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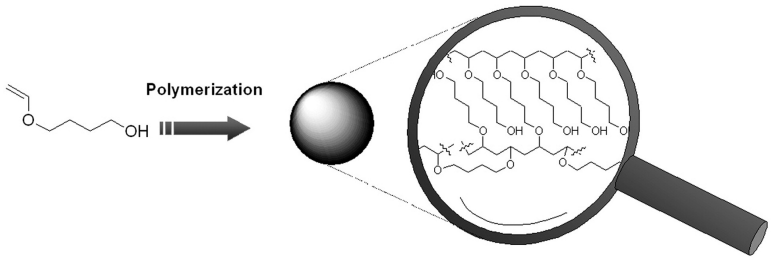

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Non-PEG-Derived Polyethers as Solid Supports. 1. Synthesis, Swelling Studies, and Functionalization

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Novel non-PEG derived polyether resins, coined SLURPS (*s*uperior *l*iquid-*u*ptake *r*esins for *p*olymer-supported *s*ynthesis), were synthesized by cationic polymerization of vinyl ethers. A functional resin was prepared with excellent control over loading levels. A sequence of synthetic transformations involving the introduction of a Wang linker followed by Mitsunobu functionalization chemistry and cleavage of the bound substrate proceeded quantitatively. These new polymers combine outstanding swelling performance in a wide range of solvents with high chemical stability and tunable loading levels up to 8.5 mmol/g. This combination of desirable features sets them apart from other polymer supports and, in particular, other polyether resins currently investigated for combinatorial chemistry.

Introduction

Polymer supports have revolutionized synthesis and separation as exemplified by combinatorial drug, polypeptide and oligonucleotide syntheses,[1−8] and immobilized (bio)catalysts and reagents,[9] as well as affinity chromatography and solid-phase extraction processes.[10−14] The main feature lies in the fact that these supports, by being insoluble, allow the easy separation of bound product from soluble reagents and contaminants. Thus, the use of excess reagents can easily be performed to drive reactions to completion. When used to support synthetic or biocatalysts, polymer supports provide a useful means of recovering and recycling the usually expensive catalyst.

Synthesis has become the progress-determining step in the race to develop new and more effective drugs and novel materials with improved performance characteristics. A revolution in robotics and high-throughput screening continues to develop at a much faster pace than the parallel and combinatorial synthesis of screenable molecular entities.[15−26] The major bottleneck is limitation in performance of currently available polymer supports.

An ideal polymer support would not interfere or interact in any way with the synthetic transformation in which it is being used; its presence would be noticed only during separation.[27−29] Obviously, in reality, interactions occur between the polymer and any of the other molecular species present, including solvent, thus rendering some supports more suitable for a particular application than others. Consequently, a wide range of chemically different supports used in a range of different physical formats had to be developed to address specific performance needs. No single support meets all of the desirable characteristics of a truly universal support. Such a support would be:

- compatible with all types of organic and aqueous solvent conditions,
- inert under chemical and enzymatic reactions conditions,
- available at any desired loading level (controllable) and with very high loading levels (for cost and process advantage),
- available with a wide range of functional groups so that any desired linker or spacer or any other molecule (e.g., catalyst ligands) of interest can be integrated, and
- mechanically robust in a flow reactor format and with control over flow properties via specific variation of cross-linking level and comonomer incorporation.

Although most successful supports exhibit some of these characteristics, no single support has been shown to combine all of them.[27−29] Critically, a support combining controlled loading levels, chemical inertness under solid-phase organic synthesis (SPOS) conditions, and compatibility with a wide range of solvents still remains elusive. Indeed, some synthetic supports (e.g., Merrifield resins or recent developments, such as the polyether cross-linked polystyrene resin *J*anda*J*el[30,31]) are not hydrophilic enough to be used in water and lower alcohols. In addition, when used in peptide and oligonucleotide synthesis, poor results have been obtained.[27−29] Sufficient hydrophilicity of the supports is traded for reduced loading levels (e.g. TentaGel, ArgoGel, POEPOP, SPOCC). Furthermore, there is little control over loading levels (POEPOP, SPOCC resins), or they are not easily achievable by simple adjustment of monomer feed (TentaGel, ArgoGel).[27−29] Other supports, such as polyacrylamides (Sheppard resin)[33] and polyether cross-linked polyacrylamides (PEGA)[34] exhibit excellent compatibility with hydrophilic solvents, which is responsible for their excellent performance in peptide synthesis. However, these supports have only limited general applicability because of their lack of chemical stability (amide groups) under reaction conditions usually encountered in organic synthesis, which precludes their use in SPOS. The

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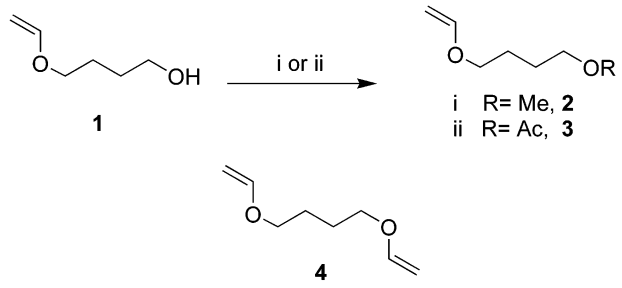
Scheme 1[a]



[a] i: CH_3I, KOH, DMSO, 65%. ii: Ac_2O, Et_3N, DMAP, 100%

ubiquitous linear, main-chain polyethers are intrinsically limited to very low loading levels but otherwise possess many desirable properties, such as chemical robustness and good solvent compatibility.[27−29] This led us to consider vinyl ethers as functional monomers for the synthesis of polymer supports, since we hypothesized that by incorporating the ether moiety and functional group within the side, chain it would be possible to achieve both high and controllable loading levels without compromising solvent compatibility and chemical stability.[27−29] Herein, we exemplify the synthesis of vinyl ether-derived supports, the study of their swelling behavior, functionalization chemistry, and chemical inertness, providing a first example of their application in SPOS.

Results and Discussion

1,4-Butanediol vinyl ether **1** (OH−BDVE) was selected as functional monomer of choice because it is commercially available and its hydroxyl side chain enables ready access to almost any functional group required in SPOS. By choosing a flexible C_4 side chain, we expected chemical transformations to proceed smoothly without compromising the ability to achieve high loading levels.

Indeed, a cross-linked polymer with 98 mol % of **1** and 2 mol % of cross-linker **4** will result in ∼8.5 mmol of OH groups/g of dry resin, a concentration significantly higher than hitherto known for any support applied to synthesis.[27−29]

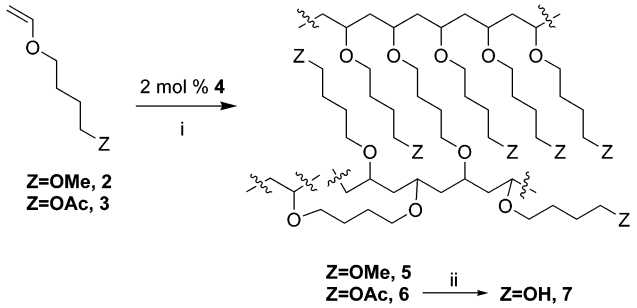
Our choice for a structural vinyl ether monomer fell on the chemically inert vinyl ether **2** (MeBDVE). Ether **2** was synthesized via methylation of **1** with methyl iodide in moderate yields (Scheme 1). Thus far, optimization attempts have resulted only in decreased yields, due to competing C-alkylation of the vinyl ether moiety.

Since vinyl ethers only polymerize poorly via free radical chemistry as a result of chain transfer processes,[35,36] we opted for well-established cationic polymerization methodology for vinyl ethers to generate the polymer network. Exclusion of nucleophilic species is paramount,[37,38] and thus, **1** was protected as acetate **3** (AcBDVE), shown in Scheme 1.

Finally, 1,4-butanediol divinyl ether **4** (BDDVE) was chosen as cross-linker because of the flexible nature of the butyl spacer linking both vinyl ether moieties and its structural similarity to the other vinyl ether monomers, ensuring comparable reactivity and, thus, essentially statistical incorporation into the polymer network structure.

Synthesis of Supports. All polymer networks were synthesized as gels via solution polymerization followed by smashing the gels into convenient particle sizes. This

Scheme 2[a]



[a] i: Catalytic BF_3-OEt_2, CH_2Cl_2, −78 to 0 °C, N_2, 3 h, 100%. ii: 6 equiv KOH, MeOH/H_2O, reflux, 24 h, 100%

procedure circumvents the time-consuming development of nonaqueous suspension polymerization conditions, thus allowing us to more speedily establish the suitability of these novel gels for solid-phase synthesis.[39−45] The suspension polymerization of these networks, required to obtain a more convenient beaded gel format, is currently being investigated and will be published in due course.

Most gel-type supports have cross-linking levels between 1 and 2 mol %. We chose to prepare a 2 mol % cross-linked resin because the higher content of cross-links ensures a mechanically more robust support, albeit with decreased levels of swelling. Since our initial swelling studies indicated already exceptional swelling behavior with 2 mol % cross-linker, we kept the level of cross-linking at 2 mol % throughout our investigation.

Monomers **2** and **3** were copolymerized cationically (see Scheme 2) in the presence of 2 mol % of 1,4-butanediol divinyl ether **4** (BDDVE) to produce gels **5** and **6** with 100% conversion. The level of conversion was determined by NMR spectroscopy and GC analysis of the filtrate, and both techniques indicated unambiguously complete monomer incorporation. With the feed ratio of monomers being identical to the composition of the gel network, it is easily possible to control loading and cross-linking levels by simple adjustment of the monomer ratio. It also enables us to obtain meaningful structure−property relationships essential for optimizing support performance.

Subsequent filtration of the polymer gel produced two gel fractions: larger-sized gels (80 wt %) and a fraction composed of smaller gel particles and microgels (20%); both gel fractions are useful formats for SPOS.

To provide gel particles of convenient size for subsequent physical and chemical studies, the fraction of larger-sized gels was smashed when swollen to obtain particle sizes between 0.5 and 2 mm.

Gel **6**, in which **1** was protected as acetate **3**, was hydrolyzed quantitatively by reflux in methanol/water (60/40% vol, 25 mL/g resin) with an excess of KOH (6 equiv per −OAc) to yield free alcohol gel **7**. Table 1 summarizes the reaction conditions for each gel.

All polymers are sticky materials that tend to agglomerate in the dry state as a consequence of their low glass transition temperature (T_g), but they can be handled and filtered very easily when brought in contact with solvent. Once the resin was swollen, drying could only be achieved through forcing conditions, such as leaving the gel for long periods under

Table 1. Polymerization Conditions for the Synthesis of Gels

gel	monomer(s) (mmol)	cross-linker (mmol)	solvent (mL)	type	initiator (mmol)	temp of gelation (°C)	conversion to polymer (%)	yield of isolated macrogel (%)
model PS−R	styrene (68.6)	DVB (1.40)	THF (8)	free radical	AIBN (0.91)	60	100	83
model PS−C	styrene (68.6)	DVB (1.40)	DCM (10)	cationic	BF_3OEt_2 (0.40)	−70 to −60	100	80
5	2 (68.6)	4 (1.40)	DCM (10)	cationic	BF_3OEt_2 (0.40)	−55 to −45	100	80
6	3 (68.6)	4 (1.40)	DCM (10)	cationic	BF_3OEt_2 (0.40)	−15 to − 5	100	80
8	2 (55.0) 3 (14.0)	4 (1.40)	DCM (10)	cationic	BF_3OEt_2 (0.40)	−15 to − 5	100	80

Table 2. Swelling Studies

	swelling ratios (mL/g)[a]					
	gel					
solvents	PS−C/PS−R	5	6	7	TentaGel S 0.25−0.30 mmol/g[b]	TentaGel S 0.40−0.60 mmol/g[b]
PhMe	6.3	11.4	11.1	0.4	4.8	4.1
THF	5.6	10.8	15.1	1.3	5.0	4.2
DCM	5.3	11.3	18.8	0.7	6.3	5.7
MeCN	0.4	4.2	11.6	0.5	4.2	3.9
DMF	3.2	6.0	12.4	5.6	4.7	4.6
MeOH	0.4	7.1	3.2	5.3	3.6	3.6
Water	0.4	1.5	1.7	3.4	3.6	3.1

[a] Preweighed, crushed, dry resins were allowed to in the corresponding solvent for 1 week. After filtration, the weight of incorporated solvent was measured, and the swelling ratios (Sw) was calculated as Sw = (Ws − Wd) ÷ (D × Wd), where Ws is the weight of the swollen resin, Wd is the weight of the dry resin, and D is the density of the corresponding solvent. [b] Data retrieved from the worldwide web on 10/11/2002 (http://www.rapp-polymere.com/).

vacuum. Therefore, the stickiness of the dry material was never an issue for resin handling.

For a direct comparison of swelling behavior, a polystyrene (**PS−C**) resin was synthesized under analogous reaction conditions as in the case of the vinyl ether networks with 2 mol % of divinylbenzene (DVB). Another model support, **PS−R**, was prepared by conventional free-radical polymerization to allow us to investigate the effect of the polymerization method on the swelling properties of the supports. As before, conversion and, therefore, monomer incorporation were found to be quantitative for both **PS−C** and **PS−R**.

Swelling Studies. For lowly cross-linked, or gel-type supports, the access of reagents to the active sites within the network is highly dependent on the swelling level of the resin in the reaction mixture.[28,29,46−55] Therefore, evaluation of the swelling performance of new gel-type resins is extremely important and a direct indication of their suitability as solid support for synthesis. The degree of swelling for gels **5**, **6**, and **7** was determined and compared to **PS−C** and **PS−R**. Interestingly, both PS gels exhibited identical swelling behavior (Table 2), suggesting that, in this particular case, swelling behavior of the final resin is independent of the polymerization method.

The swelling ratio was determined by the increase in net weight gain after swelling and was converted into the volume of solvent incorporated per weight of dry resin (swelling ratio, mL/g). We had to resort to a gravimetric method to measure swelling because of the resin's being sticky in the dry state, which precluded packing of a column, as required by the traditional syringe method.[50] However, swelling ratios measured in this way were reproducible with an experimental error of <5%. Initially, we left each gel to equilibrate for one week to ensure that equilibrium had been reached. Further studies, however, showed that equilibrium swelling is achieved in <2 h.

Data of the swelling studies are summarized in Table 2 and Figure 1. Table 2 also shows swelling data available from Rapp Polymere Inc. for TentaGel resins as a comparison; it is important to note that comparisons should be taken as a general trend, since data have been gathered from different sources, with swelling ratios being measured differently. Solvents are arranged in increasing order of dielectric constant and covering essentially the whole solvent polarity scale. Since hydrogen bonding seemed to play a particularly important role in the swelling behavior of these systems, the protic solvents have been grouped together separately.

Polymers **5** (MeBDVE) and **6** (AcBDVE) are particularly interesting because they can be viewed as "mimicking" the influence of ether and ester functionalities often encountered in solid-phase synthesis as attachment "points" for linkers and substrates.[56,57] Polymers **5** and **6** swell better than the PS gels in all solvents investigated here. They swell at least double, as compared to PS in nonpolar solvents and several times more in polar and protic solvents. Polymers **5** and **6** also exhibit higher swelling ratios than TentaGel supports in our wide selection of solvents, including polar solvents and MeOH. The exception is water, in which the amphiphilic nature of the grafted PEG gels leads to higher levels of swelling than found for our side-chain ethers.

The fully hydrolyzed gel **7** (OH−BDVE) shows extremely high levels of swelling in polar solvents and negligible levels of swelling in nonpolar ones. This is explained by the high concentration of −OH (~8.5 mmol/g), which as far as we are aware of represents the highest loading level of any polymer support used in solid-phase synthesis. Strong cooperative hydrogen bonding within the gel produces a large number of additional hydrogen-bonded cross-linking sites.

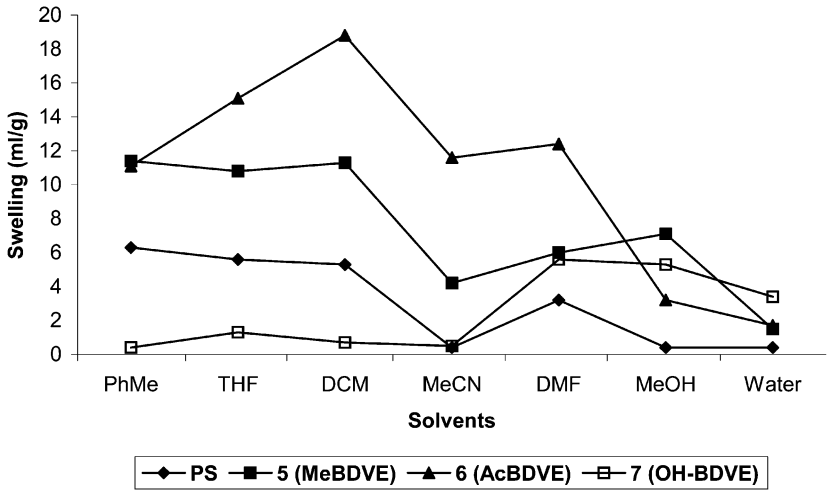


Figure 1. Swelling performance of polyvinyl ether gels and PS resins.

Only solvents capable of disrupting this hydrogen bonding network can cause swelling of the gel. DMF was found to be powerful enough and enables us to further functionalize the high loading resin and strongly hydrophilic gel **7**.

Not only is the level of solvation for these resins outstanding, especially when compared to routinely used supports, such as polystyrene and TentaGel, the rates of swelling are also remarkable. Indeed, when brought in contact with solvent, these resins swell instantly. For example, **5** reaches 95% of its maximum level of swelling in THF in <10 s. This swelling behavior prompted us to christen these supports SLURPS (*s*uperior *l*iquid-*u*ptake *r*esins for *p*olymer-supported *s*ynthesis).

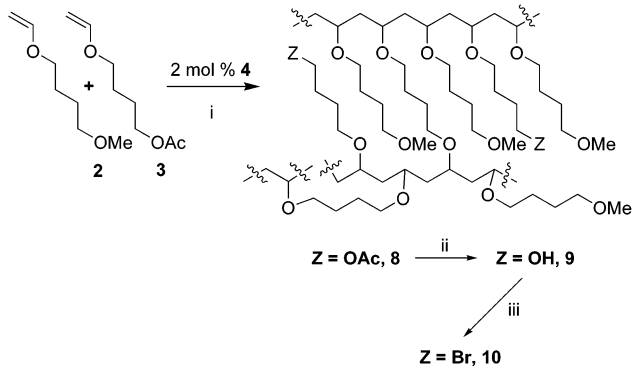
Chemical Stability Studies. SLURPS **5** (MeBDVE) was exposed to a number of chemical stability tests. The chemical structure of **5** corresponds to the basic polymer support structure in the absence of any linker or substrate and, thus, provides information about the inherent chemical stability of SLURPS.

Following an established procedure,[30] SLURPS **5** was treated with a range of common chemical reagents (>20 mmol reagent/g resin) at room temperature for 4−6 h. The resin was stable toward *m*-CPBA (sat. solution in CH_2Cl_2), aq NaOH (2.5 M), aq HCl (10%), DIBAL-H (1 M in CH_2Cl_2), CH_3I, Ac_2O, TFA (50 vol % in CH_2Cl_2), TFA (neat), and *n*-BuLi (2.5 M in hexanes). Qualitatively, no macroscopic changes were observed (i.e., fragmentation of gel particles or significant changes in particle size investigated by visual inspection, color changes, or other visually observable changes). Neither did the treatment produce any changes in the ^1H or ^{13}C NMR spectra. Crucially, levels of swelling determined after the completed set of chemical treatment were identical to those determined prior to it.

These conditions, representative of those typically encountered in SPOS, have been used by others as reliable indication for the chemical inertness of other polymer support scaffolds.[30] Although the most instructive test of chemical stability is through exposure to a much wider range of reaction conditions, we are satisfied that these vinyl ether gels are of sufficient chemical stability to be used in SPOS.

Synthesis of Functional SLURPS. SLURPS−Ac, **8**, is a copolymer of **2** and **3** and was intended to establish the extent

Scheme 3[a]

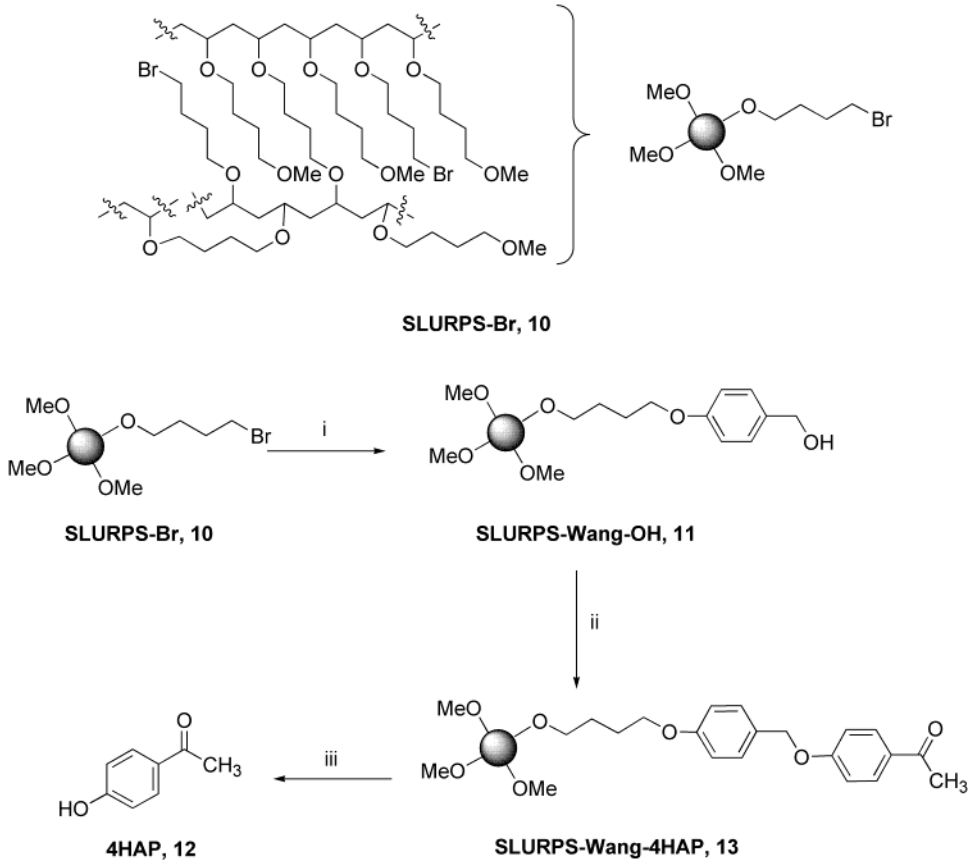


[a] i: Catalytic BF_3-OEt_2, CH_2Cl_2, −78 to 0 °C, N_2, 3 h, 100%. ii: 6 equiv KOH, MeOH/H_2O, reflux, 24 h, 100%. iii: PPh_3, Br_2, imidazole, 10 °C, overnight, 100%

to which loading levels are controllable via the polymerization process. The monomer feed ratio of **2**, **3** and cross-linker **4** was adjusted such that to a gel with 1.5 mmol/g loading and 2 mol % cross-linking would be obtained (Scheme 3). The copolymerization proceeded with quantitative conversion. SLURPS−Ac, **8**, was hydrolyzed quantitatively to give SLURPS−OH, **9.** Subsequent bromination of **9** gave SLURPS−Br, **10**. Elemental analysis of the bromine content of **10** produced a value 1.50 ± 0.02 mmol/g, which is identical to the calculated value on the basis of the feed ratio.

To further explore the applicability of SLURPS for synthetic procedures, we incorporated a Wang linker by simple substitution of SLURPS−Br with sodium 4-hydroxybenzyl phenolate to produce SLURPS−Wang−OH, **11**. This was followed by coupling 4-hydroxyacetophenone, 4HAP, **12**, via Mitsunobu chemistry to **11**, thus affording SLURPS−Wang−4HAP, **13**, as shown in Scheme 4. All reactions reached completion as monitored by IR spectroscopy. Moreover, treatment of **13** with TFA at room temperature allowed recovery of pure **12** in high yield. By being nonstyrenic, these gels allow convenient monitoring of reactions involving aromatic substrates, because the spectral regions in the NMR are free from backbone interference. Furthermore, routine IR spectroscopy with swollen gels squeezed between NaCl plates gave excellent spectral quality

Scheme 4[a]



[a] i: 4-Hydroxybenzyl alcohol, CH_3ONa, DMF, 80 °C, 24 h, 100%. ii: PPh_3, DEAD, 12, THF, 0 °C, overnight, 100%. iii: TFA, room temperature, 3 h.

without the need to resort to more sophisticated instrumentation (e.g., single-bead FTIR spectroscopy).

Conclusions

We have developed a novel class of polymer supports, SLURPS, based on the cationic copolymerization of functional vinyl ethers. It was very satisfying to see that not only polymerization but also the subsequent functionalization of SLURPS proceeded quantitatively.

To our knowledge, the level of solvent compatibility of SLURPS across the solvent polarity scale is exceptional for a polymer support which combines excellent chemical stability under SPOS reaction conditions, outstanding control over loading levels, and the possibility of achieving exceptionally high loading levels.[27−29]

Thus, SLURPS exhibit all the vital characteristics essential for solid-phase synthesis applications.

As an advantage over traditional styrenic resins, SLURPS are spectroscopically transparent in the aromatic regions, which allows for on-resin monitoring of chemical transformations, including aromatic compounds.

One could view SLURPS as being in some way isomeric to Meldal's POEPOP and SPOCC resins. However, there are a number of distinguishing features. Although Meldal's supports exhibit excellent swelling properties and have been proved to perform successfully in enzymatic reactions, their maximum loading levels are rather poor, and control over loading levels is limited. SLURPS, on the other hand, exhibit very good swelling performance (though improvement in water is desirable), excellent control over loading levels, and the opportunity to introduce exceptionally high levels of loading. Their applicability in enzymatic reactions, though, has yet to be established.

We are currently studying SLURPS in the context of polypeptide and organic synthesis with more comprehensive swelling studies also being under way, which we will report soon.

Experimental Section

General. All manipulations of air- and moisture-sensitive compounds were performed under an atmosphere of nitrogen. NMR spectra were recorded on a JEOL GSX270 AC250 (270 MHz ^{1}H, 67.5 MHz ^{13}C). NMR solvents were obtained commercially from Aldrich. Chemical shifts were quoted as δ in parts per million relative to the hydrogenous impurity in the deuterated solvent. References were $CDCl_3$ (^{1}H 7.24 ppm), CD_3OD (^{1}H 3.35 ppm), and CD_3COCD_3 (^{1}H 2.03 ppm). IR spectra were recorded on a Satellite-FTIR (Spectronic-UniCam). Reagents were obtained commercially from Aldrich, Avocado, or Acros at their highest purity available and were used as received unless otherwise stated. Styrene 99% was obtained from Aldrich and purified to remove inhibitors by filtration through silica gel (Silica gel for flash chromatography (BDH), particle size 40−63 μm) and distilled prior to use. DVB was purchased from Aldrich as an 80% mixture of isomers (the main contaminants are ethyl styrene and other alkyl styrenes) and used as received by calculating the amount of DVB 80% needed to provide the

appropriate level of cross-linker. Solution-phase organic reactions were monitored by TLC (Merck TLC aluminum sheets, Silica 60 F_{254}).

Synthesis of Monomer 2 (MeBDVE). 1,4-Butanediol vinyl ether, **1**, (29.0 mL, 27.2 g, 234 mmol) was dissolved in DMSO (50 mL) at 0 °C. KOH (15.0 g, 267 mmol) was added followed by CH_3I (20.0 mL, 45.6 g, 321 mmol). The mixture was left stirring for 10 h. The reaction mixture was poured over brine (100 mL) and extracted with DCM (3 × 100 mL). The combined organic layers were washed with brine (3 × 100 mL) and dried over $MgSO_4$. The solvent was evaporated, and the remaining oil was purified by column chromatography (Silica gel, hexane/EtOAc, 80/20 vol. %). The product was isolated as a colorless liquid. Yield: 19.8 g (65%). ^{1}H NMR (270 MHz, $CDCl_3$), δ (ppm): 6.32 (dd, ^3J = 14.5 Hz, ^3J = 6.5 Hz, 1H); 4.02 (dd, ^3J = 14.5 Hz, ^2J = 1.5 Hz, 1H); 3.82 (dd, ^3J = 6.5 Hz, ^2J = 1.5 Hz, 1H); 3.56 (t, J = 6.0 Hz, 2H); 3.26 (t, J = 6.0 Hz, 2H); 3.19 (s, 3H); 1.57 (m, 4H). ^{13}C NMR (67.5 MHz, $CDCl_3$), δ (ppm): 151.8; 86.0; 72.2; 67.5; 58.3; 26.2; 25.8. FTIR: ν_{max} (cm^{-1}) 2942 (C−H), 2871 (C−H), 2827 (C−H), 1636 (C═C), 1614 (C═C), 1203 (C−O−C), 1122 (C−O-Me). MS (EI) *m*/*z* (%): 130 (3, M$^+$), 115 (1, M − CH_3]$^+$), 102 (2, M − C_2H_4]$^+$), 98 (2, M − MeOH]$^+$), 87 (40, M − C_2H_3O]$^+$), 86 (10, M − C_2H_4O]$^+$), 45 (100, C_2H_5O]$^+$).

Synthesis of Monomer 3 (AcBDVE). 1,4-Butanediol vinyl ether, **1**, (20.0 mL, 18.8 g, 162 mmol) was dissolved in a solution of acetic anhydride (100.0 mL, 108.2 g, 1060 mmol) and triethylamine (40.0 mL, 29.0 g, 287 mmol) at 0 °C under N_2 atmosphere. DMAP (0.5 g, 4 mmol) was added, and the mixture was stirred overnight. The mixture was diluted with diethyl ether (100 mL) and placed in a 2-L beaker with ice. To the stirred mixture was added Na_2CO_3 in small portions until no further gas (CO_2) evolved and basic pH (8−9) was verified in the aqueous layer with pH indicator paper. The mixture was then extracted with diethyl ether (3 × 100 mL), and the combined organic layers were washed with $CuSO_4$ (aqueous saturated solution) (3 × 50 mL) to extract triethylamine and then with brine (portions of 100 mL until the brine layer was colorless). The organic phase was dried over $MgSO_4$, and the solvent was evaporated. The solvent was evaporated, and the remaining oil was purified by column chromatography (silica gel, hexane/EtOAc, 80/20 vol %). The product was isolated as a colorless liquid. Yield: 25.6 g (100%). ^{1}H NMR (270 MHz, $CDCl_3$), δ (ppm): 6.32 (dd, ^3J = 14.5 Hz, ^3J = 7.0 Hz, 1H); 4.02 (dd, ^3J = 14.5 Hz, ^2J = 2.0 Hz, 1H); 3.96 (t, J = 6.5 Hz, 2H); 3.83 (dd, ^3J = 7.0 Hz, ^2J = 2.0 Hz, 1H); 3.56 (t, J = 5.5 Hz, 2H); 1.90 (s, 3H); 1.60 (m, 4H). ^{13}C NMR (67.5 MHz, $CDCl_3$), δ (ppm): 170.6; 151.7; 86.1; 67.0; 63.8; 25.5; 25.2; 20.7. FTIR: ν_{max} (cm^{-1}) 2956 (C−H), 2876 (C−H), 1739 (C═O), 1636 (C═C), 1616 (C═C), 1242 (C−C(═O)−O), 1047 (C−O−C). MS (EI) *m*/*z* (%): 158 (30, M$^+$), 143 (10, M − CH_3]$^+$), 131 (10, M − C_2H_3]$^+$), 115 (25, M − C_2H_3O]$^+$), 98 (20, M − AcOH]$^+$), 73 (30, M − C_2H_3O − C_2H_2O]$^+$), 55 (70, M − C_2H_3O − C_2H_2O − H_2O]$^+$), 43 (100, C_2H_3O]$^+$).

Synthesis of PS Model via Free Radical Polymerization of Styrene. A standard PS gel (cross-linked with 2 mol % DVB) was prepared as follows: In a sealed vial, styrene (7.88 mL, 7.14 g, 68.6 mmol) and DVB 80% (0.25 mL, 1.40 mmol DVB) were dissolved in THF (8 mL). The reaction mixture was deoxygenated by bubbling nitrogen for 15 min. After that, AIBN (0.15 g, 0.91 mmol) dissolved in THF (2 mL) was added to the vial, and the deoxygenation proceeded for an additional 5 min. Finally, the sealed vial was placed in an oven at 60 °C and left until gelation occurred (<30 min) and an additional 3 h to ensure reaction completion. The polymer formed was filtered and washed several times (DCM, acetone, THF, ethyl acetate) and dried under vacuum at room temperature until constant weight was reached. Conversion to polymer materials was 100%. Isolated polymer after filtration: 6.0 g (83%). ^{1}H NMR (270 MHz, $CDCl_3$), δ (ppm): 7.33 (broad s, 5 H); 3.99 (broad s); 1.99 (broad s). ^{13}C NMR (67.5 MHz, $CDCl_3$), δ (ppm): 145.5 (broad); 129.4−128−4 (broad); 44.0 (broad); 41.2; 25.0 (CH_2−CH_3 from ethyl styrene as impurity in DVB).

General Procedure for Cationic Solution Polymerization. In a dried 50-mL round-bottomed flask under nitrogen at −78 °C, dried CH_2Cl_2 (10 mL), an appropriate monomer (68.60 mmol), and corresponding cross-linker (1.40 mmol, 2 mol % cross-linker) were added. BF_3−OEt_2 (0.05 mL, 57 mg, 0.40 mmol) was added, and the mixture was allowed to warm slowly standing under nitrogen until gelation occurred. Afterward, the mixture was allowed to stand for 2 h, slowly warming. Then chilled NH_3 (0.50 mL, 35% in H_2O, 0.88 g/mL) in MeOH (4 mL) was added. The mixture was allowed to warm to room temperature, more MeOH (30 mL) was added, and then the gel was filtered and washed several times with dichloromethane, tetrahydrofuran, ethanol, acetone, ethyl acetate, and diethyl ether (3 × 30 mL each). The gel was smashed to small particles (0.1−0.5 mm) while swollen. The final gel was dried under vacuum at room temperature until constant weight was reached. In all vinyl ether cases, the final product was an off-white sticky solid that adheres to glass and plastics but not to metals. In all vinyl ether cases, when swollen, the gel was very easy to handle and filter. Conversion: 100% of starting material converted to polymeric structures as monitored by NMR and GC analysis of the crude filtrate.

Model PS Gels (PS−C and PS−R). ^{1}H NMR (270 MHz, $CDCl_3$), δ (ppm): 7.33 (broad s, 2.6H); 3.99 (broad s, 0.5H); 1.99 (broad s, 1.3H). ^{13}C NMR (67.5 MHz, $CDCl_3$), δ (ppm): 145.5; 130−125 (broad); 44.0 (broad); 41.2; 25.0 (CH_2−CH_3 from ethyl styrene as impurity in DVB).

Gel 5 (MeBVDE). ^{1}H NMR (270 MHz, $CDCl_3$), δ (ppm): 3.46 (broad s, 1.13 H); 1.77 (broad s, 0.96 H). ^{13}C NMR (67.5 MHz, $CDCl_3$), δ (ppm): 73.9; 72.9; 68.8; 58.7; 40.7; 27.2; 26.9.

Gel 6 (AcBDVE). ^{1}H NMR (270 MHz, $CDCl_3$), δ (ppm): 4.07 (broad s); 3.51 (broad s); 2.04 (broad s); 1.67 (broad s). ^{13}C NMR (67.5 MHz, $CDCl_3$), δ (ppm): 171.1; 73.8; 68.3; 64.3; 40.4; 26.9; 25.8; 21.0.

General Procedure for the Hydrolysis of Acetate Gels. The corresponding gel (8.0 g) was swollen with a mixture of EtOH/H_2O (70/30 vol %, 20 mL/g resin), and the mixture

was refluxed for 24 h in the presence of KOH (6.0 equiv/acetate group). Afterward, the mixture was cooled to room temperature, and the gel was filtered and washed with EtOH/H_2O (66/34 vol %, 150 mL each) until the pH of the filtrates was neutral. Then the gel was washed with EtOH (3 × 100 mL), THF (3 × 100 mL), and Et_2O (3 × 100 mL), and the gel was dried under vacuum at room temperature until constant weight was reached.

Gel 7 (OH−BDVE). Yield: 100%. ^{1}H NMR (270 MHz, $CDCl_3$), δ (ppm): 3.98 (shoulder); 3.35 (broad s); 1.40 (broad s). ^{13}C NMR (67.5 MHz, $CDCl_3$), δ (ppm): 78.7−78.0; 74.0−67.0; 62.1, 41.5−39.0; 29.8; 27.3.

Synthesis of Functional Resin, SLURPS−Ac, 8. To synthesize a functional resin, **2** (7.108 g, 55.00 mmol) and **3** (2.215 g 14.00 mmol) were copolymerized cationically with **4** (200 mg, 1.40 mmol) as cross-linker. The procedure was followed. Conversion: 100%. Yield of macrogel: 7.6 g (80%). ^{1}H NMR (270 MHz, $CDCl_3$), δ (ppm): 4.02 (broad shoulder, 0.15 H); 3.29 (broad s, 0.69 H); 2.00 (broad shoulder, 0.35 H); 1.56 (broad s, 0.44 H). ^{13}C NMR (67.5 MHz, $CDCl_3$), δ (ppm): 170.0; 73.7; 72.6; 68.7; 64.4; 58.6; 41.5; 39.5; 27.1; 26.7; 25.7; 21.0. FTIR: ν_{max} (cm^{-1}) 1730 (C═O), 1111 (C−O).

SLURPS−OH, 9. Yield: 100%. ^{1}H NMR (270 MHz, $CDCl_3$), δ (ppm): 3.34 (broad s, 0.74 H); 2.62 (broad, 0.60 H). ^{13}C NMR (67.5 MHz, $CDCl_3$), δ (ppm): 73.8; 72.7; 68.8; 62.5; 58.6; 39.6; 30.1; 27.1; 26.7; 25.7. FTIR: ν_{max} (cm^{-1}) 3437 (broad, O−H), 1111 (C−O).

Synthesis of SLURPS−Br, 10. SLURPS−OH, **9**, (2.0 g, 3.3 mmol) was suspended in DCM (60 mL) and treated with triphenylphosphine (4.0 g, 15 mmol) and imidazole (1.0 g, 15 mmol). After the reagents were dissolved, the suspension was cooled to 10 °C in a water bath and treated dropwise with Br_2 (0.80 mL, 2.4 g, 15 mmol). The reaction was left stirring overnight at room temperature. The resin was filtered and washed with DMF, H_2O, DMF, acetone, THF, and DCM (3 × 60 mL each) and then dried under vacuum at room temperature until constant weight was reached. Conversion 100%.Yield: 2.3 g (>95%). ^{1}H NMR (270 MHz, $CDCl_3$), δ (ppm): 3.33 (broad s, 0.65 H); 1.60 (broad, 0.62 H). ^{13}C NMR (67.5 MHz, $CDCl_3$), δ (ppm): 73.8; 72.7; 69.0−67.8; 58.6; 41.5−39.5; 33.9; 30.0; 29.1; 27.1; 26.7. FTIR: ν_{max} (cm^{-1}) 1092 (C−O); 665 (C−Br). Elemental microanalysis: 12.0 ± 0.2% Br (1.50 ± 0.02 Br/g resin).

Synthesis of SLURPS−Wang−OH, 11. Dry SLURPS−Br, **10**, (1.0 g, 1.5 mmol) was swollen in DMF (10 mL), and then 4-hydroxybenzyl alcohol (0.43 g, 3.5 mmol) was added, followed by sodium methoxide (0.20 g, 3.5 mmol). The suspension was stirred at 80 °C for 24 h under N_2. Afterward, the resin was filtered and washed with DMF (3 × 50 mL), MeOH (3 × 50 mL), DCM (3 × 50 mL), and Et_2O (3 × 50 mL) and then dried under vacuum at room temperature until constant weight was reached. FTIR: ν_{max} (cm^{-1}) 3445 (broad, O−H), 1090 (C−O). Conversion (IR): 100%.

Synthesis of SLURPS−Wang−4HAP, 13. Dry SLURPS−Wang−OH, **11**, resin (0.5 g, 0.7 mmol) was swollen with THF (20 mL) at 0 °C under N_2. Then triphenylphosphine (0.90 g, 3.4 mmol) was added, and the mixture was stirred until all the phosphine dissolved. DEAD (0.40 mL, 2.5 mmol) was added dropwise at 0 °C, and the mixture was stirred for 15 min. A solution of 4-hydroxyacetophenone (0.310 g, 2.25 mmol) in THF (5 mL) was added dropwise, and then the mixture was left stirring overnight, allowing it to slowly reach room temperature. Afterward, the resin was filtered and washed with THF (3 × 20 mL), EtOH (3 × 20 mL), THF (3 × 20 mL), EtOH (3 × 20 mL), DCM (3 × 20 mL), and Et_2O (3 × 20 mL) and then dried under vacuum at room temperature until constant weight was reached. FTIR: ν_{max} (cm^{-1}) 1714, 1093. Conversion (IR): 100%.

Cleavage of SLURPS−Wang−4HAP, 13. SLURPS−Wang−4HAP, **13** (0.5 g, 0.6 mmol) was treated with TFA (10 mL) at room temperature for 3 h. After this period, the resin was washed with DCM (3 × 20 mL), and the combined filtrates were evaporated and dried under vacuum at room temperature for 5 h. NMR analysis showed that the residue was constituted by clean **12** (70 mg, 85%).

Swelling Studies. Dry samples of gels were weighed and placed in vials to which the appropriate solvent was added in excess. The vials were sealed, and the samples were allowed to swell for 1 week at room temperature under frequent swirling. Excess solvent was removed by filtration, the surfaces of the wet resins were rapidly dried with filter paper, and the swollen gel was weighed.

The swelling ratio was calculated as volume of solvent incorporated (mL)/weight of dry gel (g) (This parameter was calculated by converting the increase of weight of the gel during swelling into the volume using the appropriate solvent density at room temperature).

Chemical Stability Studies. Gel 5 (MeBDVE) (0.5 g) was placed in a vial in the presence of an appropriate reagent (>20 mmol reagent/g resin, > 2.7 equiv reagent/-OMe) at room temperature for 4−6 h. The treated resin was visually inspected for macroscopic changes. After that, the resin was filtered and washed extensively with DCM, dried under vacuum, and analyzed by gel-phase NMR.

The resin was shown to be stable when treated with *m*-CPBA (sat. solution in CH_2Cl_2), aq NaOH (2.5 M), aq HCl (10%), DIBAL-H (1 M in CH_2Cl_2), CH_3I, Ac_2O, TFA (50% volume in CH_2Cl_2), TFA (neat), and *n*-BuLi (2.5 M in hexanes).

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