Solid-phase synthesis of oligoethers: soluble polymer model studies

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(Received 31 August 1993; revised 25 October 1993)

A soluble chloromethylated polystyrene has been used as a support for the stepwise synthesis of oligoethers. The building block was the monotrityl ether of tetraethylene glycol, and coupling, deprotection, activation and elongation steps have been successfully developed. The progress of reactions has been demonstrated by elemental analysis of the polymer and *FT*i.r. spectral analysis. Most powerful, however, has been ^{1}H n.m.r. spectroscopy, made possible by the soluble nature of the polymer. While successive reactions on the polymer appear to be highly efficient, work-up and isolation inevitably result in loss of polymer mass, and preclude this from being a viable methodology for scale-up.

(Keywords: synthesis; oligoethers; n.m.r. spectroscopy)

INTRODUCTION

The solid-phase synthesis technique, pioneered by Merrifield[1], has been exploited in an enormous variety of chemical reactions[2,3]. The concept has found use in biochemistry and biotechnology[4]; for example, the synthesis of oligopeptides is now highly developed and routine[5], while every recombinant DNA laboratory uses similar methodology for oligonucleotide production[6]. However, successful use in other extended stepwise syntheses has not been achieved, although the efforts to do this have been restricted. We have recently attempted to use this approach to synthesize oligoethers[7], since a cheap and convenient method for producing monodisperse oligoethers[8] could be of commercial interest. In attempting to develop such a methodology we have experienced great difficulty with apparently simple strategies, our attempts being handicapped by low conversions in coupling, deprotection and activation steps. As with all solid-phase methods, structural quantification, indeed even qualification, has proved a major problem, and in an attempt to at least demonstrate the feasibility of our approach, we have carried out a stepwise synthesis on a soluble polymer support. This has enabled us to record solution ^{1}H nuclear magnetic resonance (n.m.r.) spectra at each stage of the synthesis, and this paper reports our findings.

EXPERIMENTAL

Materials

Styrene was used as supplied by Fisons. Vinyl benzyl chloride (a mixture of *meta* and *para* isomers, ~60/40) was used as supplied by the Dow Chemical Company. Toluene (supplied by Strathclyde Chemicals) was dried over $CaCl_2$ initially and then over fresh sodium wire before being fractionally distilled from P_2O_5. Dichloromethane (BDH Chemicals) was predried over $CaCl_2$ then distilled from P_2O_5. It was stored over anhydrous Linde-type 4 Å molecular sieves. Triethylamine (Aldrich Chemical Company) was dried with Linde-type 4 Å molecular sieves, then distilled from P_2O_5. Diethyl ether (BDH Chemicals) was dried using sodium wire and was distilled from this prior to use. Trifluoroacetic acid (Aldrich Chemical Company) was refluxed over, then distilled from, P_2O_5. Methane sulfonyl chloride (Aldrich Chemical Company) was distilled under reduced pressure from P_2O_5. Ethyl acetate (Strathclyde Chemicals) was predried with $MgSO_4$ then distilled from P_2O_5. Hexane (Strathclyde Chemicals), bis-(2(2-hydroxyethoxy)-ethyl)-ether (tetraethylene glycol; >99% pure, Fluka AG), 4-dimethylaminopyridine (Reilly Chemicals) and trichloroacetyl isocyanate (Aldrich Chemical Company) were used as supplied.

P_2O_5 (Aldrich Chemical Company) and $MgSO_4$ (BDH Chemicals) were dried at 100°C in an oven for several hours before use. Linde-type 4 Å molecular sieves (1.6 mm pellets; BDH Chemicals) were heated in a muffle furnace at ~500°C for several hours prior to use. $CaCl_2$ (BDH Chemicals) was dried in an oven at 100°C for several hours before use. Triphenylmethyl (trityl) chloride (Aldrich Chemical Company), NH_4HCO_3 (Fisons), NaOH (May and Baker), NaH (80% dispersion in mineral oil; Aldrich Chemical Company) and azobisisobutyronitrile (AIBN; Aldrich Chemical Company) were used as supplied.

Preparation of monotrityl-protected tetraethylene glycol

The availability of a pure, selectively monoprotected tetraethylene glycol was pivotal to our synthetic strategy,

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0032-3861/94/13/2867-07

as were the similarly protected building blocks reported by Keegstra *et al.*[8]. Triphenylmethyl (trityl) chloride (TrCl) (4 g, 14.4 mmol) in dichloromethane (15 ml) was added in portions over a 20 min period to a solution of tetraethylene glycol (20 ml, 115 mmol), triethylamine (3.7 ml, 26.3 mmol) and 4-dimethylaminopyridine (70.1 mg, 4 mol% in TrCl, 0.57 mmol) in dichloromethane (20 ml) at ice temperature. The ice bath was removed after addition was complete, and the mixture was allowed to stir at room temperature for 2 h, after which time the completion of the reaction was checked by thin layer chromatography (plate: silica gel coated aluminium sheet $60F_{254}$ (0.2 mm), Merck; eluent: diethylether). The dichloromethane solvent was removed *in vacuo* and the residue distributed between ethyl acetate (70 ml) and saturated ammonium hydrogen carbonate solution (6 × 40 ml). The ethyl acetate layer was dried ($MgSO_4$) and evaporated. This solvent was difficult to remove completely and so the product was dissolved in toluene and the mixture of solvents removed *in vacuo* to leave a viscous liquid residue (6.01 g, 96% yield).

Elemental microanalysis (%): theory, C, 74.3; H, 7.3; found, C, 74.6; H, 7.4. ^{1}H n.m.r. ($CDCl_3$), 250 MHz: δ(ppm), 7.45 (6H, m, oH–Ph–C); 7.28 (11H, m, m and pH–Ph–C); 3.68 (11H, broad s, OCH_2CH_2O); 3.58 (2H, t, $-CH_2CH_2OH$); 3.24 (2H, t, $-CH_2CH_2OTr$); 2.65 (1H, broad s, –OH). *FT*i.r. liquid film: ν (cm^{-1}) 3453 (OH); 3085–3027 (CH); 2912–2870 (CH); 1598 (C=C); 1446–1368, (CH); 1244, 1092 (C–O–C); 762/705 C···C).

This method, in particular the extraction procedure, minimizes contamination from residual diol which could adversely influence stepwise synthesis, introducing cross-links. Small amounts of ditritylated products are less important since these would simply not participate in the first and subsequent coupling reactions (see later). To assess the purity of the monotritylated product a sample was treated with trichloroacetyl isocyanate. The original $-CH_2OH$ resonance is shifted ~0.7 ppm in the product, which allows reliable integration. Making the assumption that the work-up procedure removed all unreacted diol, careful analysis of the integrated alcohol and trichloroacetyl derivative spectra indicated a purity of ~98% in terms of the monoprotected species.

Preparation of soluble chloromethylated polystyrene support

Monomers (styrene 40 cm^3, 0.34 mol) and vinylbenzyl chloride (6 cm^3, 0.043 mol) were washed with sodium hydroxide solution (1% w/v aqueous solution, 3 × 25 cm^3) to remove any polymerization inhibitors, and then with water until the pH of the washings returned to 7. AIBN (1% w/v of monomers, 0.05 g) was added to the monomers before these were poured into a 500 cm^3 round-bottomed flask equipped with a nitrogen inlet, reflux condenser and magnetic stirring bar, and containing toluene solvent (200 cm^3). The flask was placed in an oil bath and heated to 80°C for 17 h. At the end of this time most of the solvent was removed under reduced pressure using a rotary evaporator. The residue was poured dropwise into a beaker of cold stirred hexane to precipitate the polymer. The product was dried in a vacuum oven at 40°C.

Elemental microanalysis: found, C, 86.3; H, 7.2; Cl, 5.5; corresponding to ~1.6 mmol chloromethyl groups per g polymer, i.e. ~17.6% loading of aromatic groups with chloromethyl groups (see Discussion for ^{1}H n.m.r. spectrum, *Figure 1*).

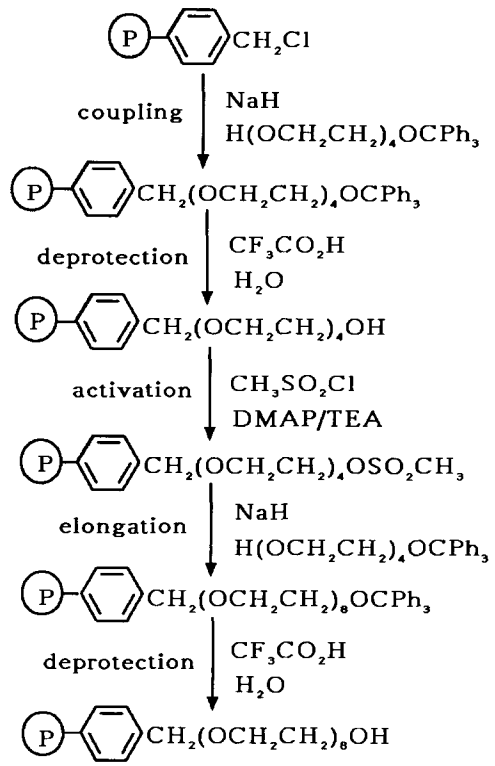
Stepwise oligoether synthesis on support

The overall strategy for stepwise assembly using a tetraethylene glycol (ether) building block is shown in *Scheme 1*. Step one involves the coupling of the first ether residue to the support, step two is cleavage of the trityl protecting endgroup, step three is the mesylation of the hydroxyl terminal group to activate it, and step four is the coupling of the second ether residue (chain elongation). Typical procedures were as follows.

Initial coupling of first ether building block. Sodium hydride (0.39 g, 80% dispersion in oil i.e. 0.32 g, 13 mmol) was placed in a two-necked round-bottomed flask (250 ml) equipped with a nitrogen inlet, drying tube and magnetic stirring bar. Diethyl ether (10 ml) was added and the mixture stirred under a nitrogen atmosphere for 10 min. The stirrer was stopped, the solvent allowed to settle and the supernatant liquid removed via a Pasteur pipette. The process was repeated once more from the addition of diethyl ether, to remove the oil from the sodium hydride.

Monotritylated tetraethylene glycol (57 g, 13 mmol), and toluene (50 ml) were added to the washed sodium hydride and the mixture was stirred at room temperature for 1 h under a nitrogen atmosphere. The nitrogen supply was removed, chloromethylated polystyrene (2 g, 3.12 mmol, CH_2Cl) dissolved in the minimum volume of toluene was added to the flask and the latter was fitted with a reflux condenser and guard tube. The mixture was allowed to reflux for 24 h.

At the end of the reaction, after washing with water, most of the toluene solvent was removed using the rotary evaporator. The remaining sticky liquid was added dropwise, by means of a Pasteur pipette, into a beaker of cold, stirred hexane (200 ml). The supernatant liquid was decanted and the polymer adhering to the sides of the beaker was collected and allowed to stand in fresh



Scheme 1 Solid-phase oligoether synthesis strategy (DMAP, dimethylaminopyridine; TEA, triethylamine)

Table 1 Elemental microanalytical data for soluble polymers isolated at each stage of oligoether stepwise synthesis

Reaction stage	Elemental microanalysis (%)				Polymer loading (mmol g^{-1})[a]	Weight of polymer (g)	
	C	H	Cl	S		Before	After
Ⓟ–CH_2Cl	86.2	7.2	5.5	–	1.6	–	–
Ⓟ–$CH_2(OCH_2CH_2)_4OC(C_6H_5)_3$	84.2	7.0	0.7	–	1.4	2.00	1.88
Ⓟ–$CH_2(OCH_2CH_2)_4OH$	83.3	7.8	0.0	–	–	1.50	0.90
Ⓟ–$CH_2(OCH_2CH_2)_4OSO_2CH_3$	78.5	7.5	0.0	2.9	0.9	0.65	0.60
Ⓟ–$CH_2(OCH_2CH_2)_8OC(C_6H_5)_3$	80.7	7.6	0.0	0.0	0.9	0.50	0.27
Ⓟ–$CH_2(OCH_2CH_2)_8OH$	72.7	7.9	0.0	–	–	0.12	0.06

[a] Loading of pendent group on polymer backbone calculated from content of heteroatom, or change in content of heteroatom

hexane. Finally, the product was filtered and dried in a vacuum oven at 40°C; yield, 1.88 g. For elemental microanalytical data see *Table 1*. The ^{1}H n.m.r. spectrum is shown in *Figure 2* (see Discussion).

Removal of trityl protecting endgroup. Monotritylated tetraethylene glycol (1.5 g) was placed in a round-bottomed flask (100 ml) along with 5% (v/v) trifluoroacetic acid in dichloromethane (10.5 ml, 4.6 mmol) and dichloromethane (20 ml). The mixture was allowed to stand, with occasional swirling, for 24 h.

At the end of the reaction, the reaction mixture was placed into a separating funnel and washed with saturated ammonium hydrogen carbonate solution (50 ml aliquots) until the evolution of gas had ceased. The organic layer was washed with water until the pH of the water washings returned to 7, and most of the solvent was removed using the rotary evaporator. The remaining sticky liquid was added dropwise, by means of a Pasteur pipette, into a beaker of cold, stirred hexane (200 ml). The supernatant liquid was decanted and the polymer adhering to the sides of the beaker was allowed to stand in fresh n-hexane. Finally, the product was dried in a vacuum oven at 40°C; yield, 0.9 g. For elemental microanalysis see *Table 1*. The ^{1}H n.m.r. spectrum is shown in *Figure 3* (see Discussion).

Activation of terminal hydroxyl group by mesylation. Methane sulfonyl chloride (0.5 ml, 7.71 mmol) in dichloromethane (5 ml) was added to a round-bottomed flask (100 ml) at 0°C containing 4-dimethylamino pyridine (0.41 g, 3.36 mmol), triethylamine (0.5 ml, 3.59 mmol), monotritylated tetraethylene glycol (0.65 g) and dichloromethane (15 ml). The mixture was allowed to stir at room temperature overnight. The polymer product was isolated as before and again dried at 40°C; yield, 0.6 g. For elemental microanalysis see *Table 1*. The ^{1}H n.m.r. spectrum is shown in *Figure 4* (see Discussion).

Chain elongation reaction. The sodium salt of monotritylated tetraethylene glycol (0.15 g, 0.32 mmol) was prepared as detailed in the first coupling reaction. Monotritylated tetraethylene glycol (0.5 g) was dissolved in the minimum volume of toluene and the reaction and work-up pursued again as described in the first coupling reaction; yield, 0.27 g. For elemental microanalysis see *Table 1*. The ^{1}H n.m.r. spectrum is shown in *Figure 5* (see Discussion).

Second deprotection step. This was carried out essentially as described earlier, using 0.12 g of monotritylated tetraethylene glycol. The final yield of polymer product was 0.06 g. No attempt was made to cleave the oligoether from the support because of the very small amount of product remaining. The elemental microanalysis is shown in *Table 1* and the ^{1}H n.m.r. spectrum is shown in *Figure 6* (see Discussion).

The model stepwise synthesis was terminated at this point.

Characterization procedures

^{1}H n.m.r. spectra were recorded in $CDCl_3$ solutions on a Bruker 250 MHz instrument. I.r. spectra were recorded in KBr discs using a Nicolet 20 SXB Fourier transform spectrometer. Elemental microanalyses were performed on a Carlo Erba Analyser 1106.

DISCUSSION

Preparation of the soluble chloromethylated polystyrene support was straightforward. From the Cl content the loading of $-CH_2Cl$ groups is $\sim$1.1 mmol g^{-1}. This implies that vinyl benzyl chloride residues are incorporated into the polymer more readily than styrene residues, and this is consistent with the published radical reactivity ratios[9]: vinyl benzyl chloride, 1.08; styrene, 0.72. The result also agrees with findings from 12 crosslinked resins prepared in this project[7]. The presence of the $-CH_2Cl$ groups was also indicated by the characteristic peak at 1260 cm^{-1} in the i.r. spectrum, and by the ^{1}H n.m.r. spectrum (*Figure 1*). The latter shows the broad aliphatic backbone CH,CH_2 resonances at $\delta = 1$–2, and the broad aromatic CH resonances at $\delta = 6.2$–7.2, together with two small broad peaks at $\delta = 4.35$ and 4.55. These correspond to the chloromethyl CH_2 protons, one being the *meta* isomer and the other the *para*[9]. The sharp peaks at $\delta = 7.25$, 2.35, 2.2 and 1.5, and the feature at $\delta = 0.9$ are associated with trapped solvent (toluene, n-hexane) and probably fragments from the inhibitor and free-radical initiator. These are absent from later polymer samples.

The initial coupling reaction proceeded to $\sim$85% conversion based on the elemental microanalysis (*Table 1*). Soluble polymer was recovered in $\sim$50% yield. The loss of the 1260 cm^{-1} absorption in the i.r. spectrum confirmed the relatively high conversion. Again, the ^{1}H n.m.r. spectrum (*Figure 2*) is highly informative. This shows the broad backbone CH,CH_2 and aromatic CH resonances as before, but in addition there is a shift in the benzylic CH_2 resonances from $\delta = 4.35$ and 4.55 for the CH_2Cl to $\delta = 4.15$ and 4.30 for the corresponding benzylic CH_2O resonances. Most obvious, however, are the appearances of the sharp and intense aromatic CH resonances at $\delta = 7.25$ and 7.45 due to the terminal trityl group, the intense and extensive resonances at $\delta = 3.4$–3.6

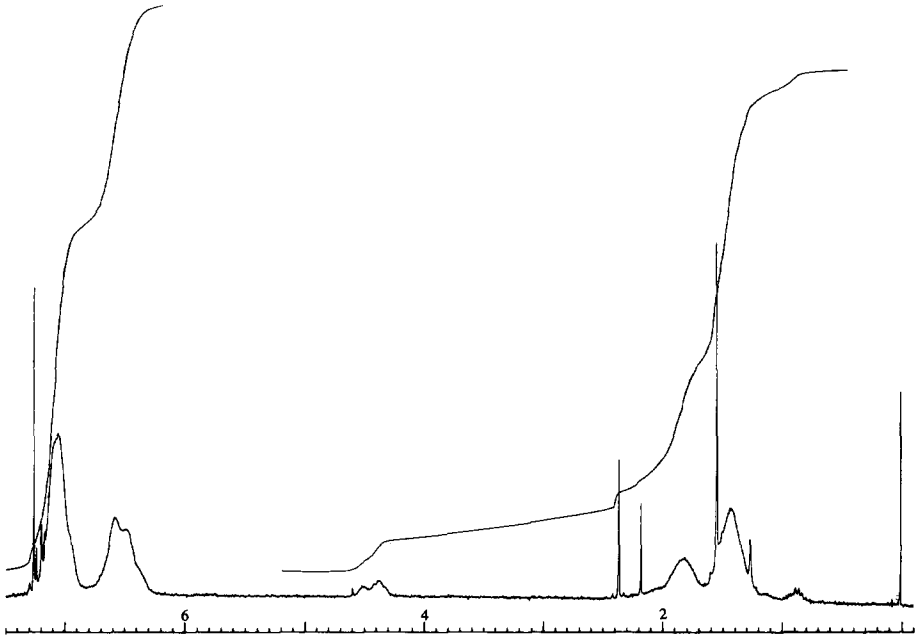


Figure 1 ^{1}H n.m.r. spectrum (250 MHz, $CDCl_3$) of soluble chloromethylated polystyrene support (δ, ppm)

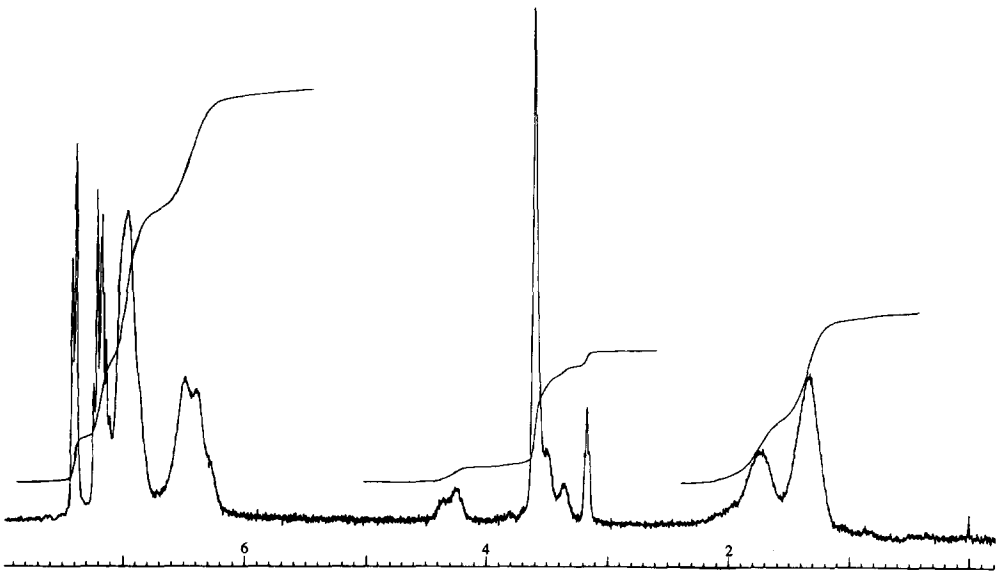


Figure 2 ^{1}H n.m.r. spectrum (250 MHz, $CDCl_3$) of support after coupling of first oligoether building block (δ, ppm)

due to the $CHOCH_2$ protons, and the relatively sharp triplet at $\delta = 3.15$ from the CHOTr protons. It is interesting to note the sharpness of the proton resonances from the oligoether sidechain compared to those of the backbone protons, presumably a reflection of relatively high sidechain mobility. No attempt was made to quantify the chemical change from this spectrum, but superficially the change is consistent with the elemental analysis and *FT*i.r. data.

The deprotonation step resulted in a further net loss of polymer mass (*Table 1*) and in this case the elemental microanalytical and *FT*i.r. data were not very informative. However, once again the ^{1}H n.m.r. spectrum (*Figure 3*) shows that the reaction proceeds with high efficiency. The complex pattern of the trityl resonances at $\delta = 7.25$ and 7.45 are completely lost and replaced by a sharp singlet at $\delta = 7.28$. Likewise, the triplet at $\delta = 3.16$ is lost. This confirms essentially total cleavage of the protecting group and we assign the sharp singlet at $\delta = 7.28$ to trapped triphenylmethanol in the polymer and $CHCl_3$ from the n.m.r. solvent. The facility and completeness of the deprotection have also been confirmed with parallel syntheses on crosslinked resin beads, where the appearance of triphenylmethanol in the bulk solution has been quantified from its u.v. absorption band.

The mesylation (activation) step yielded a polymer product with a significant S content (*Table 1*) and sulfate ester bands in the *FT*i.r. spectrum at 13 and 1168 cm^{-1}. The ^{1}H n.m.r. spectrum (*Figure 4*) shows the appearance of a resonance at $\delta = 3.05$, assigned to the $-O-SO_2CH_3$ methyl group, and an enhanced signal at $\delta = 4.35$ assigned to the $-CH_2OSO_2-$ methylene group. Again, the sharp peak at $\delta = 7.28$ is believed to be mainly due to retained triphenyl methanol, and the sharp feature at $\delta = 1.5$ to residual aliphatic hydrocarbon solvent from the precipitation.

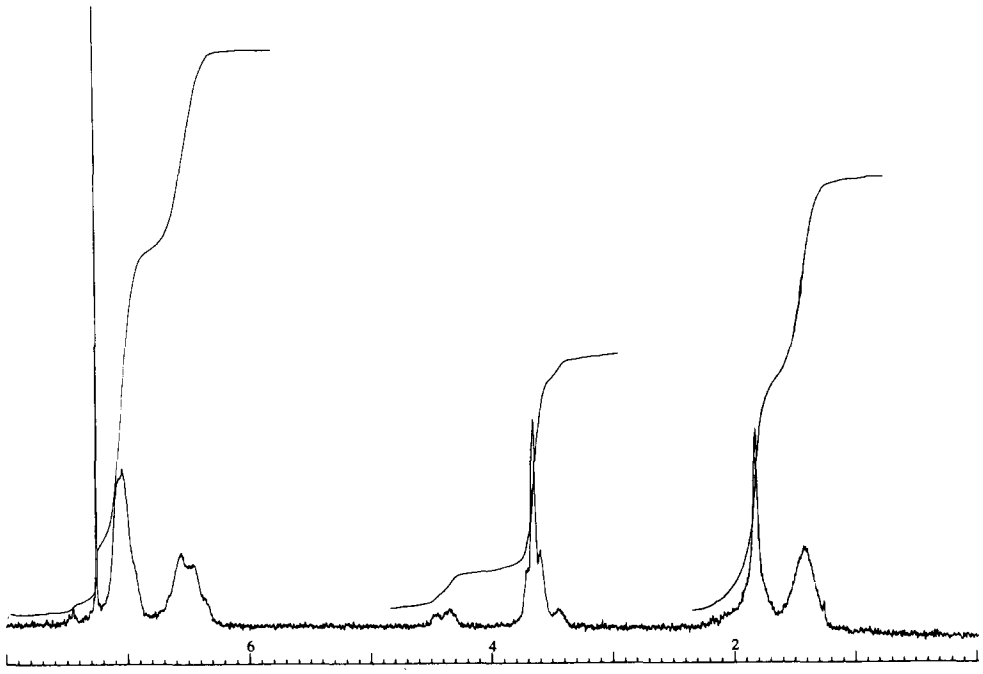


Figure 3 ^{1}H n.m.r. spectrum (250 MHz, $CDCl_3$) of support after deprotection via removal of terminal trityl group (δ, ppm)

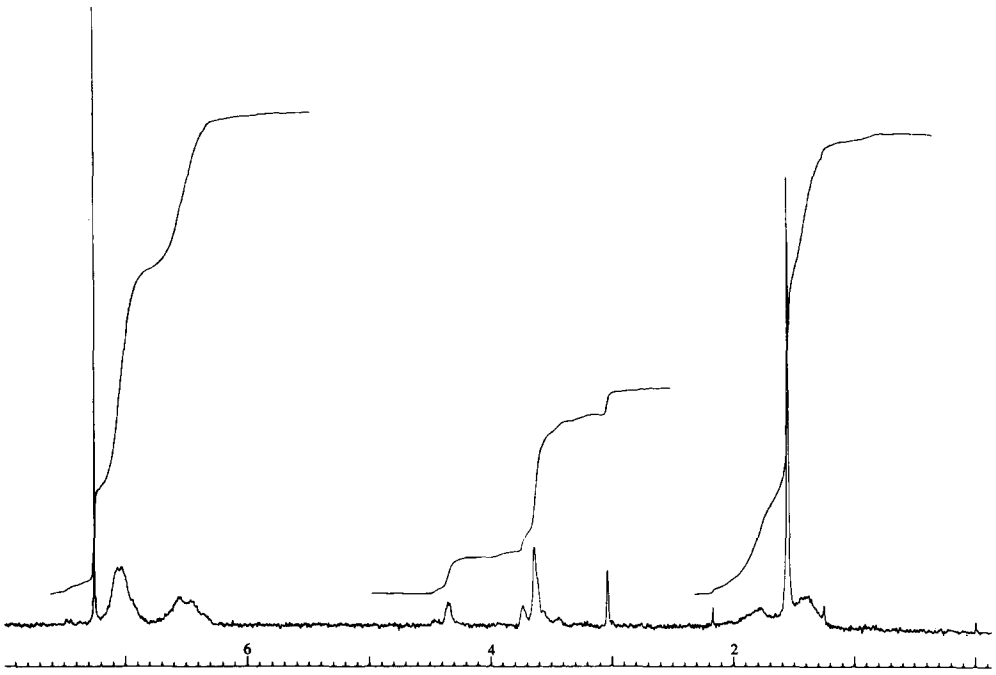


Figure 4 ^{1}H n.m.r. spectrum (250 MHz, $CDCl_3$) of support after activation of terminal hydroxyl via mesylation (δ, ppm)

The elongation step or second coupling reaction was carried out in the same way as the first. The elemental analysis confirmed complete loss of the mesylate endgroup (i.e. loss of S), and likewise the mesylate bands in the *FT*i.r. spectrum at 1344 and 1168 cm^{-1} disappeared. The ^{1}H n.m.r. spectrum (*Figure 5*) was again totally consistent with a high yielding displacement reaction coupling the second ether building block. The resonances reverted to a pattern very similar to those in *Figure 2*, corresponding to the first coupling, and very significantly the proportion of $-\underline{CH_2}O\underline{CH_2}-$ ether attached methylene groups is much higher, confirming that elongation has been achieved.

The final deprotection step was achieved as with the earlier one, and the ^{1}H n.m.r. spectrum (*Figure 6*) of the polymer confirms the loss of the trityl endgroup and the appearance of trapped triphenylmethanol. The overall spectrum mirrors that in *Figure 3* very closely. Again, the enhanced resonance in the aliphatic CH region is assigned to residual solvent.

No attempt was made to cleave the assembled octaethylene glycol from the support, because of the small quantity of polymer left and the anticipated work-up difficulties. However, in the parallel studies using cross-linked resin supports, a number of potential cleavage methodologies were investigated[7]. The most convenient

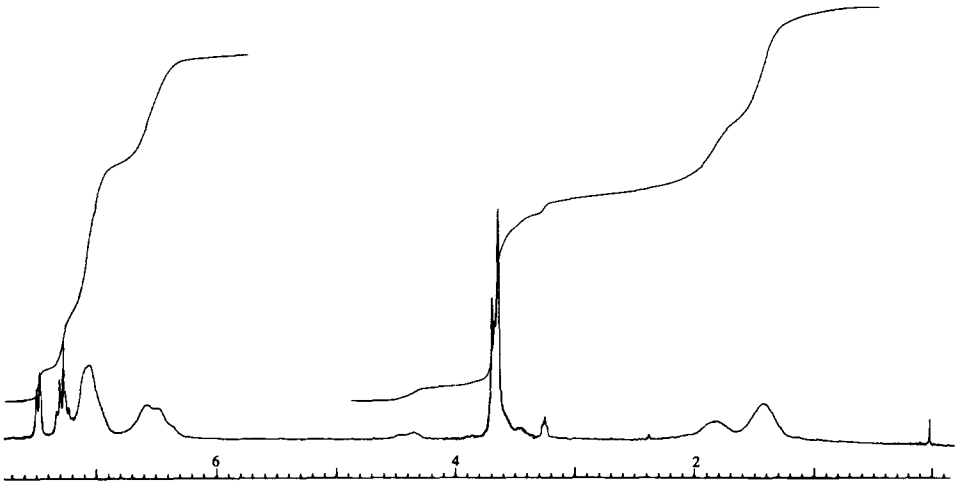


Figure 5 ^{1}H n.m.r. spectrum (250 MHz, $CDCl_3$) of support after elongation or second coupling of oligoether building block (δ, ppm)

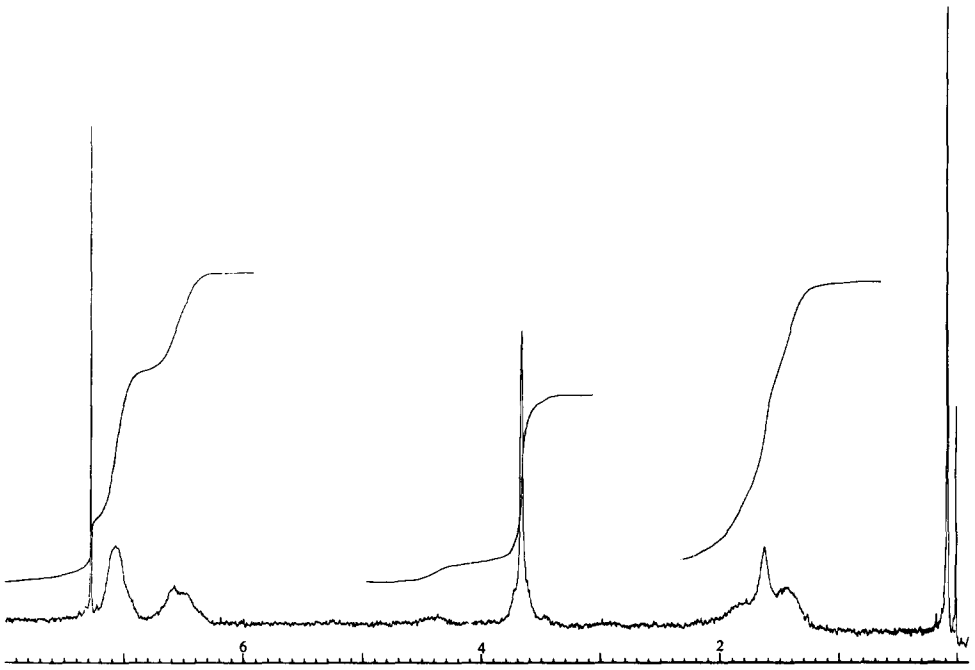


Figure 6 ^{1}H n.m.r. spectrum (250 MHz, $CDCl_3$) of support after second deprotection (δ, ppm)

and efficient involved a mixture of thioanisole and trimethyl silyl trifluoromethane sulfonate in trifluoroacetic acid[10].

CONCLUSIONS

This model study of stepwise assembly of an oligoether on a soluble polymer support suggests that the synthetic strategy is very sound, and all the experimental evidence points to relatively efficient reactions at each stage. In particular, the picture which emerges from the successive ^{1}H n.m.r. spectra is very telling and there are few studies in the literature where such compelling structural evidence has been made available. The model study has also highlighted the problems of solid-phase synthesis on soluble supports. While reactions tend to proceed rather efficiently, the recovery of polymers is a major problem. The data in *Table 1* clearly show the progressive loss of polymer mass on successive work-up, such that in this case 2 g dwindles to 0.06 g over five reactions. The other problem is in separation. Solvent residues and, in this case, free triphenylmethanol are very difficult to eliminate completely without even larger wastage of polymer, and this is a well known problem in polymer chemistry.

In parallel work using a wide range of crosslinked resin supports[7], the problems associated with work-up were almost completely eliminated. Unfortunately, however, in this oligoether work they were replaced by even more severe problems involving slow and incomplete reactions on the resins. This has proved very frustrating, and further research effort is required to combine the advantages of the clean and complete reactions on the soluble polymer support with the ease of isolation and work-up arising with the crosslinked support.

ACKNOWLEDGEMENT

H.C.H. is grateful to the SERC for the provision of a CASE studentship.

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