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

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Received (in Cambridge, UK) 19th July 2000, Accepted 14th September 2000
First published as an Advance Article on the web 3rd October 2000

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 biocompatibility[1] and the production of sensors[2] 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 diagnostics[5] 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 MacDonald[7] attached a naturally occurring segment of DNA directly to diazobenzyloxymethyl-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 polymerisation[9] 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).

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

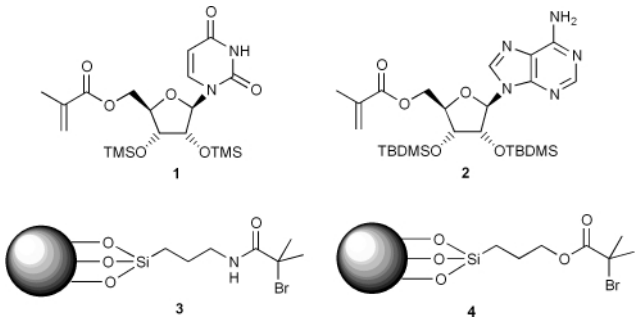
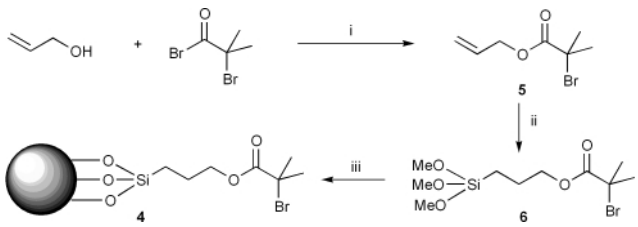


Fig. 1 Monomers and silica supported initiators used in this study.

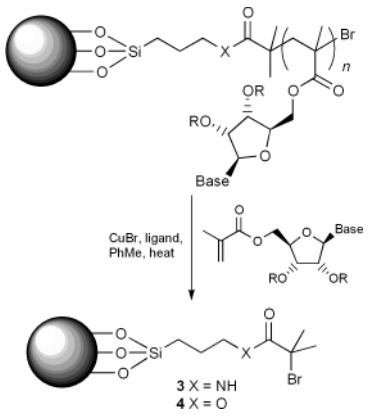
The 5′-methacryloyluridine **1** and 5′-methacryloyladenosine **2** were synthesised using a modified procedure of Moris and Gotor,[15] using the enzyme *Candida antarctica lipase* 435 (CAL 435) with an activated acetoneoxime ester.[16] In order to make these monomers soluble in suitable polymerisation 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 bromoisobutyroyl bromide in the presence of triethylamine base and THF solvent. The ester initiator **4** was synthesised as follows (Scheme 1). Firstly bromoisobutyroyl 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 acid[18] 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, Et_3N, THF (98%); ii, $(MeO)_3SiH$, H_2PtCl_6 (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 Me_6Tren[20] gave a slightly

DOI: 10.1039/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_6Tren	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′-methacryloyladenosine **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 ^{1}H 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.

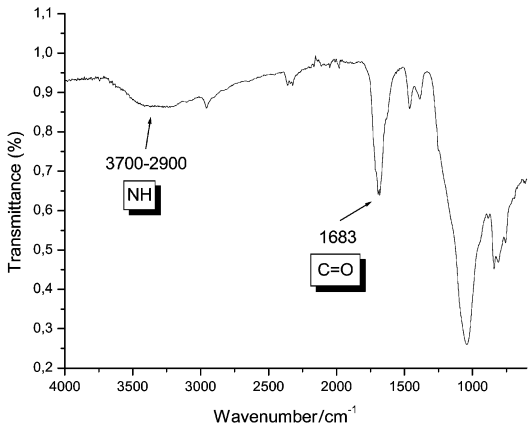


Fig. 2 IR of poly(5′-methacryloyluridine) on silica.

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 unequivocably describe this polymerisation as *living* from these experiments, we know that similar conditions bring about a controlled polymerisation. Other work has shown[22] 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.

We are grateful to the University of Warwick for a postdoctoral fellowship (A. K.), the EPSRC for a Fast Stream Studentship (M.G.; GR/L71933) and Novo Nordisk for a generous donation of CAL 435. We also thank Dr Stefan Bon for supplying the amidic solid supported initiator **3**.

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