Title: SLURPS: Novel non-PEG derived polyethers as solid supports. Part 1:

Synthesis, swelling studies and functionalisation.

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Abstract: Novel non-PEG derived polyether resins, coined SLURPS (Superior Liquid Uptake Resins for Polymer-supported Synthesis), 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 functionalisation 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.

Graphical Abstract:
Text:

Introduction:

Polymer supports have revolutionized synthesis and separation as exemplified by combinatorial drug, polypeptide and oligonucleotide syntheses,\textsuperscript{1-8} immobilized (bio)catalysts and reagents\textsuperscript{9} as well as affinity chromatography and solid phase extraction processes.\textsuperscript{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 bio-catalysts, 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 be developing at a much faster pace than the parallel and combinatorial synthesis of screenable molecular entities.\textsuperscript{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 noticed only during separation.\textsuperscript{27-29} Obviously, in reality interactions between the polymer and any of the other molecular species present, including solvent, occur 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, spacer, or any other molecule (e.g. catalyst ligands) of interest can be integrated,
- mechanically robust in a flow reactor format and with control over flow properties via specific variation of crosslinking level and co-monomer incorporation.

Although most successful supports exhibit some of these characteristics no single support has been shown to combine all of them.\textsuperscript{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 like the polyether crosslinked polystyrene resin JandaJel\textsuperscript{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.\textsuperscript{27-29} Sufficient hydrophilicity of 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).\textsuperscript{27-29} Other supports, such as polyacrylamides (Sheppard resin)\textsuperscript{33} and polyether crosslinked polyacrylamides (PEGA)\textsuperscript{34} exhibit excellent compatibility with hydrophilic solvents, responsible for their excellent performance in peptide synthesis. However these supports have only limited general applicability due to their lack of chemical stability (amide groups) under reaction conditions usually encountered in organic synthesis, which precludes their use in SPOS.
The 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, functionalisation 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 C₄ side chain, we expected chemical transformations to proceed smoothly without compromising the ability to achieve high loading levels.

Indeed, a crosslinked polymer with 98 % molar equivalent of 1 and 2 % of crosslinker 4 will result in ~8.5 mmol –OH/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. Optimization attempts have resulted so far only in decreased yields due to competing C-alkylation of the vinyl ether moiety.

Since vinyl ethers only polymerize poorly via free radical chemistry due to 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\textsuperscript{37,38} and thus 1 was protected as acetate 3 (AcBDVE) shown in Scheme 1. Finally, 1,4-butane diol divinyl ether 4 (BDDVE) was chosen as crosslinker 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 procedure circumvents the time consuming development of non-aqueous suspension polymerization conditions thus allowing us to more speedily establish the suitability of these novel gels for solid-phase synthesis.\textsuperscript{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 crosslinking levels between 1 and 2 %. We chose to prepare a 2 % crosslinked resin because the higher content of crosslinks ensures a mechanically more robust support albeit with decreased levels of swelling. Since our initial swelling studies indicated already exceptional swelling behavior with 2 % crosslinker we kept the level of crosslinking at 2 % throughout our investigation.

Monomers 2 and 3 were copolymerized cationically (see Scheme 2) in the presence of 2 mol. % of 1,4-butane diol 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 indicated unambiguously complete monomer incorporation. With the feed ratio of monomers being identical to the composition of the gel network, one can easily control loading and crosslinking levels by simply adjusting 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 % by weight) and a fraction composed of smaller gel particles and microgels (20 %); both gel fractions are useful formats for SPOS.

In order 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 particles size between 0.5 – 2 mm.

Gel 6, in which 1 was protected as acetate 3, was hydrolyzed quantitatively by refluxing it in methanol/water (60/40 % vol., 25 mL/g resin) with an excess of KOH (6 eq. 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 (Tg) but can be handled and filtered very easily once swollen. Once the resin was swollen drying could only be achieved through forcing conditions such as leaving the gel for long periods under vacuum.

Therefore, the stickiness of the dry material was never a hindrance 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 was found to be quantitative for both PS-C and PS-R.
Swelling studies

For lowly crosslinked, 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. 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 being sticky in the dry state which precluded packing of a column as required by the traditional syringe method. However, swelling ratios measured in this way were reproducible with an experimental error of less than 5 %. Initially we left each gel to equilibrate for one week to ensure that equilibrium has been reached. Further studies however showed that equilibrium swelling is achieved in less than two hours.

Data of the swelling studies are summarised in Table 2 and Figure 1. Solvents are arranged in increasing order of dielectric constant and covering essentially the whole solvent polarity scale. Since hydrogen bonding seemed to play an important role in swelling 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.
swell better than the PS gels in all solvents investigated here. They swell at least twice as much as PS in non-polar solvents and several times more in polar and protic solvents. The fully hydrolyzed gel 7 (OH-BDVE) shows extremely high levels of swelling in polar solvents and negligible levels of swelling in non-polar 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 crosslinking sites. Only solvents capable of disrupting the hydrogen bonding network can cause swelling of the gel. DMF was found to be a powerful enough, and enables us to further functionalise even a high loading resin as strongly hydrophilic as 7.

Not only is the level of solvation for these resins outstanding, the kinetics 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 less than 10 seconds. This swelling behavior prompted us to christen these supports SLURPS (Superior Liquid Uptake Resins for Polymer-supported Synthesis).

**Chemical stability studies**

SLURPS 5 (MeBDVE) was exposed to a number of chemical stability tests. The chemical structure of 5 is equivalent 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, SLURPS 5 was treated with a range of common chemical reagents (>20 mmol reagent/g resin) at room temperature for 4 to 6 hrs. The resin was stable towards m-CPBA (sat. solution in CH₂Cl₂), aq. NaOH (2.5 M), aq. HCl (10 %), DIBAL-H (1M in CH₂Cl₂), CH₃I, Ac₂O, TFA (50 vol. % in CH₂Cl₂), TFA (neat)
and n-BuLi (2.5M in hexanes). Qualitatively, no macroscopic changes (i.e. fragmentation of gel particles or significant changes in particle size investigated by visual inspection, color changes or other visually observable changes) were observed. Neither did the treatment produce any changes in the $^1$H 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. Although the most instructive test of chemical stability is through exposure to a wide 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 of control over loading levels that can be achieved by the polymerization process. The monomer feed ratio of 2, 3 and crosslinker 4 was adjusted to obtain a gel with 1.5 mmol/g loading with 2% crosslinking (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 gave 1.50 ± 0.02 mmol/g, identical to the calculated value on the basis of the feed ratio.

In order 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-hydroxy acetophenone, 4HAP, 12, via Mitsunobu chemistry, 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 yields. By being non-styrenic these gels allow convenient monitoring of reactions involving aromatic substrates as 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 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 functionalisation of SLURPS was quantitative. 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, exceptional control over loading levels AND the possibility of achieving such 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. While 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 accessibility of an extremely high maximum level 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 in the near future.

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 $\delta$ in ppm relative to the hydrogenous impurity in the deuterated solvent. References were, CDCl$_3$ ($^1$H 7.24 ppm), CD$_3$OD ($^1$H 3.35 ppm), CD$_3$COCD$_3$ ($^1$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 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 $\mu$m) 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 crosslinker. 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$_3$I (20.0 mL, 45.6 g,
The mixture was left stirring for 10 hrs. The reaction mixture was poured over brine (100 mL) and extracted with DCM (3 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL) and dried over MgSO₄. 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 %).

¹H NMR (270 MHz, CDCl₃), δ (ppm): 6.32 (dd, ³J= 14.5 Hz, ³J=6.5Hz, 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)

¹³C NMR (67.5 MHz, CDCl₃), δ (ppm): 151.8; 86.0; 72.2; 67.5; 58.3; 26.2; 25.8

FTIR: νmax (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-CH₃⁺), 102 (2, M-C₂H₄⁺), 98 (2, M-MeOH⁺), 87 (40, M-C₂H₃O⁺), 86 (10, M-C₂H₄O⁺), 45 (100, C₂H₅O⁺).

**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 triethyl amine (40.0 mL, 29.0 g, 287 mmol) at 0 °C under N₂ 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 Na₂CO₃ in small portions until no further gas (CO₂) 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 x 100 mL) and the combined organic layers were washed with CuSO₄ (aqueous saturated solution) (3 x 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 MgSO₄.
and the solvent 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$_3$), $\delta$ (ppm): 6.32 (dd, $^3$J= 14.5 Hz, $^3$J=7.0 Hz, 1H); 4.02 (dd, $^3$J=14.5 Hz, $^2$J=2.0 Hz, 1H); 3.96 (t, J=6.5 Hz, 2H); 3.83 (dd, $^3$J=7.0 Hz, $^2$J=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$_3$), $\delta$ (ppm): 170.6; 151.7; 86.1; 67.0; 63.8; 25.5; 25.2; 20.7.

FTIR: $\nu$ 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$_2$H$_5$), 115 (25, M – C$_2$H$_3$O), 98 (20, M – AcOH), 73 (30, M – C$_2$H$_5$O – C$_2$H$_5$O), 55 (70, M – C$_2$H$_3$O – C$_2$H$_5$O – H$_2$O), 43 (100, C$_2$H$_5$O$^+$).

**Synthesis of PS model via free radical polymerization of styrene:**

A standard PS gel (crosslinked with 2 % 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 minutes. After that, AIBN (0.15 g, 0.91 mmol) dissolved in THF (2 mL) was added into the vial and the deoxygenation proceeded for 5 further minutes. Finally the sealed vial was placed in an oven at 60 °C and left until gelation occurred (less than 30 minutes) and 3 more hours 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$_3$), $\delta$ (ppm): 7.33 (broad s, 5 H); 3.99 (broad s); 1.99 (broad s)
$^{13}$C NMR (67.5 MHz, CDCl$_3$), $\delta$ (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 50ml round-bottomed flask under nitrogen, at – 78 °C, dried CH$_2$Cl$_2$ (10 mL), appropriate monomer (68.60 mmol) and corresponding crosslinker (1.40 mmol, 2 % crosslinker) 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. Afterwards, the mixture was allowed to stand for 2 hrs slowly warming. Then, chilled NH$_3$ (0.50 mL, 35 % in H$_2$O, 0.88 g/mL) in MeOH (4 mL) was added. The mixture was left 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 x 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$_3$), $\delta$ (ppm): 7.33 (broad s, 2.6 H); 3.99 (broad s, 0.5 H); 1.99 (broad s, 1.3H)

$^{13}$C NMR (67.5 MHz, CDCl$_3$), $\delta$ (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$_3$), $\delta$ (ppm): 3.46 (broad s, 1.13 H); 1.77 (broad s, 0.96 H).
$^{13}$C NMR (67.5 MHz, CDCl$_3$), $\delta$ (ppm): 73.9; 72.9; 68.8, 58.7; 40.7; 27.2; 26.9.

**Gel 6 (AcBDVE):**

$^1$H NMR (270 MHz, CDCl$_3$), $\delta$ (ppm): 4.07 (broad s); 3.51 (broad s); 2.04 (broad s); 1.67 (broad s).

$^{13}$C NMR (67.5 MHz, CDCl$_3$), $\delta$ (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$_2$O (70/30 vol. %, 20 mL/g resin) and the mixture was refluxed for 24 hrs in the presence of KOH (6.0 eq./acetate group). Afterwards, the mixture was cooled to r.t. and the gel was filtered and washed with EtOH/H$_2$O (66/34 vol.%, 150 mL each) until pH of filtrates was neutral. Then the gel was washed with EtOH (3 x 100 mL), THF (3 x 100 mL), Et$_2$O (3 x 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$_3$), $\delta$ (ppm): 3.98 (shoulder); 3.35 (broad s); 1.40 (broad s).

$^{13}$C NMR (67.5 MHz, CDCl$_3$), $\delta$ (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 crosslinker. The procedure shown above was followed. Conversion: 100 %. Yield of macrogel: 7.6 g (80 %).

$^1$H NMR (270 MHz, CDCl$_3$), $\delta$ (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: $\nu$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: $\nu$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 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 r.t. The resin was filtered and washed with DMF, H$_2$O, DMF, acetone, THF and DCM (3 x 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: $\nu$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 hrs under N₂. Afterwards the resin was filtered and washed with DMF (3 x 50 mL), MeOH (3 x 50 mL), DCM (3 x 50 mL) and Et₂O (3 x 50 mL) and then dried under vacuum at room temperature until constant weight was reached.

FTIR: νmax (cm⁻¹): 3445 (broad, O-H), 1090 (C-O).

**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 N₂. 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 minutes. 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 to slowly reach r.t. Afterwards the resin was filtered and washed with THF (3 x 20 mL), EtOH (3 x 20 mL), THF (3 x 20 mL), EtOH (3 x 20 mL), DCM (3 x 20 mL) and Et₂O (3 x 20 mL) and then dried under vacuum at room temperature until constant weight was reached.

FTIR: νmax (cm⁻¹): 1714, 1093.

**Cleavage of SLURPS-Wang-4HAP, 13:**

SLURPS-Wang-4HAP, 13 (0.5 g, 0.6 mmol) was treated with TFA (10 mL) at r.t. for 3 hrs. After this period the resin was washed with DCM (3 x 20 mL) and the combined filtrates were evaporated and dried under vacuum at room temperature for 5 hrs. 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 left to swell for a week at room temperature under frequent swirling. Excess of 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 appropriate reagent (>20 mmol reagent/g resin, > 2.7 eq. reagent/-OMe) at room temperature for 4 to 6 hrs. 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 showed to be stable when treated with m-CPBA (sat. solution in CH₂Cl₂), aq. NaOH (2.5 M), aq. HCl (10 %), DIBAL-H (1M in CH₂Cl₂), CH₃I, Ac₂O, TFA (50 % volume in CH₂Cl₂), TFA (neat) and n-BuLi (2.5M in hexanes).

**Acknowledgements**

Support of this research by the Department of Chemistry, Imperial College (T.A. for GC), CVCP (ORS Award for GC) and Avecia Ltd. (Case Award) is gratefully acknowledged.
References


### Tables:

#### Table 1:

<table>
<thead>
<tr>
<th>Gel</th>
<th>Monomer(s) (mmol)</th>
<th>Crosslinker (mmol)</th>
<th>Solvent (mL)</th>
<th>Type</th>
<th>Initiator (mmol)</th>
<th>Temp. of gelation (°C)</th>
<th>Conversion to polymer (%)</th>
<th>Yield of isolated macrogel (%)</th>
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<tbody>
<tr>
<td>Model PS –R</td>
<td>Styrene (68.6)</td>
<td>DVB (1.40)</td>
<td>THF (8)</td>
<td>Free radical</td>
<td>AIBN (0.91)</td>
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<td>100</td>
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<td>DVB (1.40)</td>
<td>DCM (10)</td>
<td>Cationic</td>
<td>BF₃OEt₂ (0.40)</td>
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<td>80</td>
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<td>5</td>
<td>2 (68.6)</td>
<td>4 (1.40)</td>
<td>DCM (10)</td>
<td>Cationic</td>
<td>BF₃OEt₂ (0.40)</td>
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<td>100</td>
<td>80</td>
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<td>8</td>
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Table 2:

<table>
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<td>3.4</td>
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</table>
Figure Legends:

Legend to Table 1:

Table 1. Polymerization conditions for the synthesis of gels

Legend to Table 2:

Table 2. Swelling studies.

*Pre-weighed, crushed, dry resins were left equilibrating in the corresponding solvent for a week. After filtration, weight of incorporated solvent was measured and the swelling ratios (Sw) calculated as Sw = (Ws-Wd) / (D × Wd) where Ws: weight of swollen resin; Wd: weight of dry resin; D: density of the corresponding solvent.

Legend to Figure 1:

Figure 1: Swelling performance of polyvinyl ether gels is better than PS resins.

Legend to Scheme 1:

Scheme 1. i: CH₃I, KOH, DMSO, 65 %. ii: Ac₂O, Et₃N, DMAP, 100 %.

Legend to Scheme 2:

Scheme 2: i: catalytic BF₃-OEt₂, CH₂Cl₂, - 78 up to 0 °C, N₂, 3 hrs, 100 %. ii: 6 eq. KOH, MeOH / H₂O, reflux, 24 hrs, 100 %.

Legend to Scheme 3:

Scheme 3: i: catalytic BF₃-OEt₂, CH₂Cl₂, - 78 up to 0 °C, N₂, 3 hrs, 100 %. ii: 6 eq. KOH, MeOH / H₂O, reflux, 24 hrs, 100 %. iii: PPh₃, Br₂, Imidazole, 10 °C, overnight, 100 %.

Legend to Scheme 4:

Scheme 4: i: 4-hydroxybenzyl alcohol, CH₃ONa, DMF, 80 °C, 24 hrs, 100 %. ii: PPh₃, DEAD, 12, THF, 0 °C, overnight, 100 %. iii: TFA, r.t., 3 hrs.
Schemes:

Scheme 1:

\[
\begin{align*}
&1 &\xrightarrow{i \text{ or } ii} & OR \\
&O-\text{CH}_2\text{-CH}_2\text{-OH} & & \text{OR}
\end{align*}
\]

i \( R = \text{Me}, \ 2 \)

ii \( R = \text{Ac}, \ 3 \)
Scheme 2:

Z=OMe, 2
Z=OAc, 3

2 mol % 4

Z=OMe, 5
Z=OAc, 6

Z=OH, 7
Scheme 3:

\[ \text{Scheme 3:} \]

\[ \begin{array}{c}
\text{2 mol %} \quad \text{4} \\
\text{Z = OAc, 8} \\
\text{Z = OH, 9} \\
\text{Z = Br, 10}
\end{array} \]
Scheme 4:

SLURPS-Br, 10

SLURPS-Br, 10 → SLURPS-Wang-OH, 11

4HAP, 12 → SLURPS-Wang-4HAP, 13
Figures:

Figure 1:

![Swelling vs Solvents Graph](image)

Solvents: PhMe, THF, DCM, MeCN, DMF, MeOH, Water

Swelling (ml/g) for:
- PS
- 5 (MeBDVE)
- 6 (AcBDVE)
- 7 (OH-BDVE)