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Synthesis of beaded poly(vinyl ether) solid supports with unique solvent compatibility

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ABSTRACT

Poly(vinyl ether) gels SLURPS (Superior Liquid Uptake Resin for Polymer-supported synthesis) with low cross-linking levels have been synthesized for the first time in beaded form using a non-aqueous inverse suspension polymerisation approach. The synthetic protocol was optimized with regards to several parameters including reactions conditions, type and concentration of suspension stabilizer and controlled low temperature addition of co-initiator. Particle size measurements confirm the production of beads with average diameters of 700–950 μm. Optimization of the monomer composition of the poly(vinyl ether) gels resulted in a novel beaded polymer support with considerably improved as well as unique swelling characteristics in solvents ranging from hexane to water. The synthetic utility of the new gel was confirmed by carrying out a set of transformations with complete conversion leading to a useful amino and hydroxy terminated solid-phase precursor resin. Reaction progress could be monitored easily by ^{1}H and ^{13}C gel-phase NMR.

1. Introduction

Over many years polymer supports have become a common tool in synthesis and are of particular importance in solid-phase synthesis of peptides, oligonucleotide and for drug discovery [1–9]. Since the pioneering experiments by Merrifield [10] the use of polymer supports in the laboratory has become ubiquitous, driven in many cases by the ease of use, separation and automation expanding its utility into high-throughput experimentation and combinatorial drug and materials synthesis [11–15]. Although soluble polymers have received some attention [6,16,17] insoluble, inert and cross-linked supports form the majority of solid-phases exploited for chemical transformations [4]. Typically, a starting material of interest is attached at a specific location to the support *via* a linker molecule, the latter designed to withstand all reaction conditions used in a multi-step synthetic sequence, before release of the final product from the polymer support under a set of specific cleavage conditions [4,9,18,19]. This process is amenable to simplify and automate purification and isolation steps. Polymer supports for iterative chemical reaction schemes like those used in peptide and oligonucleotide syntheses have been developed into commercially important processes. On the other hand multi-step transformations have proven to be more difficult to translate into solid-phase processes. Perhaps the most crucial reason is the unavailability of a polymer support that is chemically inert to reagents and catalysts while being compatible with the widest possible range of solvent polarities. In the limit a support is desirable that, other than imparting insolubility to the substrate, performs as if the same reaction had taken place in solution.

To approach a solvent-like reaction environment a considerable range of polymer supports have been designed and evaluated since Merrifield opted for chloromethylated polystyrene (PS) gel beads in his seminal work of synthesising a tetrapeptide [1,10]. The PS gel format itself has been modified and made more solvent compatible through grafting of mainly hydrophilic polymers (poly(ethylene glycol) (PEG) in particular). Greater structural variations to improve on the original support have included individually or in combination chemically different polymer backbones, various polymer architectures and developments of new physical formats [4,18,19].

Our work in this area has been aimed at developing a “universal” support, which we have defined as one inert to most common reaction conditions and reagents in addition to being compatible with as broad a spectrum of solvents as possible. Towards this goal we identified gel-type cross-linked poly(vinyl ether)s (PVE) as suitable candidates for this task which we termed SLURPS (Superior

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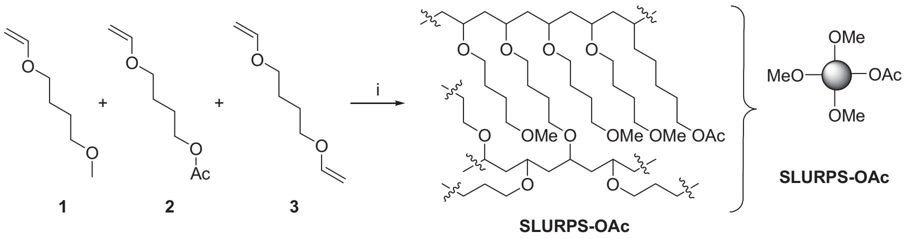


Scheme 1. Synthesis of SLURPS-C4-OAc. i) CH_2Cl_2, BF_3OEt_2, −78 °C to −10 °C, H_2O/NH_3, 100% conversion, 80% yield.

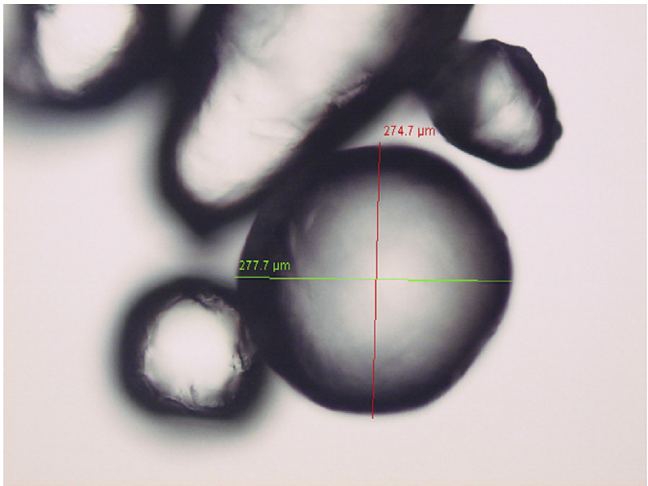


Fig. 1. Optical image of a representative sample of beaded SLURPS-gels.

Liquid Uptake Resin for Polymer-supported synthesis) [20,21]. In our initial report we demonstrated that these poly(vinyl ether) networks can be synthesized with precise control over loading levels, are amenable to efficient functionalization whilst maintaining good swelling performance across a wide spectrum of solvent polarities. More recently we showed that SLURPS-gels perform well as solid-phase in peptide synthesis producing *penta*peptide Leu-enkephalin [21]. Purity levels were equivalent to those achieved using the best available commercial resins for this synthesis at comparable loading levels without any need for resin optimization. In addition we showed SLURPS to produce the pentapeptide even at more than a five-fold increased loading level (8.5 mmol/g, a loading level unprecedented in peptide synthesis) albeit with some loss of product purity. Furthermore through organic transformation needing aqueous reaction conditions we illustrated the excellent compatibility of SLURPS for highly polar water-based reaction milieus.

As we have so far produced our SLURPS-gels as random particles we were keen on producing a support format which would be more convenient for resin handling and thus more widely usable. Despite some reservation that we may not be able to identify a biphasic solvent system to carry out suspension polymerisation, as our polymer support swells in most solvents, we set out to produce SLURPS directly as beaded polymer supports to enhance their versatility.

2. Results and discussion

2.1. Beaded SLURPS synthesis

Beaded polymer supports are typically produced by radical polymerisation of a suspension with water as the continuous phase. Vinyl ethers used in this study can only be homopolymerized *via* cationic polymerisation methods proceeding at temperatures well below 0 °C, ruling out water as continuous phase. Accounting for these restrictions, precedent for a cationic suspension polymerisation of vinyl ethers has been provided by deLeuze and co-workers a few years ago [22]. Their system uses a partially fluorinated copolymer as inverse suspension stabilizer and perfluorooctane as non-aqueous continuous phase. Chemical initiation at low temperatures still proved too reactive, but they found that photopolymerisation at room temperature was successful, albeit requiring 50 mol% cross-linking levels to impart enough rigidity on the polymer beads to minimize agglomeration during the reaction. SPOCC (Superpermeable Organic Combinatorial Chemistry) supports developed by Meldal et al. have also been described in beaded form as the result of a cationic ring-opening polymerisation of oxetane-capped monomers employing silicone oil as water substitute and a custom-designed stabilizer copolymer containing trimethylsiloxy-dimethylsilylpropyl sidechains [23]. It is apparent from these two examples, which are the only ones applicable to our target, that identifying appropriate conditions for a cationic inverse suspension polymerisation is non-trivial. Successful bead production requires an effective suspension stabilizer, especially in this case as the low T_g of the resulting polymer beads increases further the tendency of the forming beads to agglomerate. Good control over the strongly exothermic nature of vinyl ether polymerisation is

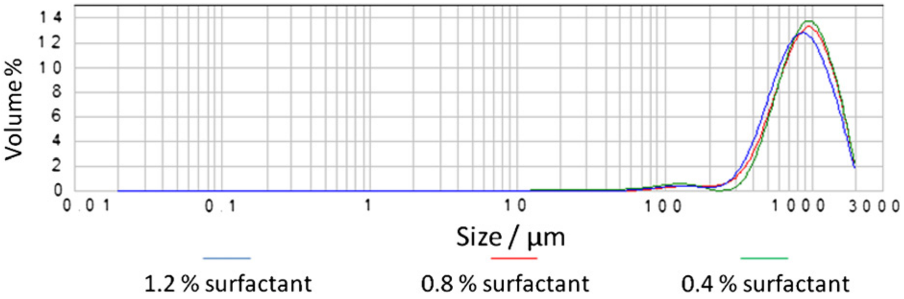
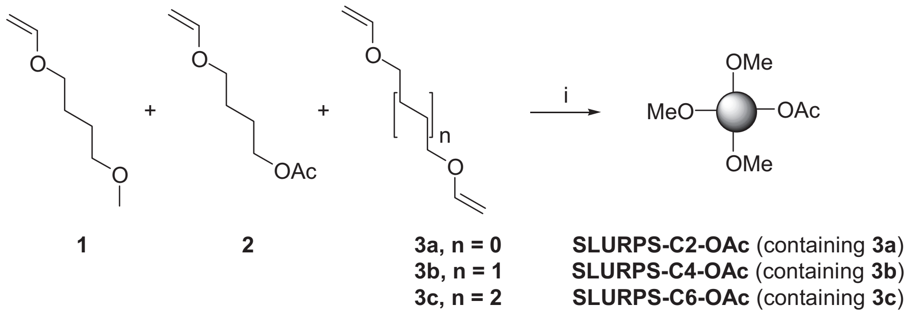


Fig. 2. Analysis of the particle size distribution of SLURPS-beads in MeOH as a function of surfactant levels.



Scheme 2. Synthesis of SLURPS-gels with varying spacer groups in the cross-linker. i) BF_3OEt_2, −78 °C, 100% conversion (all gels), isolated yields: 80% SLURPS-C2-OAc, 76% SLURPS-C4-OAc; 75% (SLURPS-C6-OAc).

also needed and proved problematic for Deleuze et al. [22]. In our particular case additional challenges were to produce beads with only a few mol% of cross-linker (given by the composition of the random particle SLURPS-gels) and to find a continuous phase solvent that was immiscible with a monomer composition which results in a polymer network with a very broad range of solvent compatibility. As we will show in the following, careful optimization of reaction conditions and the right choice of solvent and suspension stabilizer allowed us to obtain the desired beaded support.

During our initial work on bulk SLURPS-gel,[20] synthesized as random gel particles at low temperature, we had conducted a thorough optimization of the reaction conditions, focusing sequentially on reaction temperature, co-initiator, quenching agent and solvent (Scheme 1).

This optimization process resulted in identifying conditions that gave 100% conversion of the vinyl ether monomers and 80% isolated yield of the SLURPS-gel, with the remainder being microparticles which passed though the sintered glass filter. It was clearly judicious to seek conditions to produce SLURPS-beads that mimicked these reaction conditions as closely as possible. As discussed previously, it was imperative that we had to identify a solvent replacement for the aqueous phase as water would be incompatible with the cationic polymerisation chemistry which we optimized for the bulk synthesis of SLURPS. Eventually, therefore, we selected perfluorohexane (PFH) as a relatively inexpensive, readily available, aprotic and fluorophilic continuous phase. We paired the perfluorinated solvent with bromochloro methane (BCM), which we found to produce a more stable suspension than CH_2Cl_2, as a result of the increased incompatibility with the continuous phase at the polymerisation temperature (≈−50 °C). With the selection of a fluorous continuous phase we tested a small number of dispersants with a nonionic fluorinated polymeric surfactant (FC-4430 from 3M) producing the best results.

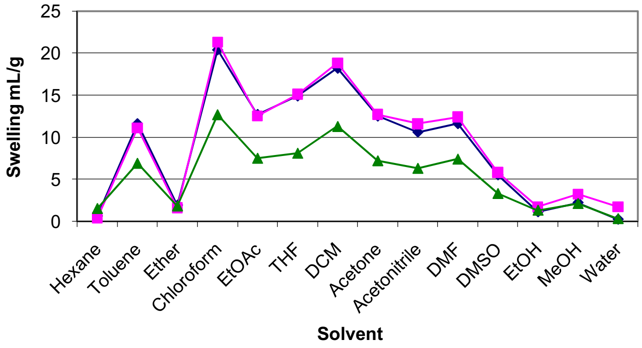
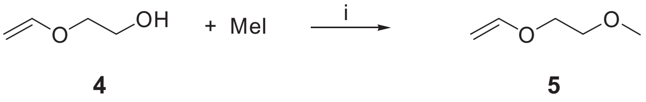


Fig. 3. Equilibrium swelling performance of SLURPS-gels with varying cross-linker (XL) spacer lengths.

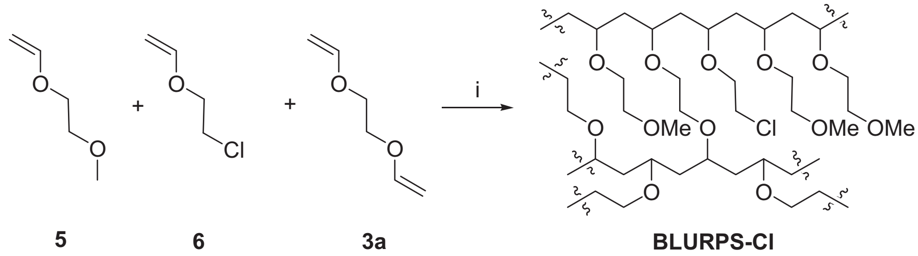
Addition of a solution of monomers **1**, **2** and **3** in BCM to PFH containing the polymeric surfactant produced a biphasic system containing about 10% by volume of monomers. Stirring this mixture at room temperature using a three blade metal propeller driven by an overhead stirrer at speeds of up to 800 rpm was ineffective in producing a stable emulsion. Only upon cooling of the system to −78 °C phase separation into dispersed droplets occurred, as indicated by the appearance of milk-like, opaque heterogeneous mixture. All attempts to initiate the reaction adding $BF_3.EtO_2$ at −78 °C followed by allowing the reaction mixture to warm to room temperature resulted in the rapid formation of a viscous sludge rather than discrete beads. The gel-phase ^1H NMR spectrum of this material was identical to that of SLURPS-gels synthesized *via* bulk polymerisation though. This suggested that whilst the new "suspension" reaction condition did not inhibit the polymerisation, under these specific conditions the biphasic system was not stable enough to produce the desired beaded materials.

We speculated that addition of the co-initiator (kept at ambient temperature) into the chilled suspension may be increasing the temperature of droplets enough to break down the suspension, whilst simultaneously initiating the polymerisation, or vice versa, producing the observed unbeaded product. Our rationale was consistent with the observations that a suspension only forms at temperatures below −30 °C, and that during our studies into the bulk polymerisation of SLURPS we found that whilst the polymerisation kinetics are very slow at −78 °C the reaction proceeds quickly at slightly raised temperatures (−65 °C to −55 °C) [20].

Thus, we concluded that it may be possible to retain suspension stability if a way could be found to introduce the co-initiator so that the temperature remain close to −78 °C during addition and to agitate the biphasic system long enough to ensure homogeneous distribution of the co-initiator throughout the suspension droplets. Therefore as a second iteration of beaded SLURPS-gel synthesis, the co-initiator was precooled *via* dropwise addition onto the metal propeller shaft with drops forming a trail of liquid slowly traveling down the cold (≈−78 °C) metal shaft of the propeller into the vigorously stirred emulsion held at −78 °C (internal reaction temperature). After addition of the co-initiator was complete the reaction was left for 30 min at this temperature to allow the co-initiator to disperse homogeneously throughout the droplet phase without any apparent polymerisation taking place. Slowly increasing the internal reaction temperature to −40 °C over approximately 25 min resulted in individual spheres of gel



Scheme 3. Synthesis of methoxyethyl vinyl ether. i) KOH, 0 °C to r.t., 18 h, 72%.



Scheme 4. Synthesis of BLURPS-Cl with monomer ratio 5:6:3a = 85:11:4 mol%. i) BF_3OEt_2, −78 °C, 100% conversion, 78% yield.

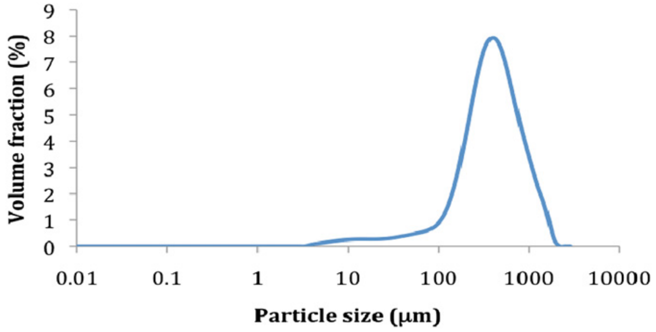


Fig. 4. Analysis of the particle size distribution for BLURPS-Cl.

appearing in the reaction flask. After 2 h at this temperature the surface of the reaction vessel was coated with beads and the liquid phase(s) had become transparent, suggesting complete consumption of the starting materials. This was confirmed by analyzing an aliquot of the liquid phase by ^{1}H NMR spectroscopy which revealed the absence of any residual vinylic protons associated with the starting monomers. Finally, the reaction was allowed to warm to room temperature and subsequently quenched with an ammonia/water mixture whereupon the colourless beads were easily collected by filtration.

Analysis of the resulting beads by optical microscopy showed that isolated beads were in most cases only approaching a uniform spherical shape, some though turned out to possess ideal spherical topology (Fig. 1).

In order to evaluate reproducibility and to what extent we could exert control over the size of the beads, the synthesis was repeated with three different levels of surfactant concentration (0.4, 0.8 and 1.2 wt%). With increasing surfactant concentration the bead size decreased as was determined by particle sizing using static laser light scattering (Fig. 2). All distributions were bimodal, with the local maximum at around 120 μm representing less than 3% of the total particle volume. The vast majority of polymer beads possessed an average diameter of between 870 and 930 μm. A decrease of the bead size of about 60 μm requires an increase in surfactant concentration from 0.4% to 1.2% and does not affect significantly the polydispersity of bead sizes (Fig. 2). The influence of the surfactant concentration is modest though and does not allow us to control the size of the beads within a broader range.

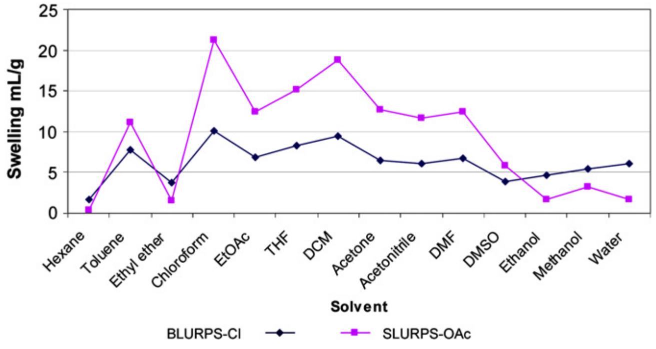


Fig. 5. Equilibrium swelling properties of SLURPS-C4-OAc and BLURPS-Cl.

The obtained beads exhibited low surface roughness and, together with the absence of bead clusters or insoluble lumps of beads, both achieved whilst maintaining complete monomer conversion, lead us to conclude that conditions have been identified which are close to those needed for a typical suspension polymerisation.

For a support to become truly “universal” one key aspect we needed to enhance is the already promising solvent compatibility of our original SLURPS further [20,21]. Criteria for improvements are extension of the solvent range as well as a more even swelling response of the gel across a wide range of solvent polarities. Thus we decided to revisit the original SLURPS synthesis (Scheme 1) and investigate the effect that altering the monomers and their relative feed ratios has on the swelling characteristics of the resulting gels. It was apparent that the original one pot polymerisation of SLURPS-gels could be readily adapted to include a range of monovinyl (**1, 2**) and divinyl monomers (**3**) thus enabling a family of related SLURPS-gels to be generated without the need of re-optimizing the polymerisation conditions each time.

For the first iteration of this work it was decided to change the length of the spacer between the vinyl ether groups on the cross-linker, as this would represent the smallest structural change from the original SLURPS-gel. Thus two new SLURPS-gels were synthesized with either an ethyl (Scheme 2, **3a**, $n = 0$) or a hexyl (Scheme 2, **3c**, $n = 2$) spacer group in the cross-linking monomer (XL).

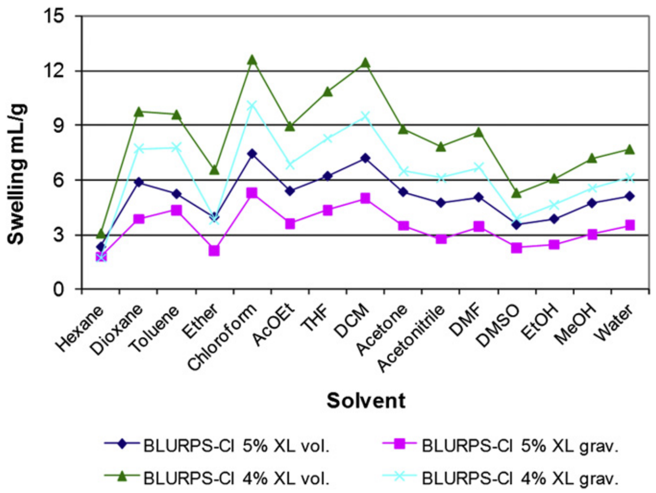
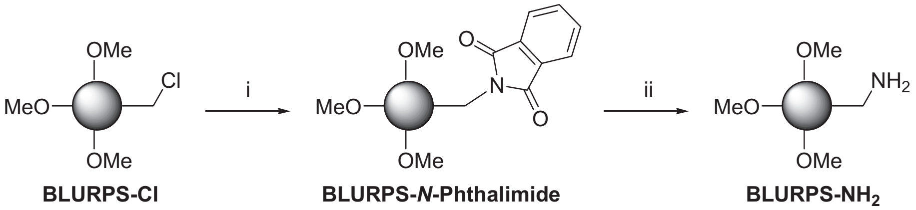


Fig. 6. Comparison of the equilibrium swelling of BLURPS-Cl beads with differing XL ratios as determined by volumetric and gravimetric analysis.



Scheme 5. Synthesis of BLURPS-NH_2. i) Potassium phthalimide, NaI, DMF, 100 °C, 18 h, 82%; ii) EtOH, H_2NNH_2, reflux, 18 h, 94%.

Comparison of the swelling profiles of the three SLURPS-gels (Fig. 3) revealed that introduction of a hexyl spacer (SLURPS-C6-OAc) decreased the swelling performance markedly in almost all the solvents tested, whilst shortening the cross-linker to an ethyl group (SLURPS-C2-OAc) had little effect on the swelling performance over the original gel composition (SLURPS-C4-OAc). One could rationalize the swelling response for the shorter cross-linker as a balance between its increased polarity, yet the shorter spacer length generates a gel network with a reduced maximum volume of swelling, in effect the benefits of the polarity increase are counteracted by a less extendable network. The exception being the response to water which we cannot explain at the moment. The more lipophilic nature of the hexyl-spaced cross-linker is reflected in the reduced swelling in polar solvents and the significant increase for swelling in hexane, but surprisingly not for toluene. Possibly solvent interactions with the cross-linker are only significant in hexane, and the lack of swelling in water and methanol could be attributed to a gel in which all cross-linking points have collapsed and severely restrict the level to which the linear polymer chain segment of the network can interact and respond to polar solvents. Although the use of the hexyl spacer has reduced the maximum swelling levels in all solvents but hexane; the absolute differences in the levels of swelling between individual solvents has become less (i.e. more balanced) which is desirable.

2.2. Varying the monovinyl methoxy monomer (2)

The set of cross-linkers studied brought to the fore that in order to improve the swelling performance of the gels towards individual solvents it would be necessary to alter the monovinyl constituents (**1**, **2**) of the polymer, which make up the majority of the structure. It was hoped that by positioning the methoxy groups on **1** closer to

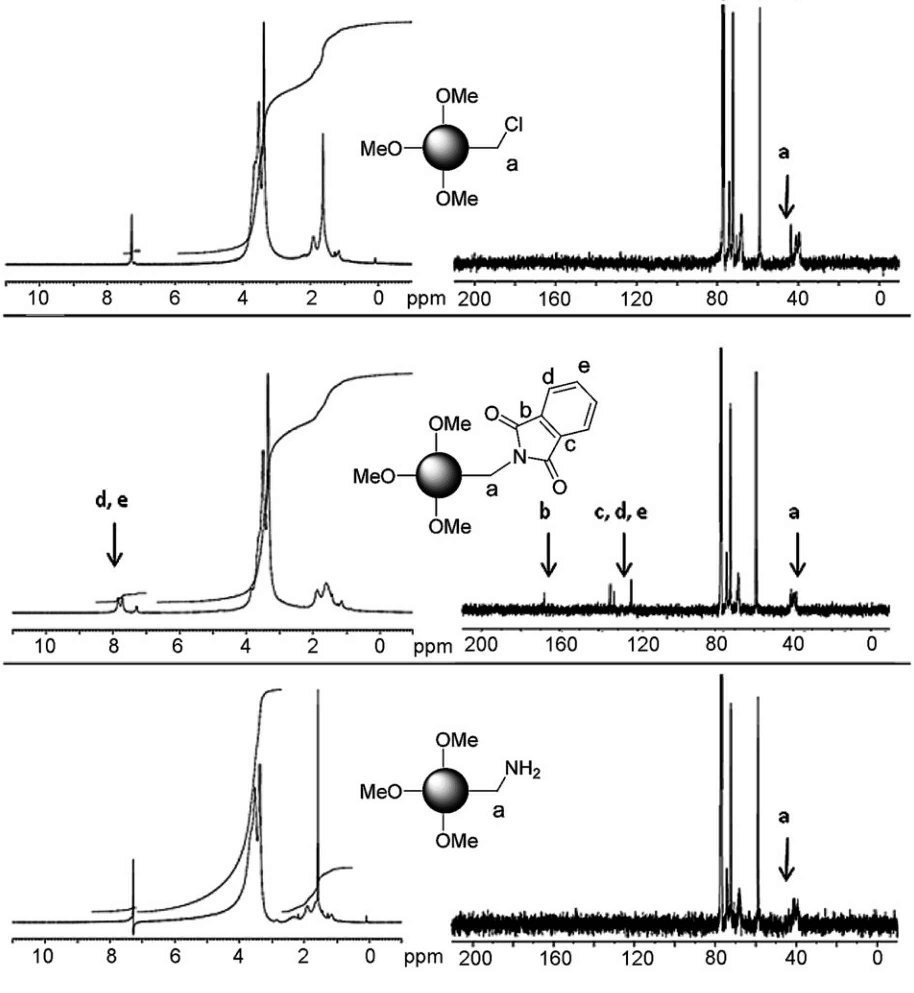
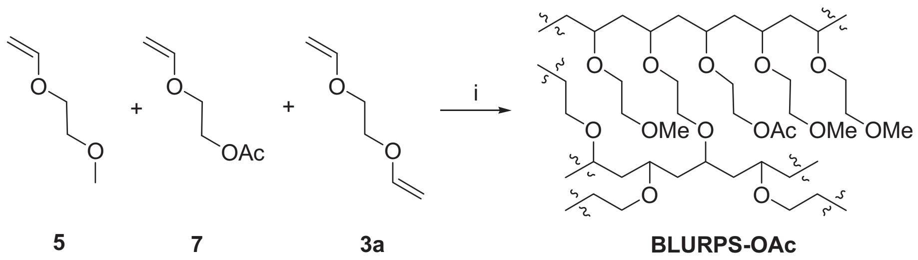


Fig. 7. ^1H and ^{13}C NMR spectra of BLURPS-Cl gel, BLURPS-N-phthalimide and BLURPS-NH_2 (top to bottom respectively).



5 **7** **3a**

Scheme 6. Synthesis of BLURPS-OAc with monomer ratio 5:7:3a = 85:11:4 mol%. i) BF_3OEt_2, −78 °C, 77% yield.

the polymer backbone the resulting material would behave more akin to linear polyethylene glycol (PEG) and extend the range of solvent interactions to those solvents at the extremes of the polarity scale. Accordingly, the known methoxyethyl vinyl ether (**5**) [24] was synthesized in 72% yield (Scheme 3) as the shorter-chain analogue for the original methoxybutyl vinyl ether monomer (**1**). Additionally, it was possible to make use of the commercially available 2-chloro vinyl ether (**6,** Scheme 4) as the short chain analogue rather than functional monomer **2**, which has to be synthesized.

Submitting monomers **5**, **6** and **3a**, to the same reaction conditions as described earlier for the synthesis of the beaded SLURPS-gel resulted in the formation of essentially colourless beads of what we elected to call BLURPS-Cl (in good analogy to SLURPS and highlighting the significantly improved performance, we propose the acronym BLURPS being "Beguiling Liquid Uptake Resins for Polymer-supported Synthesis") (Scheme 4).

The ability to prepare these novel gel beads from easily accessible starting materials in a robust suspension polymerisation process has clear advantages in producing larger quantities of this material for further evaluation and potential commercial exploitation. Analysis of the particle size distribution for BLURPS-Cl (Fig. 4) showed essentially the same bimodal size distribution as observed during the SLURPS bead synthesis with the majority of the beads in the sample (~93%) falling within the 0.1–2 mm size range.

This pleasing result showed the polymerisation conditions to be tolerant of chlorinated, as well as acetylated monomers (Scheme 6) which effectively shortens the synthetic route to halogenated gels (versatile intermediates) for the introduction of common linkers used in SPOS (Solid-Phase Organic Synthesis) and SPPS (Solid-Phase Peptide Synthesis) by three steps when compared to the initial SLURPS-Br synthesis.

The swelling behaviour of the new gel (BLURPS-Cl) was determined in an identical manner to that of SLURPS and is compared Fig. 5 for SLURPS-C4-OAc and BLURPS-Cl. The solvent response of BLURPS-Cl is superior to that of SLURPS-C4-OAc. Not only do we observe a much improved swelling in water and protic solvents (by a factor 2 or greater), but BLURPS-Cl swells when exposed to hexane (~2 ml/g). Indeed across the entire polarity scale the deviation from a swelling level average has been reduced substantially (i.e. more balanced response to solvent interactions), suggesting that BLURPS-Cl has the rather unique ability to interact with solvents as diverse (and incompatible) as hexane and water. Indeed BLURBS-Cl out-performs SLURPS-C4-OAc in nonpolar solvents, in highly polar solvents, and also exhibits a significantly improved response to diethyl ether, a solvent not only commonly used in organic synthesis but also one for which SLURPS-gels showed rather poor swelling characteristics.

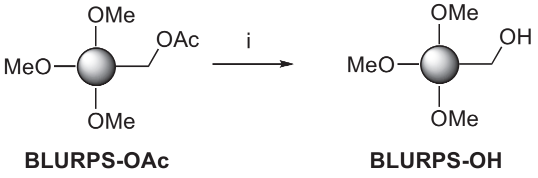
In order to try to increase the swelling performance of the new gel further, the cross-linker feed was varied by synthesising gels containing 3 mol% or 5 mol% cross-linker (**3a**, $n = 0$) respectively for comparison with BLURBS-Cl which contained 4 mol% XL. At least up to now we have not been able to obtain the intended beaded gels containing 3% mol XL. Instead we were only able to produce viscous oils, suggesting that the minimum level of cross-linker needed to confer mechanical properties to the gel during the polymerisation had previously been reached. Conversely, beads containing 5 mol% cross-linker could readily be synthesized but showed, as expected, reduced levels swelling across the entire solvent polarity range (Fig. 6).

In the course of our investigations we also experimented with faster methods to screen gels more quickly for their changes in solvent responses. In Fig. 6 we show the swelling ratios of the 4 and 5 mol% cross-linked gels obtained by our well-established gravimetric method [20] are compared to a much simpler volumetric alternative. During this new procedure the gels were packed loosely inside a plastic syringe and a constant stream of solvent (and solvent gradients when switching from one solvent to the next in a continuous mode) was passed through the syringe barrel, accompanied by gentle agitation to increase the packing efficiency. In this manner it is possible to screen a polymer gel like ours within a few hours for its solvent response across the entire polarity scale of interest as the overall swelling response pattern is very similar to that obtained *via* the gravimetric method. The increased absolute values of swelling can be explained by inefficient packing and can only be used as a rough guide for comparing the trends in the solvent responses of gels with each other.

2.3. On bead transformations

We then studied the synthetic utility of the new gel to see if it was matched the clearly attractive physical properties of BLURPS. We carried out a conventional functional group interconversion to deliver the amine terminated analogue of the original gel. The chloroethyl terminated BLURPS gel was converted to the *N*-phthalimide under standard conditions and subsequently the primary amine was revealed upon exposing the gel to hydrazine at elevated temperatures (Scheme 5).

The gel-phase ^1H and ^{13}C NMR spectra for the starting BLURPS-Cl gel, BLURPS-*N*-phthalimide and BLURPS-NH_2 are shown in Fig. 7. Each were produced using routine solution phase acquisition techniques and demonstrate the excellent signal to noise ratios that we observed previously when analysing the SLURPS-gels. Analysis of the spectra in sequence proves that each reaction proceeded to completion which also is consistent with our experience of SLURPS-gels. For



Scheme 7. Synthesis of BLURPS-OH. i) MeOH/H_2O (3:2 v/v), K_2CO_3, 89% yield.

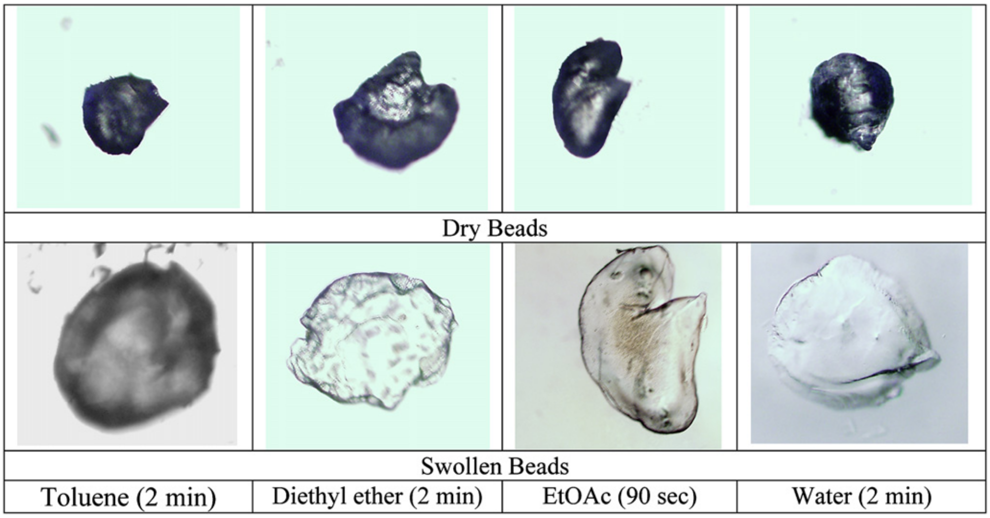


Fig. 8. Optical micrographs of individual dry beads of BLURPS-OH and the same bead after swelling in various solvents at room temperature for the stated time.

example, the resonance for the methylene group alpha to the chloride in the starting BLURPS-Cl gel at 43.6 ppm is absent in the spectrum of the BLURPS-*N*-phthalimide gel whilst the signals for the aromatic protons of the phthalimide moiety (7.87–7.72 ppm) and associated ^{13}C resonances (168.0, 133.8, 132.1, 123.2 ppm) are clearly resolved in the ^{1}H and ^{13}C NMR spectra of the product. The complete removal of the phthalimide protecting group by action of hydrazine was confirmed by the absence of all corresponding signals from the proton spectra of the final BLURPS-NH_2 product.

To complete our synthetic investigations into the utility of BLURPS based beads, the synthesis of an alcohol functionalised variant, BLURPS-OH was attempted. Thus, the known acetylated vinyl ether **7** was subjected to suspension polymerisation with methoxy vinyl ether **5** and divinyl ether **3a** (Scheme 6) under the conditions established during the synthesis of BLURPS-Cl, subsequent removal of the acetyl group under basic conditions furnished the desired hydroxyl functionalised gel, BLURPS-OH in 89% yield (Scheme 7). Complete deprotection of the hydroxyl group was readily verified by IR spectroscopy (loss of the carbonyl signal at 1734 cm^{-1}) and by ^{1}H NMR spectroscopy (loss of the methyl signal at 4.05 ppm).

The solvent compatibility of BLURPS-OH could be readily demonstrated by subjecting a single bead to an excess of solvent whilst observing them in real time under an optical microscope. Fig. 8 shows four isolated beads of dry BLURPS-OH and an image of the same bead after up to 2 min in contact with solvents of varying polarity. It can be seen that even within this short timescale, BLURPS-OH beads typically double in diameter (4 fold increase in volume) in solvents as diverse as water and toluene.

Encouraged by the outcome of this preliminary set of chemical transformations, with a performance comparable to the excellent solid-phase synthesis properties of SLURPS, we are now evaluating the new gels in multi-step transformations including peptide synthesis.

3. Conclusions

We have shown how our original SLURPS-gels can be readily synthesized on gram scale quantities in a beaded form which is convenient for manual manipulation during solid-supported synthesis. We have carried out optimization of the physical properties of the beaded gels by altering both the constituent monomers and the cross-linking ratio to deliver a gel that exhibits uniquely excellent swelling properties across the entire solvent polarity scale. We significantly improved upon the solvent compatibility of the original SLURPS-gel not only by increasing the range of solvents in which the support swells well in but also by obtaining a more balanced swelling response across the solvent polarity scale (hexane to water). As BLURPS-Cl can be prepared entirely from commercially available monomers this establishes a synthetically shortened entry to functionalised varieties of this support with common linker units as a generic and economical solid support platform. Additionally, by carrying out a short, on bead set of chemical transformations we have shown that the new BLURPS-gels have retained the high performance levels of the progenital SLURPS-gels and thus represent a significant advance in the quest for a truly universal solid support.

4. Experimental

Nuclear magnetic resonance (NMR) spectra were acquired on a Varian 400 spectrometer operating at 400 MHz and 100 MHz for proton and carbon spectra respectively. All signals are quoted in parts per million (ppm) referenced to the residual protic solvent signal as internal standard ($CDCl_3$, ^{1}H 7.26 ppm, ^{13}C 77.0 ppm). The multiplicities of the signals have been abbreviated as follows: (s)-singlet, (d)-doublet, (t)-triplet, (q)-quartet, (m)-multiplet. Infrared spectra were measured with a Mattson Satellite 3000 FTIR spectrometer. Spectra were obtained from either a thin film (small molecules) or from $CHCl_3$ swollen beads (polymer gels) held between two KBr discs. The values obtained are quoted in wavenumbers (cm^{-1}). Particle size distributions were acquired on a Mastersizer Model 2000 Hydro (Malvern Ltd., Malvern, U.K.) using water as dispersant.

All non-fluorinated reagents were bought from commercial suppliers, either Sigma Aldrich, Lancaster Synthesis, Avocado or Fisher Scientific, had purities greater than 97% and were used without further purification. The surfactant used in this work was sourced from 3M (FC-4430). FC-4430 is a combination of fluoroaliphatic polymeric esters (85–95 wt%), a polyether polymer (5–10 wt%), 1-methyl-2-pyrrolidinone (1–2 wt%), toluene (<1 wt%) and 2-propenoic acid, 2-(methyl(nonafluorobutyl) sulfonyl)amino) ethyl ester (0–0.5 wt%). DMSO and CH_2Cl_2 were distilled from CaH_2 prior to use. Anhydrous DMF was purchased from Sigma Aldrich and used as received. Perfluorohexane was purchased from Fluorochem and used as received.

All reactions were carried out oven dried (120 °C) glassware, cooled under nitrogen. Reaction temperatures refer to that of the external medium either an oil or ice bath, except for the bead synthesis where temperatures refer to the internal reaction temperature. During bead synthesis, the emulsion was maintained using a metal three blade 25 mm diameter propeller with a metal shaft driven by an IKA RW 20 digital overhead stirrer at the speed specified in the relevant experimental.

4.1. Synthesis of methoxyethyl vinyl ether (4)

MeI (55.5 mL, 892 mmol) was added to a stirring slurry of ethyleneglycol vinyl ether (40.0 mL, 446 mmol) and KOH (27.5 g, 491 mmol) at 0 °C. After 30 min the ice bath was removed and the reaction stirred at room temperature for 3 h before water (50 mL) was added. After stirring for a further 30 min the organic phase was separated and washed with water (50 mL) and brine (50 mL), then dried over $MgSO_4$, and the solvents removed on a rotary evaporator at r.t. Distillation under reduced pressure gave the title compound (32.8 g, 72%).^{1}H (400 MHz, $CDCl_3$) $\delta = 6.49$ (dd, $J = 6.8, 14.3$, 1H), 4.18 (dd, $J = 2.2, 14.3$, 1H), 4.00 (dd, $J = 2.1, 6.8$, 1H), 3.83–3.81 (m, 2H), 3.63–3.61 (m, 2H), 3.40 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) $\delta = 151.5$, 86.4, 70.6, 66.8, 58.9; IR (neat) ν_{max}: 2986, 2817, 1622, 1455, 1397, 1363, 1321, 1293, 1293, 1242, 1204, 1128, 1099, 1039, 966, 848, 820, 702; HRMS (CI with NH_3) calc. for $C_5H_{14}NO_2$ = 120.1025, found = 120.1025.

4.2. Beaded SLURPS-C4-OAc (2% XL)

An oven dried 250 mL 3 neck round bottom flask was charged with FC-4430 (800 mg). A three blade 25 mm propeller from an overhead stirrer was inserted and the flask flushed with nitrogen. After 30 min CH_2BrCl (10.0 mL), 4-acetoxybutyl vinyl ether (1.58 g, 10.0 mmol), methoxybutyl vinyl ether (7.95 g, 61.1 mmol) and 1,4-butanediol divinyl ether (0.206 mL, 1.42 mmol) were added and stirred (400 rpm) at room temperature for 5 min. Perfluorohexane (100 mL) was added and the solution stirred at 800 rpm whilst being cooled to −78 °C (approx. 30 min) over which time the reaction took on a milky appearance. A solution of BF_3 diethyletherate (0.15 mL) in CH_2BrCl (1.8 mL) was added dropwise down the shaft of the stirring rod. After 30 min the acetone/cardice bath was lowered and the reaction allowed to warm to −40 °C over 15 min and the reaction maintained at this temperature for 70 min, warmed to −30 °C for 60 min then held at −20 °C for 20 min. The reaction was quenched at −10 °C (33% NH_3 in H_2O, 10 mL) whilst warming to ambient temperature. The spheres were collected by vacuum filtration (Büchner funnel and filter paper) then washed sequentially with methanol, acetonitrile, acetone, tetrahydrofuran and ether (2 × 50 mL of each) and dried under vacuum (at r.t.) overnight to give SLURPS-C4-OAc as sticky colourless spheres 7.64 g (76%). ^{1}H (400 MHz, $CDCl_3$) $\delta = 4.10$–2.90 (4.06, 3.64, 3.36, 3.30, 30H), 2.10–0.90 (2.04, 1.78, 1.59, 1.55, 0.93, 25H); ^{13}C (400 MHz, $CDCl_3$) $\delta = 170.1$, 73.8, 72.6, 68.6, 64.4, 58.6, 41.5, 39.5, 27.2, 26.6, 25.8, 21.0; IR ($CHCl_3$) ν_{max} = 3018, 2928, 2869, 2830, 1731, 1518, 1475, 1447, 1387, 1261, 1115, 352, 757, 668, 626.

4.3. Synthesis of BLURPS-Cl

A 250 mL 3 neck round bottom flask was charged with FC-4430 (500 mg). A three blade 25 mm propeller from an overhead stirrer was inserted and the flask flushed with nitrogen. After 30 min CH_2BrCl (10.0 mL), 2-chloroethyl vinyl ether (1.02 g, 0.97 mL, 10.0 mmol), methoxyethyl vinyl ether (8.58 g, 80.9 mmol) and 1,2-divinyl ethylene glycol (0.432 g, 0.472 mL, 3.79 mmol) were added and stirred (400 rpm) at room temperature for 5 min. Perfluorohexane (100 mL) was added and the solution stirred at 800 rpm whilst being cooled to −78 °C (approx. 15 min) over which time the reaction took on a milky appearance. A solution of BF_3 diethyletherate (0.12 mL) in CH_2BrCl (1.9 mL) was added dropwise down the shaft of the stirring rod. After 30 min the acetone/cardice bath was lowered and the reaction allowed to warm to −30 °C over 25 min during which time small spheres appeared in the suspension. The temperature was carefully maintained around −30 °C for 1 h then at −20 °C for 40 min before the temperature was allowed to rise to −10 °C and quenched with an ammonia solution (33% NH_3 in H_2O, 2 mL) and allowed to warm to ambient temperature. The colourless spheres were collected by vacuum filtration (Büchner funnel and filter paper) then washed sequentially with methanol, THF, ether (2 × 100 mL of each) and dried under vacuum overnight to give BLURPS-Cl as sticky colourless spheres 7.37 g (74%). ^{1}H (400 MHz, $CDCl_3$) $\delta = 3.89$–3.20 (br, 3.67, 3.64, 3.53, 3.38, 1H), 2.00–1.10 (br, 1.91, 1.63, 1.26, 1.16, 0.30H); ^{13}C (100 MHz, $CDCl_3$) $\delta = 74.4$–73.7, 72.5–71.9, 70.5, 68.9–67.7, 59.1–58.6, 43.6, 41.3–40.6, 40.0–38.7. IR ($CHCl_3$) ν_{max}: 3017, 2939, 2871, 1478, 1448, 1376, 1216, 1113, 755, 668.

4.4. Synthesis of BLURPS-N-phthalimide

To a slowly stirring suspension of BLURPS-Cl (5.30 g, 5.3 mmol) in DMF (100 mL) was added potassium phthalimide (4.90 g, 26.5 mmol) and KI (176 mg, 1.06 mmol). The suspension was stirred at 100 °C for 19 h. After cooling to r.t. the salts were dissolved by adding MeOH (approx. 100 mL) and the yellowish beads collected by filtration and washed with MeOH, THF, Et_2O (2 × 150 mL of each) to give BLURPS-*N*-phthalimide (4.47 g, 82%) as yellow beads. ^{1}H (400 MHz, $CDCl_3$) $\delta = 7.87$–7.75 (br, 1H), 3.70–2.90 (br, 3.60, 3.50, 3.37, 20H), 2.07–0.95 (1.92, 1.57, 1.16, 5.25H); ^{13}C (100 MHz, $CDCl_3$) $\delta = 168.0$, 133.8, 132.1, 123.2, 74.1, 68.1, 68.8–67.4, 58.8, 41.4–40.7, 39.5–39.2, 38.1; IR ($CHCl_3$) ν_{max}: 3025, 2873, 1775, 1711, 1615, 1520, 1450, 1393, 1214, 1130, 1034, 928, 849, 789, 671, 626.

4.5. Synthesis of BLURPS-NH$_2$

Hydrazine monohydrate (0.43 mL, 9.0 mmol) was added BLURPS-*N*-phthalimide (3.00 g, 2.98 mmol) in EtOH (60 mL), and heated under reflux for 18 h. After cooling to r.t. the slightly yellow spheres were collected by vacuum filtration and washed with EtOH, THF, and Et_2O (2 × 50 mL each) followed by drying under vacuum to give BLURPS-NH_2 (2.80 g, 94%) as yellow spheres. ^{1}H (400 MHz, $CDCl_3$) $\delta = 4.10$–2.80 (br, 0.8H), 2.50–1.10 (br, 0.2H); ^{13}C (100 MHz, $CDCl_3$) $\delta = 74.1$, 72.3, 68.2–67.5, 58.9, 41.5, 40.9, 39.4; IR ($CHCl_3$) ν_{max} = 3479, 3387, 3041, 2824, 1654, 1600, 1519, 1454, 1397, 1217, 1041, 928, 774, 627.

4.6. Synthesis of 2-acetoxyethyl vinyl ether (7)

To a stirring solution of 1,2-ethanediol vinyl ether (25.0 mL, 279 mmol) in AcOAc (171 mL, 1.81 mol) at 0 °C was added Et_3N (43.1 mL, 419 mmol) and DMAP (1.70 g, 14.0 mmol). The reaction was stirred at 0 °C for 1 h then allowed to warm to room temperature and stirred for 18 h. The reaction mixture was poured into a 2 L beaker containing ice (1.0 kg) and ether (300 mL) and stirred whilst solid Na_2CO_3 was added until the aqueous layer was at pH 8–9 and no more bubbling was seen. The organic layer was separated and the aqueous layer extracted with ether (3 × 250 mL). All the combined organic layers were then washed with brine (2 × 150 mL), dried over $MgSO_4$, filtered and the solvent removed on a rotary evaporator. The product was isolated *via* vacuum distillation (b.p. 37–44 °C, water pump vacuum) to give the title compound as a colourless oil (28.9 g, 80%). ^{1}H (400 MHz, $CDCl_3$)

$\delta = 6.46$ (dd, $J = 6.8, 14.4$, 1H), 4.31–4.29 (m, 2H), 4.19 (dd, $J = 2.3, 14.3$, 1H), 4.04 (dd, $J = 2.3, 6.8$, 1H), 3.88–3.87 (m, 2H), 2.09 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) $\delta = 171.0, 151.4, 87.1, 65.7, 62.6, 20.9$; IR (neat) ν_{max}: 2959, 2937, 2881, 1743, 1620, 1457, 1374, 1323, 1237, 1200, 1123, 1061, 1007, 983, 825, 639, 605; HRMS (CI with NH_3) calc for $C_6H_{14}NO_3 = 148.0974$, found $= 148.0975$.

4.7. Synthesis of BLURPS-OAc

An oven dried 250 mL 3 neck round bottom flask was charged with FC-4430 (400 mg). A three blade 25 mm propeller from an overhead stirrer was inserted and the flask flushed with nitrogen. After 30 min CH_2BrCl (8.0 mL), 2-acetoxyethyl vinyl ether (1.04 g, 8.00 mmol), methoxyethyl vinyl ether (7.30 g, 71.2 mmol) and 1,2-divinyl ethylene glycol (0.40 mL, 0.32 mmol) were added and stirred (400 rpm) at room temperature for 2 min. Perfluorohexane (80 mL) was added and the solution stirred at 800 rpm whilst being cooled to −78 °C over which time the reaction took on a milky appearance. A solution of BF_3 diethyletherate (0.090 mL) in CH_2BrCl (2.0 mL) was added dropwise down the shaft of the stirring rod. After 30 min the acetone/cardice bath was lowered and the reaction was allowed to warm to −35 °C over 25 min during which time small spheres appeared in the suspension. The temperature was carefully maintained between −35 °C and −40 °C for 1 h then at −30 °C for 10 min and finally allowed to rise to −12 °C over 7 min. At this temperature spheres collected around the outside of the flask began to yellow and the reaction was quenched with ammonia solution (33% NH_3 in H_2O, 2 mL) whilst the reaction was allowed to warm to ambient temperature. The spheres were collected by vacuum filtration (Büchner funnel and filter paper) then washed sequentially with methanol, acetonitrile, acetone, tetrahydrofuran and ether (2 × 20 mL of each) and dried under vacuum overnight to give BLURPS-OAc as sticky colourless spheres 6.70 g (77%). ^{1}H (400 MHz, $CDCl_3$) $\delta = 4.0$–2.2 (br, 0.8H), 2.1–1.0 (br, 0.25H); ^{13}C (100 MHz, $CDCl_3$) $\delta = 74.1, 72.3, 68.3, 64.0, 58.9, 41.2, 39.4, 21.0$; [C=O carbon not seen] IR ($CHCl_3$) $\nu_{max} = 3014, 2913, 2875, 2826, 2735, 1734, 1519, 1455, 1382, 1216, 1169, 1046, 928, 849, 768, 671$.

4.8. Synthesis of BLURPS-OH

BLURPS-Ac (5.00 g) was added to a stirring (magnetic stirrer) solution of MeOH (75 mL), H_2O (50 mL) and K_2CO_3 (5.00 g). After 4 h the reaction was filtered and washed sequentially with MeOH/H_2O (3:2 v/v) (2 × 50 mL), MeCN (2 × 50 mL), THF (2 × 50 mL), and ether (2 × 50 mL). The solid was dried under vacuum at room temperature to constant weight to give of BLURPS-OH (4.42 g, 89%). ^{1}H (400 MHz, $CDCl_3$) $\delta = 4.0$–2.2 (br, 0.8H), 2.1–1.0 (br, 0.25H); ^{13}C (100 MHz, $CDCl_3$) $\delta = 74.1, 72.3, 70.5, 68.2, 62.0, 58.9, 40.9, 39.5$. IR (neat) $\nu_{max} = 3447, 3011, 2926, 2827, 1625, 1603, 1520, 1454, 1384, 1218, 1119, 1033, 928, 849, 771, 672, 626$.

4.9. Determination of equilibrium swelling values

Both gravimetric and volumetric determinations of the degree of swelling have been carried out. The gravimetric procedure has been described in detail elsewhere [20].

The procedure for the volumetric measurement is as follows. Dry polymer beads (of an equivalent volume of approx. 0.1 ml) were placed in a graduated plastic syringe (1 ml) and weighed. A continuous flow of solvent was passed through the syringe at a rate of approx. 1 ml/min, while the polymer beads started to swell. After 10–30 min (depending on the swelling response of the gels by visual inspection), interrupted by occasional gentle agitation of the polymer gel with a thin metal rod, a reading was taken after gently squeezing most of the excess (interstitial) solvent from the swollen gel beads using a plunger. This process was then repeated with another solvent. The solvents used and the sequence in which they were measured is given in Fig. 6 starting from one end of the solvent scale, usually water, and arrive back at water by following the sequence in reverse order. The experimental error of the swelling values is ±0.5 ml/g. The benefit of the volumetric method is the relative speed with which it can be carried out in providing a trend in swelling behaviour for the polymer gels. It is not a substitute to the gravimetric method [20] to obtain accurate equilibrium swelling values.

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