Poly(vinyl alcohol)-*graft*-poly(ethylene glycol) resins and their use in solid-phase synthesis and supported TEMPO catalysis†

Juntao Luo, Christophe Pardin, William D. Lubell* and X. X. Zhu*

Received (in Cambridge, UK) 8th January 2007, Accepted 6th February 2007
First published as an Advance Article on the web 28th February 2007
DOI: 10.1039/b700215g

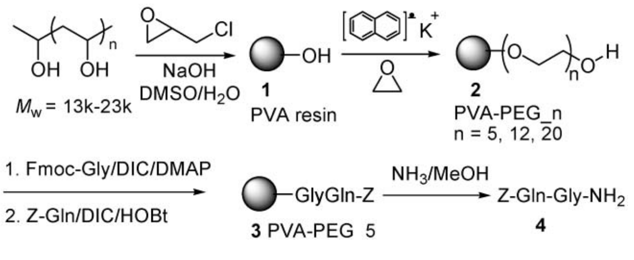
New poly(vinyl alcohol)-*graft*-poly(ethylene glycol) (PVA-*g*-PEG) resins with various PEG chain lengths, which have high loadings and good swelling both in water and organic solvents, have been prepared *via* an anionic polymerization of ethylene oxide onto PVA beads and applied in solid-phase synthesis, supported TEMPO catalysis and in HR-MAS ^{1}H NMR spectral analysis.

As new strategies in combinatorial chemistry and solid supported chemistry emerge,[1–4] new solid supports are required having effective loading of functional groups and good swelling in a variety of solvents (including aqueous solutions).[5] Crosslinked polystyrene-divinylbenzene (PS-DVB) matrices[6] have been the proven paradigm in solid-phase chemistry to produce peptides and small molecules. The hydrophobic PS backbone has, however, poor compatibility with aqueous and polar solvents and is generally unsuitable for on-bead magic angle spinning (MAS) NMR analysis.[7] Poly(ethylene glycol) (PEG) has been used to improve swelling and overcome the shortcomings of the PS-DVB resins for use in water and polar solvents, with the development of PEG-grafted PS-DVB resins[8–10] and PEG cross-linked resins.[11–14] The rigidity and hydrophobicity of the PS-DVB core necessitated grafting long PEG chains (>3 kDa) to optimize hydrophilicity with the inherent drawback of lowered loading (0.2–0.5 mmol g^{-1}). Contemporary PEG crosslinked resins also have normally low loading (0.2–0.4 mmol g^{-1})[15] and may possess sensitive benzyl ether and amide bonds that restrict certain chemistry. As an alternative to PEG, polyglycerol was grafted onto PS resin to increase loading (up to 4.3 mmol g^{-1}) and improve swelling in water (up to 2.6 mL g^{-1}).[16] However, a relatively low grafting yield and the presence of both primary and secondary alcohols that may exhibit different reactivities are drawbacks to this strategy. High-loading resins are effective scavengers[17–19] and offer promise for a variety of chemistry. High loading on a PS-derived resin with high swelling in a wide range of media has yet to be achieved, because of the restrictions of the hydrophobic PS-DVB core.

In a new approach for making resins with high loading and good swelling in a variety of solvents, we have grafted PEG chains onto a crosslinked poly(vinyl alcohol) (PVA) core. The hydrophilic PVA resins are mechanically-stable and possess high loading (15–17 mmol g^{-1}) and good swelling in water and *N*,*N*-dimethylformamide (DMF).[19–21] By grafting short PEG chains onto the PVA core, novel amphiphilic supports possessing chemically stable C–C and C–O–C bonds, high loading and optimal swelling properties in a variety of solvents have now been synthesized and employed in solid-phase synthesis and solid supported catalysis in aqueous and organic solvents.

Crosslinked PVA beads that exhibited good mechanical stability were prepared by employing dimethyl sulfoxide (DMSO) as a co-solvent for solvating the more hydrophobic epichlorohydrin crosslinker and the alkalized aqueous solution of linear PVA in a modification of our previously published procedure.[19–22] Anionic polymerization of ethylene oxide was used to graft PEG onto PVA resin in a controlled fashion to provide PVA-PEG resins **2** possessing various chain lengths (Scheme 1). Naphthalene potassium was used as base for deprotonating the OH groups on the PVA beads to generate alkoxide anions which initiate the ring opening polymerization of ethylene oxide on the resins.

Spherical and free-flowing PVA-PEG resins were observed by optical microscopy with sizes of 30–100 μm in diameter and PVA-PEG beads have a smooth surface as observed under scanning electron microscopy (Fig. 1). The PVA resins can be made with different porosity by adjusting the degree of crosslinking.[20] The size of the PVA-PEG beads resembled that of the PVA beads selected for the anionic polymerization. The mechanical properties of the PVA resins have been studied previously.[21] The PVA-PEG resins were mechanically stable in the swollen state, and very resistant to shaking and mechanical stirring. The new resins were unaffected by treatments with 6 M HCl and with 6 M NaOH, showing good chemical stability. The hydroxyl group loadings were titrated with Ac_2O[19–22] to be 6.2, 3.4 and 2.0 mmol g^{-1} for the PVA-PEG resins with 5, 12 and 20 PEG units, respectively, in reasonable agreement with theoretical loadings calculated from mass gain (6.7, 3.6 and 2.1 mmol g^{-1}, respectively). PEG-grafted PVA resin **2** displayed increased swelling in less polar solvents relative to PVA resin **1**, and uniformly higher swelling in a variety



Scheme 1 Preparation of PVA-PEG resin **2** and peptide synthesis.

Département de Chimie, Université de Montréal, C.P. 6128, Succ. Centre-ville, Montréal, QC, H3C 3J7, Canada.
E-mail: julian.zhu@umontreal.ca; Fax: (01-514)340-5290;
Tel: (01-514)340-5172

† Electronic supplementary information (ESI) available: Experimental details for the characterization of the resins, the solid-phase reactions and TEMPO oxidation. See DOI: 10.1039/b700215g

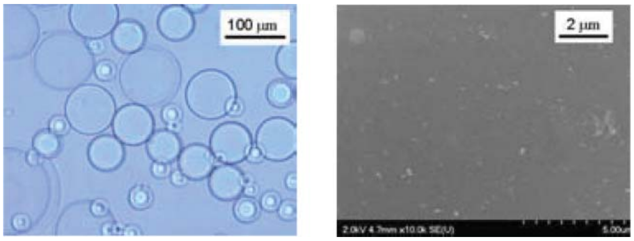


Fig. 1 Optical (left, in water) and scanning electron micrographs (right, dry) of PVA-PEG resin **2** with five PEG units.

of solvents in comparison with TentaGel, Merrifield and Wang resins (Fig. 2).

The utility of the PVA-PEG resin was demonstrated first by the synthesis of the transglutaminase substrate[23] dipeptide **4** (Z-Gln-Gly-NH_2) on PVA-PEG_5 resin in 98% isolated yield and 92% purity as ascertained by LC-MS analysis (Scheme 1).[24] Considering the advantages of high loading for solid supported catalysis in aqueous and organic media, the catalyst 2,2,6,6-tetramethylpiperidinyloxy (TEMPO)[25] radical was next attached onto PVA-PEG_5 resin **2** using the Cu(I)-catalyzed [2 + 3] dipolar cycloaddition reaction[26,27] (Scheme 2) between a polymer-supported azide **6** and an alkyne-derivatized TEMPO species **7**. TEMPO resin **9** catalyzed efficiently alcohol oxidations to aldehydes and ketones in a biphasic bleach/dichloromethane (DCM) media likely due to its high loading (1.8 mmol g^{-1} by nitrogen elemental analysis) and effective swelling in both DCM and water. TEMPO resin **9** floated at the interface between DCM and water. Such physical properties are considered to enhance catalytic activity by facilitating the transfer of the reaction intermediates between the two phases. A series of primary and secondary alcohols were subjected to the PVA-PEG-TEMPO/bleach/DCM oxidation (Table 1) for 5 to 240 min and the corresponding carbonyl compounds were isolated by simple filtration and phase separation in 80–98% yields. The recycling property of TEMPO resin **9** was examined with benzyl alcohol and monitored by thin layer chromatography (TLC). After twelve cycles of repeated catalysis, the time for complete oxidation of benzyl alcohol to benzaldehyde increased from 5 to 18 min, indicating relatively stable catalytic performance.

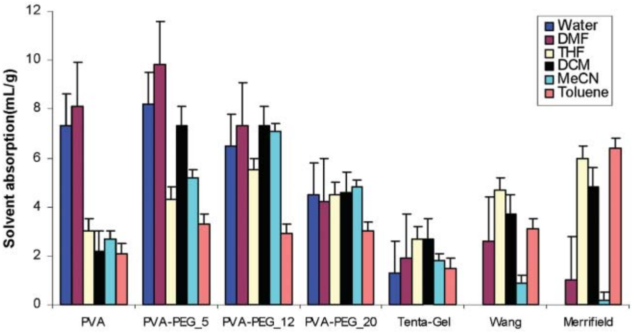
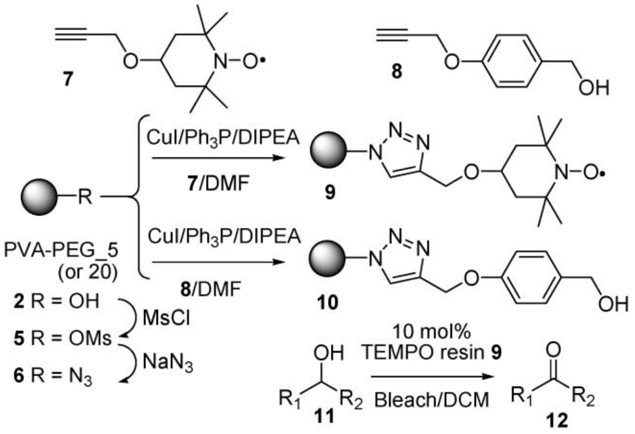
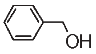
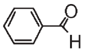
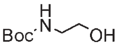
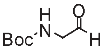
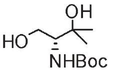
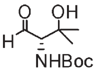
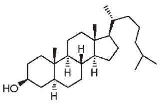
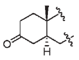
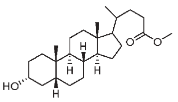
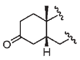


Fig. 2 Swelling of PVA, PVA-PEG and commercial resins as ascertained by weighing beads saturated with absorbed solvent. Merrifield (2% DVB crosslinking, 100–200 mesh, 2.0 mmol g^{-1} loading) and Wang resins (1% DVB crosslinking, 100–200 mesh, 1.0 mmol g^{-1} loading) were purchased from Fluka, and Tenta Gel S OH resin (90 μm, 0.2–0.3 mmol g^{-1} loading) from Rapp Polymere GmbH.



Scheme 2 Preparation of PVA-PEG-supported TEMPO catalyst **9** for alcohol oxidations and of Wang linker resin **10**.

Table 1 Bleach/DCM alcohol oxidation with TEMPO resin **9**

Alcohol **11**	Product **12**	Time	Conv. (%)	Yield[c] (%)
		5 min	100[a]	98
		30 min	100[a]	87
		30 min	100[a]	90
		30 min	100[a]	86
		4 h	96[b]	80
		4 h	99[b]	87

[a] Monitored by TLC. [b] Determined by ^1H NMR. [c] Isolated yields.

A PVA-PEG Wang linker resin **10** was similarly made by dipolar cycloaddition using *p*-propargyloxy benzyl alcohol **8** and azide resin **6** with PEG chains of 20 units (Scheme 2).[24] The MAS ^1H NMR spectrum of PVA-PEG Wang resin **10** in DMF-d_7 (Fig. 3) exhibited relatively high resolution of the proton signals of the resin matrix and linker. The splittings of the aromatic proton doublets were observed to be 6.5 Hz at 7.50 and 7.22 ppm. Furthermore, the PVA-PEG matrix exhibited a main signal around 3.6 ppm and three weak signals between 1.0 and 2.0 ppm, which may avoid overlaps with signals from supported structures during on-bead HR-MAS ^1H NMR analysis.

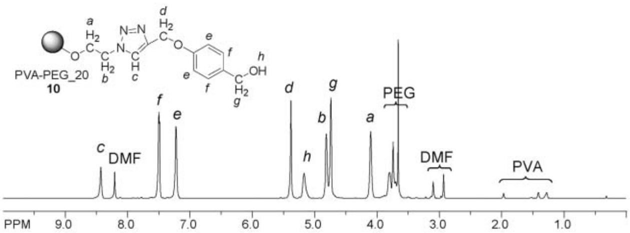


Fig. 3 HR-MAS ^{1}H NMR (600 MHz, nanoprobe spin rate: 6 kHz, DMF-d_7) spectrum of PVA-PEG Wang linker resin **10**.

In summary, a novel effective approach for producing high-loading resins with high uniform swelling in aqueous and organic solvents has been developed by grafting PEG chains onto hydrophilic PVA core. The new resins were suitable for on-bead MAS NMR analysis and possessed attributes for solid-phase chemistry. The strong potential for applying the new PVA-PEG resins as supports for catalysis in biphasic solvent systems was demonstrated by the synthesis and use of TEMPO resin **9** in catalytic alcohol oxidations. Considering these advantages, this methodology and the polymer matrices may find many practical applications for solid-phase chemistry.

Financial support from the Natural Sciences and Engineering Research Council (NSERC) of Canada, Valorisation-Recherche Québec (VRQ) and the Canada Research Chair program is gratefully acknowledged.

Notes and references

‡ *Preparation* of PVA-PEG resin **2**: All glassware and needles were flame-dried under vacuum and purged three times with nitrogen. PVA beads **1** (0.4 g) were placed into a 100 mL flask, equipped with a Dean–Stark trap, containing 20 mL of dry benzene and heated under reflux overnight to remove the water–benzene azeotrope. Benzene was distilled off under vacuum and 25 mL of dry DMSO was charged into the flask to swell the PVA resin. A calibrated amount of potassium naphthalene in THF (0.45 M, 6 mL, 0.45 eq.) was introduced dropwise into the flask using a double-tip needle and argon pressure. The mixture was stirred for 2 h to allow the green color from the naphthalene potassium to completely disappear. Ethylene oxide of a known volume was passed through a calcium hydride drying-column and condensed into a dry flask containing 2 mL of *n*-butyllithium (1.6 M) solution in hexane at −78 °C. The dry ice/acetone bath was removed and, as the flask warmed, ethylene oxide was distilled into the resin suspension which was cooled to −78 °C. Once the transfer of ethylene oxide was completed, the polymerization mixture was heated and magnetically stirred at 40 °C for 48 h. The resin was filtered off and rinsed with water and THF and subsequently extracted successively with THF and water using a Soxhlet extractor for 24 h per solvent. The beads were finally freeze-dried for 48 h to give copolymer resin **2** and stored below 5 °C under nitrogen.

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