Novel monodisperse PEG-grafted polystyrene resins: synthesis and application in gel-phase ^{13}C NMR spectroscopy

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ABSTRACT

A series of novel polystyrene-oligo(oxyethylene) graft copolymers containing monodisperse PEG units ($n = 2$–12) have been synthesized and examined concerning their applicability for gel-phase ^{13}C NMR spectroscopy. A strong correlation between the graft length and the line widths in the gel-phase spectra was observed. By grafting a PEG chain with only eight units, it was possible to obtain results similar to TentaGel resin. Additionally, TOF-SIMS images were recorded in order to evaluate the homogeneity of the resin.

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Solid-phase organic synthesis (SPOS) has historically been the most important method for synthesis of polypeptides and oligonucleotides. The extension of SPOS to the broader area of small, drug-like organic molecules has more recently become important for combinatorial chemistry. Due to the establishment of high-throughput-screening (HTS) processes over the last years, there has been immense work devoted to developing suitable resins. The most commonly used solid supports are cross-linked polystyrene (PS) and poly(styrene-oxyethylene) graft copolymers (PS-PEG).

The last mentioned supports, first reported by Bayer and Rapp,[1] display good swelling in a variety of solvents from medium to high polarity. In addition, they provide good quality gel-phase ^{13}C NMR spectra, which are useful for non-destructive on-resin analysis.[2] The copolymers are produced by grafting ethylene oxide to the PS backbone creating long flexible polydisperse chains (the commercial resins TentaGel and ArgoGel bear about 60–70 PEG units) that provide a 'solution-like' environment for attached moieties. The main drawback of such resins is the low degree of substitution (about 0.2–0.3 mmol/g) compared to classical PS resin (e.g., Merrifield, 1–1.5 mmol/g) and a huge signal in the gel-phase spectra resulting from the 60–70 oxyethylene units. In our strategy, we substituted this long PEG chain against shorter monodisperse oligo(oxyethylene) tethers ($n = 2$–12 units) with the objective of increasing the loading and minimizing the PEG signal in the gel-phase spectra. In this letter, we report a systematic investigation of the effect of PEG group length on the quality of gel-phase ^{13}C NMR spectra, using the line width of an attached sensor molecule as the major criterion.

As shown in Scheme 1, the initial step in the resin synthesis was the monoprotection of glycols **1a–f** ($n = 2, 4, 6, 8, 10, 12$) by conversion with *tert*-butyldimethylsilyl chloride (TBSCl)[3] (glycols **1a,b,c** ($n = 2, 4, 6$) are commercially available; the higher homologues have been synthesized according to a procedure by Keegstra and co-workers[4]). In the second step, these protected glycols (**2a–f**)[5] were attached to polymer-bounded phenol by applying a Mitsunobu reaction[6] (DEAD, PPh$_3$) as key step in this reaction scheme. For deprotection, the resins **3a–f** were swollen in THF and were treated with a 1.0 M solution of TBAF in THF to give the novel monodisperse PEG-grafted resins **4a–f** in quantitative yield. Each reaction step on solid phase was monitored using IR and gel-phase ^{13}C NMR spectroscopy.

We have selected a number of small molecules with easily assignable NMR spectra as sensor molecules in a recent study of gel-phase ^{13}C NMR spectroscopy covering commercial resins.[7] Of these, 4-(dimethylamino)-butyric acid hydrochloride was chosen for the present work as its high polarity makes it a very demanding sensor for gel-phase NMR, which is usually carried out in solvents of low to medium polarity due to the swelling abilities of the resin backbone. The acid was attached to the resins' hydroxyl groups using a carbodiimide-based coupling method.[8]

A gel-phase ^{13}C NMR spectrum was recorded for each of the loaded resins **5a–f**. Figure 1 shows spectra of **5d** and commercially

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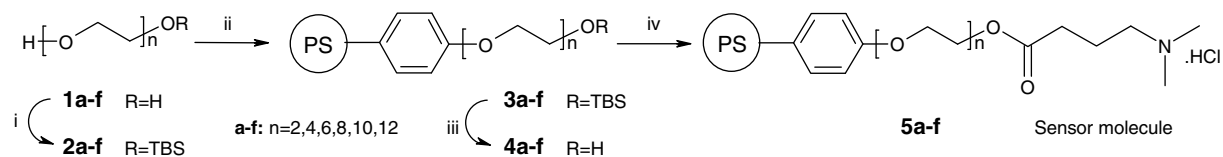
Scheme 1. Reagents and conditions: (i) TBSCl (0.5–1 equiv), imidazole or pyridine, DCM, 24 h; (ii) polymer-bounded phenol, DEAD (5 equiv), Ph₃P (5 equiv), DCM/THF = 1/1, 24 h; (iii) TBAF (5 equiv), THF, 1 h; (iv) 4-(dimethylamino)-butyric acid hydrochloride (5 equiv), DIC (5 equiv), HOBt (5 equiv), DMAP (1 equiv), DCM/DMF = 9/1, 24–48 h.
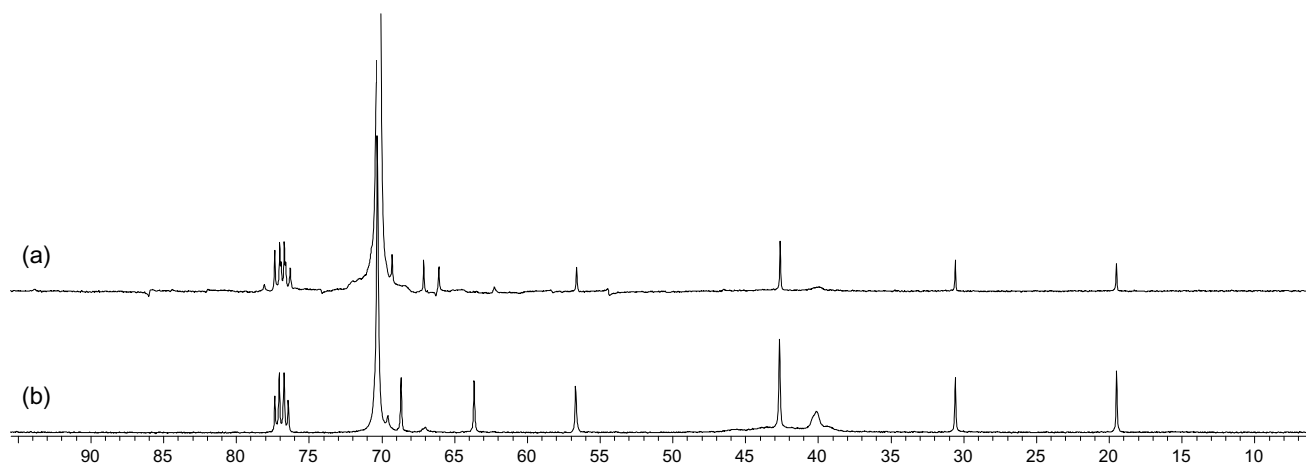

Figure 1. Gel-phase ^{13}C NMR spectra of resin **5d** (b) compared to TentaGel loaded with the same sensor molecule (a).

available TentaGel resin loaded with the same sensor molecule recorded under identical conditions. The increase of signal intensity and the decrease of the PEG peak height in the spectrum of **5d** are clearly visible. In order to characterize each spectrum by a single value, an average half-height line width of all non-quaternary carbon peaks of the immobilized sensor molecule was determined. In Figure 2, the results of the line width analysis are shown: due to the improving solvation and mobility of the attached moiety, the line width decreases with increasing number of ethylene glycol units. Already eight units (resin **5d**, avg. line width 10.1 Hz) are sufficient to obtain high-quality spectra, although the higher homologues get a little closer to TentaGel resin ($n \approx 68$, avg. line width 9.5 Hz).

Table 1 shows the loadings (which of course show a small decrease with increasing PEG length) and swelling ability of the novel PEG resins in different solvents. Except for methanol (where swelling is known to be generally poor), the new resins provide good swelling from four glycol units and above.
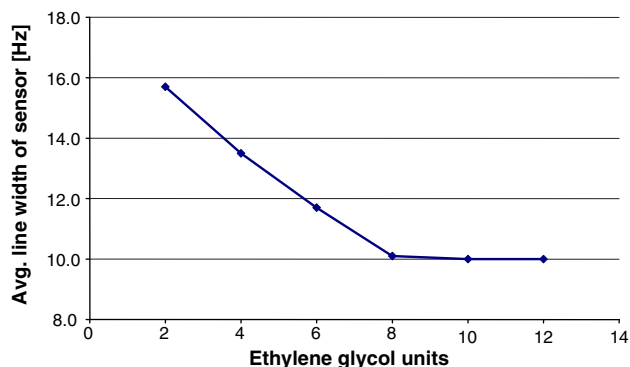

Figure 2. Effect of PEG group length on the average half-height line width of the sensor molecule.

Table 1
Swelling volume (mL/g)[b] of selected resins at 25 °C in different solvents

Entry	Resin	loading[c]	MeOH	DMF	THF	DCM
1	Merrifield[a]	1.5	0.7	4.3	7.5	7.3
2	**4b** ($n = 4$)	1.1	1.5	6.8	8.5	7.8
3	**4d** ($n = 8$)	0.9	2.1	6.7	7.1	8.0
4	**4f** ($n = 12$)	0.7	2.1	6.0	7.3	8.6
5	TentaGel[a]	0.3	2.7	4.1	4.2	5.7

[a] Obtained from Advanced ChemTech.
[b] Based on the weight difference between dry and swollen beads, recalculating the data to express it as mL/g.
[c] In mmol/g, for resins **4b,d,f** determined gravimetrically.

In order to test the ability of our resins to perform as support, we carried out a known reaction sequence leading to 3,5-dibenzylhydantoin[9] using one of our resins (**4d**, $n = 8$) as well as commercially available Tentagel support. This four-step sequence was selected because it involves a variety of reactions and reagents in different solvents. Although in both cases an overall yield of approximately 50% was obtained, this is equivalent to an amount of 90 mg of the final product when starting from 1 g of **4d**, but only 25 mg when using 1 g of Tentagel. Thus, a substantially lower amount of our resin is needed to obtain an intended quantity of a target compound.

In conclusion, we have shown that polystyrene resins grafted with short, monodisperse PEG units can easily be synthesized from polymer-bounded phenol and offer advantageous properties for gel-phase NMR spectroscopy. In combination of loading and spectral quality resin **4d** with eight ethylene glycol units showed best results. The advantage of the higher loading of our resins has been shown in a four-step reaction sequence.

TOF-SIMS measurements:[10] Additionally, secondary ion mass spectrometry was performed on some selected examples of the resins loaded with the sensor molecule 4-(dimethylamino)-butyric acid hydrochloride (**5b,d,f**; see Fig. 3 as well as Supplementary data).
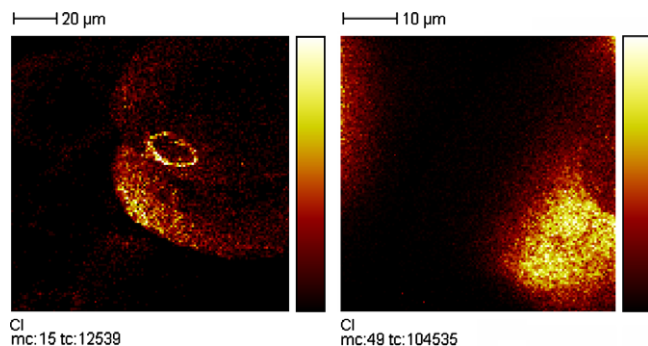
Figure 3. TOF-SIMS images of immobilized sensor molecule on TentaGel (left) and resin **5d** (right).[11]

The figures display the elemental distribution of ^{35}Cl within the samples. Thus, the attached molecules on individual beads of the resin can be depicted directly via their chlorine atoms, and the corresponding intensity gives an indication of the amount of loading. Further investigations to utilize the TOF-SIMS technique to study SPOS resins will be undertaken.

Supplementary data

Some representative IR spectra and more examples of gel-phase ^{13}C NMR spectra of prepared resins, as well as TOF-SIMS images of further resins. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.128.

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5. *Characterization data for compound* **2d**: ^{1}H NMR (CDCl$_3$): δ 3.75–3.44 (m, 32H), 2.76 (br s, 1H), 0.83 (s, 9H), 0.00 (s, 6H). ^{13}C NMR (CDCl$_3$): δ 72.6 (t), 72.5 (t), 70.7 (t), 70.5 (t, 10C), 70.3 (t), 62.6 (t), 61.7 (t), 25.9 (q, 3C), 18.3 (s), −5.3 (q, 2C). Anal. Calcd for C$_{22}$H$_{48}$O$_9$Si: C, 54.52, H, 9.98. Found: C, 54.48, H, 9.72.
6. *Experimental procedure for Mitsunobu reaction on solid phase*: Diethyl azodicarboxylate (5 equiv) was added dropwise to a mixture of 1.0 equiv of polymer-bounded phenol (100–200 mesh, 1% divinylbenzene, Aldrich, 1.7 mmol/g) in dry DCM/THF = 1/1 (50 mL/g resin) under argon. Then, the monoprotected glycol **2** (5 equiv), dissolved in dry THF, was added and finally triphenylphosphine was added slowly. The reaction mixture was stirred overnight, filtered, and the solid residue was washed three times with DCM/THF = 1/1, DCM, isopropanol, DCM and finally with methanol. The resulting resin **3** was dried to constant weight in vacuo.
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8. *General procedure for preparation of resin* **5:** Resin **4** was suspended in dry DCM/DMF = 9/1 (15 mL/g resin), and then 4-(dimethylamino)-butyric acid hydrochloride (5.0 equiv) and 1-hydroxybenzotriazole (5.0 equiv) were added in a minimum amount of dry DMF. 4-(N,N-dimethylamino)-pyridine (1.0 equiv) in dry DMF and N,N′-diisopropylcarbodiimide (5.0 equiv.) were added to the mixture and were stirred under argon at room temperature for 2 days. The resulting suspension was filtered and the solid residue was washed three times with DMF, then with DCM, and finally with methanol. The resin was dried to constant weight in vacuo.
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11. The field of view is always 128 × 128 pixels, independent from the μm scale. The color scale depends on 'mc value' (maximum counts per pixel), not on the 'tc value' (total counts).
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