. The monomer mixture (~1.0−1.5 mL) was added to a stirred aqueous solution of PVA (10 mL) under a nitrogen atmosphere and the resultant suspension stirred for 30 min. The temperature was increased to 72 °C and stirring continued for an additional 4 h. The mixture was cooled to room temperature and the polymeric product collected by filtration. The beaded polymeric product was washed with distilled water (3 × 50 mL), MeOH (50 mL), 1/1 MeOH/THF (50 mL), THF (50 mL), and MeOH (50 mL) and then dried to a constant mass.

General Procedure 2 (GP2): Bulk Polymerization. A functionalized monomer, cross-linking monomer, and AIBN (0.76 equiv) were placed into a glass vial (1.5 mL). The vial was held in an ultrasound bath for 2 min. Nitrogen gas was bubbled through the monomer mixture for 5 min, and the vial was then placed in an oven at 60 °C overnight. The resulting polymer was washed with MeOH (30 mL), 1/1 MeOH/THF (30 mL), THF (30 mL), and MeOH (30 mL) and then dried to a constant mass.

General Procedure 3 (GP3): Mass-Solvent Uptake Study. The polymer (~25 mg) was packed into the bottom of a polypropylene disposable syringe (1 mL), with the tip removed, housing a nylon frit (0.45 μm). The syringe was suspended from a microbalance and the balance reading set at zero. A reservoir containing solvent was placed below the syringe and raised until the solvent was just brought into contact with the bottom of the syringe. A mass reading was recorded every 2 s. When the solvent was water, the surface tension of the water (72.3 mN/m) was lowered below that of the plastic syringe and frit assembly by addition of TWEEN 20 (1% v/v). For each solvent studied, a blank control assay was carried out. This procedure was identical in every respect to that described above except that no polymer sample was placed in the syringe. This procedure allowed for the "wetting" of the syringe/frit assembly by the solvent to be taken into account.

General Procedure 4 (GP4): Fmoc-Gly-OH Coupling to Polymer Supports. 2,6-Dichlorobenzoyl chloride (2.9 equiv) and pyridine (6 equiv) were added to the polymer (1 equiv) and Fmoc-Gly-OH (3 equiv) in DMF (35 mL/g), and the resultant mixture was stirred overnight. The polymer was collected by filtration and washed in situ with DCM (3 × 30 mL) and methanol (3 × 30 mL). The Fmoc-Gly-OH derived polymer was predried under suction before being placed in an oven at 60 °C overnight and dried to a constant mass.

General Procedure 5 (GP5): Fmoc Release Assay.[16] A polymer sample of approximately 1 mg was weighed accurately into a sample vial. A 20% solution of piperidine in DMF (3.00 mL) was added to the vial and the resultant suspension agitated using a Pasteur pipet. The suspension in the vial was filtered through a plug of cotton wool into a quartz cuvette. The absorption of the Fmoc/piperidine adduct was measured at 290 nm against a 20% piperidine/DMF blank. The above protocol was repeated four times for each polymer sample and the average absorbance per mg of each sample calculated. The loading (mmol/g) of each polymer was determined by dividing the average absorbance per mg at 290 nm by 1.65.

(17) Homer, J.; Perry, M. C. *J. Chem. Soc., Chem. Commun.* **1994**, 373.

Tri(ethylene glycol) Di-*p*-toluenesulfonate (1). A solution of tosyl chloride (TsCl) (21.643 g, 111.3 mmol) in CH_2Cl_2 (100 mL) was added dropwise over 2 h to an ice-cooled solution of tri(ethylene glycol) (5.00 mL, 37.1 mmol), triethylamine (31.3 mL, 222.5 mmol), and DMAP (0.0458 g, 0.37 mmol) in CH_2Cl_2 (200 mL) and the resultant mixture left to stir overnight while warming to room temperature. The reaction mixture was washed with distilled water (2 × 200 mL), saturated sodium bicarbonate solution (2 × 100 mL), and saturated citric acid solution (2 × 100 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give tri(ethylene glycol) di-*p*-toluenesulfonate **1** as a pale yellow oil (15.107 g, 89%), which was used in subsequent reactions without further purification: IR (thin film) ν_{max} 2877, 1597, 1497, 1450, 1354, 1176 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.40 (6H, s), 3.48 (4H, s), 3.61 (4H, t, J = 3.0), 4.10 (4H, t, J = 3.0), 7.31 (4H, d, J = 9.0), 7.75 (4H, d, J = 6.0); ^{13}C NMR (75 MHz, $CDCl_3$, PENDANT) δ_C 21.7, 69.1, 69.6, 71.0, 128.6, 130.6, 133.0, 145.7; LRMS (APCI) m/z 459 (M + H$^+$); HRMS (EI) m/z 481.0967 (M + Na$^+$), calcd for $C_{20}H_{26}O_8NaS_2$ 481.0957.

α,ω-Bis-styryl-tri(ethylene glycol) (3). 4-Acetoxystyrene (1.00 mL, 6.3 mmol) was added to a solution of potassium hydroxide (0.524 g, 7.94 mmol) dissolved in EtOH (12.5 mL) and the resultant mixture stirred at room temperature for 1 h. A solution of sodium ethoxide (0.548 g, 7.73 mmol) in EtOH (13.15 mL) was added and the resultant mixture brought to reflux for 1 h. A solution of tri(ethylene glycol) di-*p*-toluenesulfonate **1** (1.437 g, 3.134 mmol) in EtOH (39.50 mL) was added and the reaction mixture subsequently refluxed overnight. The reaction mixture was concentrated under reduced pressure, suspended in distilled water (50 mL), and extracted with Et_2O (3 × 100 mL). The combined organic fractions were dried over anhydrous sodium sulfate and concentrated under reduced pressure. Flash column chromatography (20% v/v ethyl acetate in hexanes) gave α,ω-bis-styryl-tri(ethylene glycol) **3** as a white solid (0.342 g, 31%): mp 68−69 °C; IR (thin film) ν_{max} 3085, 3041, 2975, 2934, 2903, 1626, 1605 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.72 (4H, s), 3.83 (4H, t, J = 4.2), 4.09 (4H, t, J = 4.0), 5.13 (2H, d, J = 11.0), 5.61 (2H, d, J = 17.5), 6.66 (2H, dd, J = 17.5, 11.0), 6.87 (4H, d, J = 8.4), 7.32 (4H, d, J = 8.4); ^{13}C NMR (75 MHz, $CDCl_3$, PENDANT) δ_C 67.2, 69.5, 70.6, 111.3, 114.4, 127.1, 130.3, 136.0, 158.4; LRMS (APCI) m/z 355 (M + H$^+$); HRMS (EI) m/z 377.1731 (M + Na$^+$), calcd for $C_{22}H_{26}O_4Na$ 377.1729. Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.6; H, 7.4; O, 18.0. Found: C, 74.4; H, 7.5; O, 18.1.

α,ω-Bis-styryl-penta(ethylene glycol) (4). According to the procedure described for α,ω-bis-styryl-tri(ethylene glycol) **3**, 4-acetoxystyrene (2.8 mL, 17.4 mmol) was reacted sequentially with ethanolic solutions of potassium hydroxide (1.452 g, 22.0 mmol) and sodium ethoxide (1.518 g, 21.42 mmol). An ethanolic solution of penta(ethylene glycol) di-*p*-toluenesulfonate **2** (5.00 g, 8.68 mmol) was then added to the refluxing reaction mixture to give α,ω-bis-styryl-penta(ethylene glycol) **4**, after flash column chromatography (60% v/v ethyl acetate in hexanes), as a white solid (1.818 g, 48%): mp 73−74 °C; IR (thin film) ν_{max} 3078, 3042, 2971, 2936, 2900, 2860, 1626, 1604, 1511, 1456, 1110 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.62−3.65 (12H, m), 3.78 (4H, t, J = 4.6), 4.06 (4H, t, J = 4.6), 5.09 (2H, d, J = 11.0), 5.57 (2H, d, J = 17.7), 6.62 (2H, dd, J = 17.5, 11.0), 6.83 (4H, d, J = 8.6), 7.29 (4H, d, J = 8.6); ^{13}C NMR (75 MHz, $CDCl_3$, PENDANT) δ_C 63.4, 67.3, 69.5, 70.5, 70.6, 111.4, 114.5, 127.1, 130.4, 136.0, 158.4; LRMS (APCI) m/z 443 (M + H$^+$); HRMS (EI) m/z 465.2264 (M + Na$^+$), calcd for $C_{26}H_{34}O_6Na$ 465.2253.

Hexa(ethylene glycol) Mono-*p*-toluenesulfonate (5). According to the procedure described for tri(ethylene glycol) di-*p*-toluenesulfonate **1**, a solution of TsCl (9.970 g, 0.051 mol) in CH_2Cl_2 (75 mL) was added to a solution of hexa(ethylene glycol) (60.390 g, 0.205 mol), triethylamine (28.90 mL, 0.21 mol), and DMAP (0.316 g, 2.56 mmol) in CH_2Cl_2 (150 mL) to give hexa(ethylene glycol) mono-*p*-toluenesulfonate **5** as a pale

yellow oil (20.403 g, 92%), which was used in subsequent reactions without further purification: IR (thin film) ν_{max} 3478, 2874, 1598, 1097 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.36 (3H, s), 2.98 (1H, s), 3.51−3.62 (22H, m), 4.08 (2H, t, J = 4.7), 7.26 (2H, d, J = 8.2), 7.71 (2H, d, J = 8.2); ^{13}C NMR (75 MHz, $CDCl_3$, PENDANT) δ_C 21.5, 61.5, 68.6, 69.2, 70.1, 70.4, 70.5, 70.6, 127.8, 129.7; LRMS (APCI) m/z 437 (M + H$^+$); HRMS (EI) m/z 459.1653 (M + Na$^+$), calcd for $C_{19}H_{32}O_9NaS$ 459.1665.

The distilled water from the aqueous workup was combined and concentrated under reduced pressure to give a white precipitate suspended in oil. The suspension was stirred with diethyl ether (200 mL) overnight and the filtrate concentrated under reduced pressure to give recovered hexa(ethylene glycol) ether as a colorless oil (31.85 g, 83%). Spectroscopic analysis of this material was identical to that of the starting material, and thus the recovered material was used in subsequent reactions without further purification.

Poly(oxyethylene glycol)$_{400}$ Mono-*p*-toluenesulfonate (6). According to the procedure described for tri(ethylene glycol) di-*p*-toluenesulfonate **1**, a solution of TsCl (6.809 g, 0.035 mol) in CH_2Cl_2 (60 mL) was added to a solution of poly(oxyethylene glycol)$_{400}$ (50.0 mL, 0.14 mol), triethylamine (19.3 mL, 0.14 mol), and DMAP (0.216 g, 1.75 mmol) in CH_2Cl_2 (250 mL) to give poly(oxyethylene glycol)$_{400}$ mono-*p*-toluenesulfonate **6** as a pale yellow oil (18.794 g, 88%), which was used in subsequent reactions without further purification: IR (thin film) ν_{max} 3475, 2873, 1597, 1453, 1353, 1177, 1098 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.35 (3H, s), 2.48−3.60 (35H, m), 4.06 (2H, t, J = 4.9), 5.22 (1H, s), 7.25 (2H, d, J = 7.7), 7.69 (2H, d, J = 8.2); ^{13}C NMR (75 MHz, $CDCl_3$, PENDANT) δ_C 21.4, 61.4, 68.4, 69.0, 70.1, 70.3, 70.4, 72.3, 127.7, 129.6, 132.7, 144.6; LRMS (APCI) m/z 613 (100%, [M + H]$^+$), 657 (90%, [M + C_2H_4O + H]$^+$), 569 (82%, [M + H − C_2H_4O]$^+$), 701 (69%, [M + 2(C_2H_4O) + H]$^+$), 525 (57%, [M + H − 2(C_2H_4O)]$^+$), 745 (43%, [M + H + 3(C_2H_4O)]$^+$), 481 (27%, [M + H − 3(C_2H_4O)]$^+$).

According to the procedure described for hexa(ethylene glycol) mono-*p*-toluenesulfonate **5**, unreacted poly(oxyethylene glycol)$_{400}$ was recovered as a very pale yellow oil (31.5 g, 75%). Spectroscopic analysis of this material was identical to that of the starting material, and thus the recovered material was used in subsequent reactions without further purification.

α-Styryl-hexa(ethylene glycol) (7). According to the procedure described for α,ω-bis-styryl-tri(ethylene glycol) **3**, 4-acetoxystyrene (0.50 mL, 3.14 mmol) was reacted with an ethanolic solution of potassium hydroxide (0.828 g, 12.55 mmol) at room temperature and then under reflux. An ethanolic solution of hexa(ethylene glycol) mono-*p*-toluenesulfonate **5** (1.728 g, 3.14 mmol) was added to the refluxing reaction mixture to give α-styryl-hexa(ethylene glycol) **7**, after flash column chromatography (5% v/v EtOH in CH_2Cl_2), as a pale yellow oil (0.651 g, 54%): IR (thin film) ν_{max} 3443, 2872, 1606, 1510, 1454, 1114 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.37−3.53 (20H, m), 3.64 (2H, t, J = 4.6), 3.92 (2H, t, J = 4.6), 4.93 (2H, d, J = 10.9), 5.42 (1H, d, J = 17.6), 6.48 (1H, dd, J = 10.9, 17.5), 6.69 (2H, d, J = 8.8), 7.14 (2H, d, J = 8.8); ^{13}C NMR (75 MHz, $CDCl_3$, PENDANT) δ_C 60.1, 62.3, 66.2, 68.4, 69.0, 69.3, 69.5, 71.5, 110.3, 113.4, 126.2, 129.2, 135.1, 157.5; LRMS (APCI) m/z 385 (M + H$^+$); HRMS (EI) m/z 407.2050 (M + Na$^+$), calcd for $C_{20}H_{32}O_7Na$ 407.2046.

α-Styryl-poly(oxyethylene glycol)$_{400}$ (8). According to the procedure described for α,ω-bis-styryl-tri(ethylene glycol) **3**, 4-acetoxystyrene (0.87 mL, 5.4 mmol) was reacted with an ethanolic solution of potassium hydroxide (0.677 g, 10.8 mmol) at room temperature and then under reflux. An ethanolic solution of poly(oxyethylene glycol)$_{400}$ mono-*p*-toluenesulfonate **6** (3.323 g, 5.43 mmol) was added to the refluxing reaction mixture to give α-styryl-poly(oxyethylene glycol)$_{400}$ **8**, after flash column chromatography (5% v/v EtOH in CH_2Cl_2), as a pale yellow oil (0.803 g, 29%): IR (thin film) ν_{max} 3477, 3087, 3042, 2872, 1607, 1454, 1110 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.38−3.52 (32H, m), 3.65 (2H, t, J = 4.8), 3.93 (2H, t, J = 5.1), 4.93 (1H, d, J = 10.8), 5.42 (1H, d, J = 17.7), 6.46 (1H, dd, J = 10.8, 17.5), 6.69 (2H, d, J = 8.4), 7.14 (2H, d, J = 8.6); ^{13}C NMR (75 MHz, $CDCl_3$, PENDANT) δ_C 60.9, 63.0, 66.9, 69.1, 69.7, 69.9, 70.1, 72.1, 111.0, 114.1, 126.8, 129.9, 135.6, 158.0; LRMS (APCI) m/z 517 (100, [M + H]$^+$), 473 (82, [M − (C_2H_4O)]$^+$), 429 (26, [M − 2(C_2H_4O)]$^+$); HRMS (EI) m/z 451.2326 [29, (M − 2(C_2H_4O) + Na$^+$], calcd for $C_{22}H_{36}O_8Na$ 451.2308; 495.2579 [89, (M − (C_2H_4O) + Na$^+$], calcd for $C_{24}H_{40}O_9Na$ 495.2570; 539.2809 [100, M + Na$^+$], calcd for $C_{26}H_{44}O_{10}Na$ 539.2832.

Polymer 9: Styrene, 2% Cross-Linked with α,ω-Bis-styryl-penta(ethylene glycol) 4. Styrene (920 μL, 7.9 mmol), α,ω-bis-styryl-penta(ethylene glycol) **4** (71.3 mg, 0.161 mmol), and AIBN (10.5 mg, 0.064 mmol) were combined according to GP1 to give polymer **9**, after washing, as a white beaded product (223 mg, 25%): IR (KBr disk) ν_{max} 3058, 3024, 2920, 2845, 1601, 1508 cm^{-1}.

Polymer 10: Styrene, 14% Cross-Linked with α,ω-Bis-styryl-penta(ethylene glycol) 4. Styrene (810 μL, 6.9 mmol), α,ω-bis-styryl-penta(ethylene glycol) **4** (500 mg, 1.13 mmol), and AIBN (10.5 mg, 0.064 mmol) were combined according to GP1 to give polymer **10**, after washing, as a white beaded product (985 mg, 80%): IR (KBr disk) ν_{max} 3051, 3016, 2924, 2856, 1601, 1510 cm^{-1}.

Polymer 11: Styrene, 20% Cross-Linked with α,ω-Bis-styryl-penta(ethylene glycol) 4. Styrene (750 μL, 6.4 mmol), α,ω-bis-styryl-penta(ethylene glycol) **4** (724 mg, 1.638 mmol), and AIBN (10.5 mg, 0.064 mmol) were combined according to GP1 to give polymer **11**, after washing, as a white beaded product (1.0 g, 71%): IR (KBr disk) ν_{max} 3051, 3025, 2919, 2856, 1609, 1508 cm^{-1}.

Polymer 12: Styrene, 2% Cross-Linked with α,ω-Bis-styryl-tri(ethylene glycol) 3. Styrene (226 μL, 1.95 mmol), α,ω-bis-styryl-tri(ethylene glycol) **3** (14.1 mg, 0.04 mmol), and AIBN (13 mg, 0.08 mmol) were combined according to GP1 to give polymer **12**, after washing, as a white beaded product (195 mg, 89%): IR (KBr disk) ν_{max} 3051, 3025, 2927, 2856, 1510 cm^{-1}.

Polymer 13: α-Styryl-hexa(ethylene glycol) 7, 2% Cross-Linked with Divinyl Benzene (DVB). α-Styryl-hexa(ethylene glycol) **7** (0.741 g, 1.93 mmol), DVB (0.0064 g, 0.039 mmol), and AIBN (2.5 mg, 0.015 mmol) were combined according to GP2 to give, after washing, polymer **13** as an opaque white gel (0.566 g, 76%): IR (gel compressed between NaCl disks) ν_{max} 3439, 3025, 2920, 2847, 1610, 1506, 1451 cm^{-1}.

Polymer 14: α-Styryl-poly(oxyethylene glycol)$_{400}$ 8, 2% Cross-Linked with DVB. α-Styryl-poly(oxyethylene glycol)$_{400}$ **8** (0.3011 g, 0.564 mmol), DVB (0.0021 g, 0.013 mmol), and AIBN (0.6 mg, 0.004 mmol) were combined according to GP2 to give, after washing, polymer **14** as a clear gel (0.155 g, 51%): IR (gel compressed between NaCl disks) ν_{max} 3370, 3076, 3033, 2909, 2867, 1608, 1109 cm^{-1}.

Polymer 15: α-Styryl-hexa(ethylene glycol) 7, 2% Cross-Linked with α,ω-Bis-styryl-penta(ethylene glycol) 4. α-Styryl-hexa(ethylene glycol) **7** (0.50 g, 1.3 mmol), α,ω-bis-styryl-penta(ethylene glycol) **4** (0.0117 g, 0.027 mmol), and AIBN (1.7 mg, 0.010 mmol) were combined according to GP2 to give, after washing, polymer **15** as a clear gel (0.210 g, 41%): IR (gel compressed between NaCl disks) ν_{max} 3414, 3025, 2954, 2918, 2847, 1607, 1501, 1451, 1067 cm^{-1}.

Polymer 16: α-Styryl-poly(oxyethylene glycol)$_{400}$ 8, 2% Cross-Linked with α,ω-Bis-styryl-penta(ethylene glycol) 4. α-Styryl-poly(oxyethylene glycol)$_{400}$ **8** (0.3308 g, 0.640 mmol), α,ω-bis-styryl-penta(ethylene glycol) **4** (0.0058 g, 0.013 mmol), and AIBN (0.8 mg, 0.005 mmol) were combined according to GP2 to give, after washing, polymer **15** as a clear gel (0.168 g, 50%): IR (gel compressed between NaCl disks) ν_{max} 3416, 3025, 2920, 2847, 1611, 1506, 1452, 1098, 1069, 1040 cm^{-1}.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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