

Copper(I) mediated radical polymerisation of uridine and adenosine monomers on a silica support†

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Copper(I) mediated radical polymerisation is used to polymerise uridine and adenosine substituted methacrylates onto a silica surface giving supported polymers with potential as re-usable templates and for interaction with nucleic acids.

The immobilisation of polymers on solid supports and surfaces is of considerable interest for a number of applications. For example, derivatisation of surfaces for biocompatibility¹ and the production of sensors² is of interest to the biotechnology industry and new resins are being sought for application to solid supported organic synthesis.³ Automated synthesis of oligonucleotides on solid supports is performed routinely for the production of short strands of DNA and RNA or their synthetic analogues.⁴ Solid supported oligonucleotides are finding applications in medical diagnostics⁵ and hence numerous methods have appeared in the literature for derivatising solid supports for oligonucleotide synthesis and attaching oligonucleotides to support media.⁶ Having placed an oligonucleotide onto a solid support it has been shown to be possible to employ this as a re-usable template to synthesise complementary strands of DNA. Ashley and MacDonald⁷ attached a naturally occurring segment of DNA directly to diazobenzoyloxymethyl-cellulose and then used this to synthesise complementary strands of DNA which could be washed away and the template re-used repeatedly. This work involved using enzymes and primers however, and the solid supported template was only made on a very small scale. We have recently shown that it is possible to carry out the templated polymerisation of an unnatural backbone polyacryloylnucleoside by using non-polar solvents to maximise interactions between complementary base pairs.⁸ This communication describes the synthesis of a re-usable template prepared on a silica support for use in such a polymerisation reaction.

Transition metal mediated living radical polymerisation⁹ is an efficacious method for the preparation of narrow polydispersity (PDI) methacrylic and styrenic polymers, as it allows controlled synthesis of structurally diverse polymers due to its living or pseudo-living nature.¹⁰ Such polymerisations can be performed in the presence of many functional groups and solvents which other living polymerisation methods, such as ionic or group transfer polymerisations cannot tolerate.¹¹ Metal mediated radical polymerisation on solid supports has been the subject of a number of recent reports. Tsujii and co-workers modified the surface properties of silica by immobilising a chlorosulfonyl phenyl moiety on silica wafers and using this for living polymerisation of MMA.¹² Matyjaszewski and co-workers carried out atom transfer radical polymerisation of styrene and acrylates on silica wafers to give homopolymers and block co-polymers.¹³ Nitroxide mediated polymerisation has been utilized on Merrifield resin to produce 'designer resins' with functional properties.¹⁴ This present work describes the application of copper(I) mediated radical polymerisation to the biologically significant nucleoside derivatives 5'-methacryloyluridine **1** and 5'-methacryloyladenosine **2** on silica gel functionalised with a bromoisobutyrate initiator (**3** or **4**) to give surfaces of considerable potential (Fig. 1).

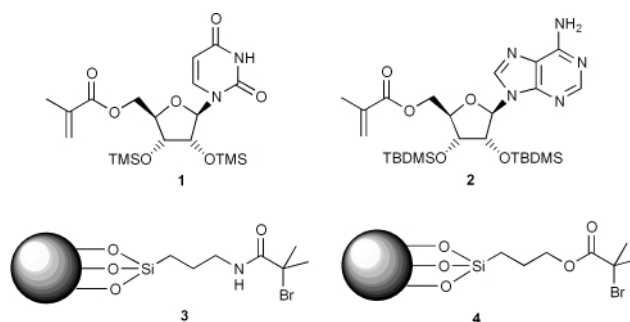
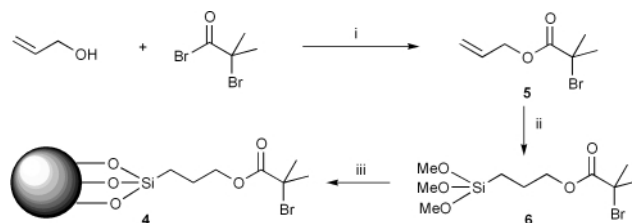


Fig. 1 Monomers and silica supported initiators used in this study.

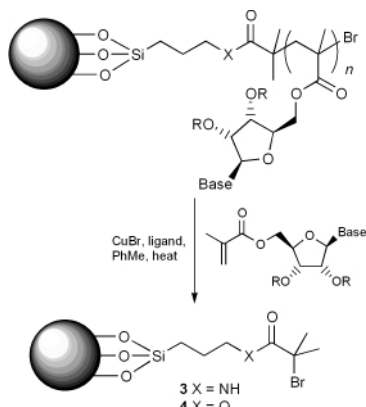
The 5'-methacryloyluridine **1** and 5'-methacryloyladenosine **2** were synthesised using a modified procedure of Moris and Gotor,¹⁵ using the enzyme *Candida antarctica* lipase 435 (CAL 435) with an activated acetoneoxime ester.¹⁶ In order to make these monomers soluble in suitable polymerisation solvents and to aid polymer characterisation the 2'- and 3'-hydroxy groups were protected as silyl ethers. The adenosine monomer, being more polar, required the larger *tert*-butyldimethylsilyl (TBDMS) protecting groups. The amidic initiator **3** was synthesised using commercially available 3-aminopropylsilica and bromoisobutyryl bromide in the presence of triethylamine base and THF solvent. The ester initiator **4** was synthesised as follows (Scheme 1). Firstly bromoisobutyryl bromide was reacted with allyl alcohol in the presence of triethylamine to give **5** in 98% yield.¹⁷ This was then treated with trimethoxysilane in the presence of a catalytic amount of hexachloroplatinic acid¹⁸ to give the trimethoxysilyl bromoisobutyrate initiator **6** in 62% yield. The derivatised silica was then prepared by refluxing trimethoxysilyl bromoisobutyrate **6** with TLC grade silica gel in toluene for 22 h (Scheme 1). TLC grade silica gel was used because of its larger surface area and it has been shown previously that attachment of a trimethoxysilyl group to silica gel gives better loading than powdered silica due to the former having porous particles.¹⁹ This was found to have a loading of 0.61 mmol g⁻¹ as determined by Thermal Gravimetric Analysis (TGA).



Scheme 1 Reagents and conditions: i, Et₃N, THF (98%); ii, (MeO)₃SiH, H₂PtCl₆ (98%); iii, silica gel, PhMe, reflux.

Copper(I) mediated radical polymerisation of uridine monomer **1** with the amidic solid supported initiator **3** was attempted using *N*-(*n*-pentyl)-2-pyridylmethanimine (NPMI) as a ligand in conjunction with copper(I) bromide (Scheme 2). However, this initiator was found to give a loading of only 0.87 mmol g⁻¹ (Table 1). Changing the ligand to Me₆Tren²⁰ gave a slightly

† Electronic supplementary information (ESI) available. Experimental procedures and details. See <http://www.rsc.org/suppdata/cc/b0/b005832g/>



Scheme 2 Copper(I) mediated radical polymerisation of 5'-methacryloylnucleosides.

Table 1 Monomer loading for initiators **3** and **4**

Initiator	Monomer	Ligand	Loading (mmol g ⁻¹)	Increase in initiator weight(%)
3	1	NPMI	0.87	53
3	1	Me ₆ Tren	0.80	48
4	1	NPMI	1.51	188
4	2	NPMI	1.11	117
4	1/2	NPMI	1.04	105

lower loading of 0.80 mmol g⁻¹. It has been suggested by Matyjaszewski that amidic initiators are prone to intramolecular reactions in the early stages of living radical polymerisation caused by the nitrogen lone pair.²¹ The non-amidic solid supported initiator **4** was therefore synthesised. Use of this initiator for polymerisation of **1** almost doubled the loading to 1.51 mmol g⁻¹ using NPMI as the ligand. Fig. 2 shows the FT-IR of the immobilised polymer clearly demonstrating the broad N-H signal from 3700–2900 cm⁻¹ and the carbonyl stretch at 1683 cm⁻¹. Polymerisation of 5'-methacryloyladenine **2** using initiator **4** gave a lower loading of 0.96 mmol g⁻¹. This reflects the lower yields obtained with this functionally more complex monomer during solution phase copper(I) mediated radical polymerisations (see ref. 16). Statistical co-polymerisation of **1** and **2** was also successful giving a loading of 1.04 mmol g⁻¹. This was calculated by taking into account the ¹H

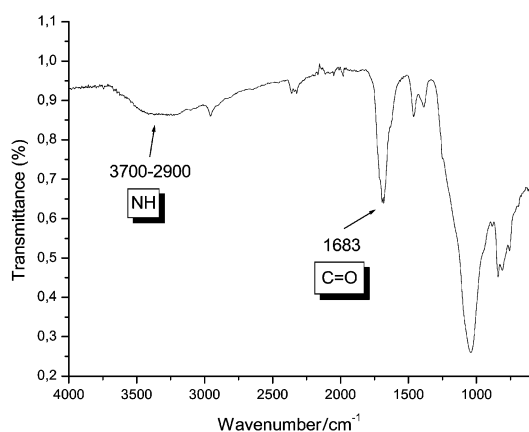


Fig. 2 IR of poly(5'-methacryloyluridine) on silica.

NMR of the unreacted monomers in the filtrate which showed a 15:85 ratio of **1**:**2**, indicating that the co-polymer is rich in uridine.

In summary it has been shown that copper(I) mediated radical polymerisation of the multifunctional nucleosides uridine and adenosine methacrylates is possible using a bromoisobutyrate initiator bound to silica giving surface attached homopolymers and statistical co-polymers with good loading. Although we cannot unequivocally describe this polymerisation as *living* from these experiments, we know that similar conditions bring about a controlled polymerisation. Other work has shown²² that these conditions favour narrow polydispersity products, indicative of a living radical polymerisation.²³ To our knowledge this is the first time controlled radical polymerisation has been used to immobilise biologically important nucleosides to a solid support. Investigations into the use of these immobilised biopolymers as re-usable templates for polymerisations and their interaction with nucleic acids are under way.

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