Precise synthesis of poly(macromonomer)s containing sugars by repetitive ring-opening metathesis polymerisation†

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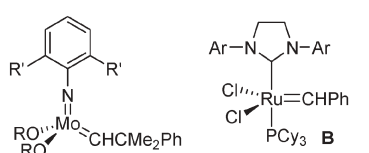
Various poly(macromonomer)s containing sugars have been prepared by ROMP of norbornene macromonomers substituted with ROMP block copolymers containing acetal-protected sugars as the side chain, which upon removal of the protecting group affords a novel amphiphilic architecture.

Amphiphilic block copolymers (ABCs) attract considerable attention because they exhibit unique structures and properties like surface activity on the formation of micelles (aggregates), *via* self-association in both hydrophilic and hydrophobic media.[1,2] The preparation of highly branched (densely grafted) polymers, poly(macromonomer)s, consisting of ABCs should introduce promising properties, not only because of their unique cylindrical, spherical and worm-like shapes in solution and bulk, by varying the axisymmetric distribution of branching points along the central contour backbone,[3–6] but also because the building blocks (hydrophobic/hydrophilic parts) in the ABCs can be tuned for the formation of various phase separated microstructures and nano-architectures.[6] Poly(macromonomer)s containing carbohydrates should thus be promising, because specific, strong affinities with cell surface proteins can be expected by the tuning of the protein–carbohydrate recognition events, that has thus far been one of the most promising routes in cellular specific targeting drugs.[7] However, one major limitation associated with the homopolymerisation of a macromonomer is the difficulty in obtaining complete conversion with precise size control of the branched structure formed.[3,4,6,8] We herewith present the first example of the synthesis of poly(macromonomer)s containing carbohydrates being achieved in a precisely controlled manner with complete conversion by using the repetitive ring-opening metathesis polymerisation (ROMP) approach.

We focused on the repetitive ROMP approach using well-defined molybdenum-alkylidene initiators of the type, (ArN)Mo(CHCMe$_2$Ph)(OR)$_2$ (**A**, Chart 1),[9] because the ROMP proceeds in a living manner with quantitative initiation. This is also because the approach encompasses the following three key steps that are required for their preparation: (i) exclusive end-capping of block ROMP copolymer with TMS (SiMe$_3$) protected 4-hydroxybenzaldehyde; (ii) exclusive removal of the TMS protection from the terminus,[10,11] and (iii) exclusive preparation of macromonomer by esterification of the OH group at the terminus with norbornene carboxylic acid chloride.[10] Moreover, various (linear, triarms, ABA type) amphiphilic multi-block ROMP copolymers containing acetal-protected sugars could be prepared by the coupling of an end-functionalized ROMP copolymer with poly(ethylene glycol) (PEG) by a "grafting to" approach.[11]

Norbornene derivatives containing acetal protected galactose (**a**) or ribose (**b**) were chosen, because the synthesis and purification procedures for these monomers were already established.[11,12] Mo(CHCMe$_2$Ph)(N-2,6-^{i}Pr$_2$C$_6$H$_3$)(O^{t}Bu)$_2$ (**A1**) was also chosen as the initiator due to its ability to prepare the multi-block copolymers in a precise manner.[11–13] As shown in Table 1,† various block ROMP copolymers, poly(**1a–b**), consisting of NBE and the sugar-substituted NBE (**a–b**) were prepared in high yields (> 95%) by the sequential addition and the subsequent termination with 4-Me$_3$SiOC$_6$H$_4$CHO (Scheme 1). The M_n values for the resultant copolymers were dependent on the initial feedstock ratio, and the M_w/M_n values were low in all cases (M_w/M_n = 1.11–1.17), strongly suggesting that the polymerisation proceeded in a living manner.[10–13] The M_n values by GPC *versus* polystyrene standards were somewhat higher than those calculated by the initial monomer/initiator feed ratios, but, as reported previously,[11] the M_n values estimated from the ^{1}H NMR spectra (integration ratio with SiMe$_3$ group) were in good agreement with the calculated values, strongly suggesting that the polymerization took place in a living manner with quantitative initiation as seen in the ROMP with **A1**.[9–13] The TMS group in the polymer termini could be cleanly hydrolysed using 0.5 M HCl in THF to afford poly(**2**) exclusively (> 95% in all cases) without any significant changes in the M_n values by GPC, as also reported previously.[11]† The removal was also confirmed by the ^{1}H NMR spectra (disappearance of the resonance assigned to the TMS, 0.3 ppm). The reaction of poly(**2**) with norbornene carboxylic acid chloride (1.5 equiv.) in THF in the presence of NEt$_3$ afforded the macromonomer, poly(**3a–b**) in high yield, (> 98%, Table 1), confirmed by presence of the key resonances in the ^{1}H and ^{13}C NMR data.[10]† The M_n values by GPC were in good correlation with those calculated, and the values were also close to those estimated by the ^{1}H NMR



R = ^{t}Bu, R' = ^{i}Pr (**A1**);
R = CMe(CF$_3$)$_2$, R' = ^{i}Pr (**A2**);
R = CMe(CF$_3$)$_2$, R' = Me (**A3**).

Chart 1

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† Electronic supplementary information (ESI) available: experimental details, some GPC traces, their ^{1}H, ^{13}C NMR spectra, FT-IR spectra for poly(**4**) and poly(**5**). See http://dx.doi.org/10.1039/b506877k

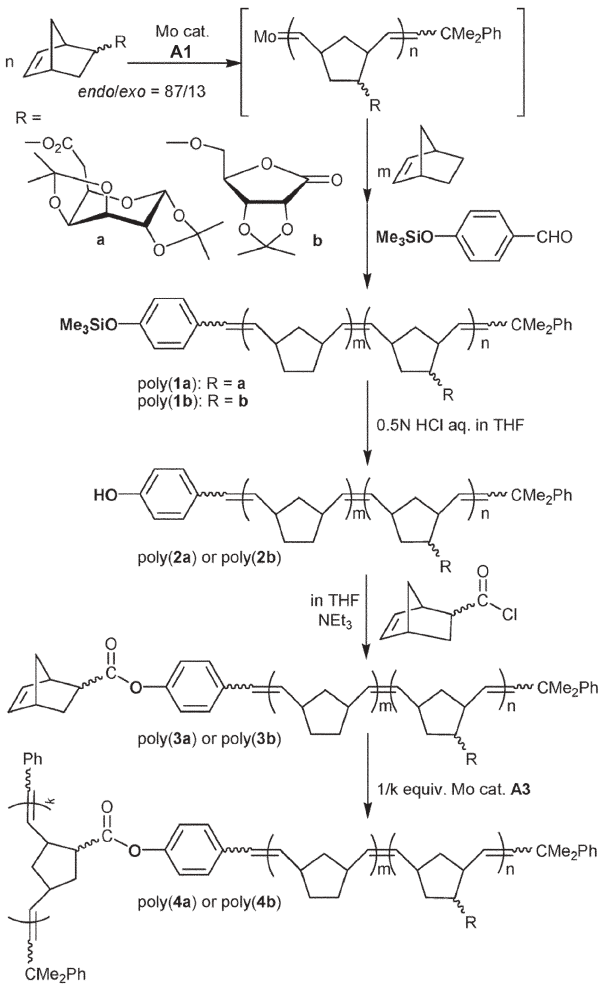
Table 1 Preparation of macromonomer, poly(**3a–b**)

Run no.	monomer NBE/**a** or **b** (m/n)[a]	poly(**1a–b**) $M_{n(calc)}$[b] $\times 10^{-4}$	$M_{n(GPC)}$[c] $\times 10^{-4}$	$M_{n(NMR)}$[d] $\times 10^{-4}$	M_w/M_n[c]	poly(**2a–b**) $M_{n(GPC)}$[c] $\times 10^{-4}$	M_w/M_n[c]	Yield[e]/ %	poly(**3a–b**) $M_{n(calc)}$[b] $\times 10^{-4}$	$M_{n(GPC)}$[c] $\times 10^{-4}$	$M_{n(NMR)}$[d] $\times 10^{-4}$	M_w/M_n[c]	Yield[e]/ %
1	NBE/**a** (20/20)	0.95	1.33	0.98	1.14	1.31	1.09	99	0.95	1.28	1.02	1.11	99
2	NBE/**a** (20/20)	0.95	1.25	0.96	1.11	1.29	1.10	98	0.95	1.33	1.03	1.13	98
3	NBE/**a** (25/25)	1.18	1.53	1.22	1.20	1.60	1.12	95	1.18	1.58	1.24	1.10	99
4	NBE/**a** (25/25)	1.18	1.57	1.25	1.12	1.54	1.09	99	1.18	1.58	1.24	1.10	99
5	NBE/**b** (20/20)	0.83	1.04	0.85	1.18	1.01	1.16	99	0.84	1.02	0.92	1.18	99
6	NBE/**b** (20/30)	1.14	1.43	1.18	1.16	1.41	1.16	99	1.15	1.40	1.24	1.16	98

[a] Conditions: toluene (3.5 g) at 25 °C. [b] Calculated from initial feedstock ratios. [c] GPC data in THF *vs.* polystyrene standards. [d] Estimated from ^{1}H NMR spectra. [e] Isolated yield.

spectra (the integration of olefinic signals of the NBE *versus* those of the internal polymer chain).

Mo(CHCMe$_2$Ph)(N-2,6-^{i}Pr$_2$C$_6$H$_3$)[OCMe(CF$_3$)$_2$]$_2$ (**A2**) was chosen for the polymerisation of poly(**3**) because we previously succeeded in preparing poly(macromonomer)s containing ring-opened poly(NBE).[10] Ru(CHPh)(Cl)$_2$(IMesH$_2$)(PCy$_3$) (**B**, IMesH$_2$ = 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene) was also chosen because high reactivity toward the olefinic double bond was expected.[14] However, as shown in Table 2, the polymerisation of norbornene containing ring-opened poly(NBE)$_{25}$-*bl*-poly(**a**)$_{25}$ (prepared in runs 3–4) did not complete if **A2** was employed (run 7). The attempt with **B** gave a polymer with decreased M_n value with increasing M_w/M_n values (run 8), suggesting that the metathesis (degradation) with internal olefins took place instead of ROMP.[15]



Scheme 1

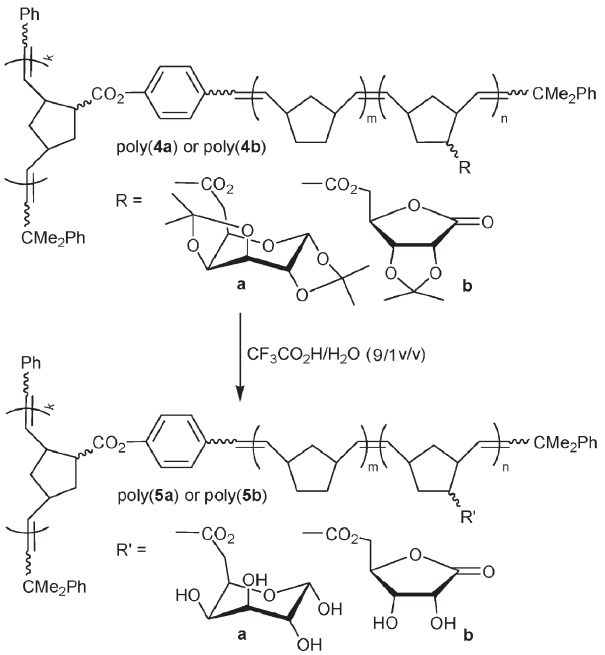
Note that the repetitive ROMP attained exclusive conversion when Mo(CHCMe$_2$Ph)(N-2,6-Me$_2$C$_6$H$_3$)[OCMe(CF$_3$)$_2$]$_2$ (**A3**) was chosen as the initiator, which was more effective than **A2** for the synthesis of high molecular weight *trans*-poly(9,9-di-*n*-octylfluorene-2,7-vinylene) by acyclic diene metathesis polymerisation.[16] The completion of this polymerisation could also be confirmed by the ^{1}H NMR spectra of the resultant polymers by the disappearance of the olefinic protons ascribed to the norbornene derivatives. Also note that the M_n values for the poly(**4a–b**) by GPC were close to the estimated values based on both the M_n value by GPC for poly(**3a–b**) and the molar ratios, and the M_w/M_n values were low in all cases. [For example, poly[(NBE)$_{20}$-*bl*-(**a**)$_{20}$] (run 1): $M_n = 1.28 \times 10^4$ (GPC), 1.02×10^4 (NMR), 0.95×10^4 (calcd.), after polymerisation {poly(**3a**)/**A3** = 10/1, molar ratio}: $M_n = 11.76 \times 10^4$ (GPC), $M_w/M_n = 1.07$, yield 96% (run 10)]. The analogous polymerisation using 5 and 3 equivalents of [poly(**3a**)] afforded poly(**4a**) with unimodal MWD (M_w/M_n = 1.09, 1.19, respectively), with molecular weights close to those calculated from the initial feedstock ratio, clearly indicating that the polymerisation proceeded in a living manner. These results clearly suggest that precise control of the main chain is possible by this approach, and that synthesis of various poly(macromonomer)s containing not only carbohydrates but also other functionalities is possible in a precise manner by this repetitive ROMP approach.

The cyclic acetals in the poly(macromonomer)s, poly(**4a–b**), could be removed (Scheme 2) by treatment with a mixed solution of CF$_3$CO$_2$H/H$_2$O according to the reported procedure,[11,12] and the deprotected polymer, poly(**5**), could be isolated as a white precipitate by pouring the reaction mixture into a vigorously stirred cold THF solution (0 °C).† Both the ^{1}H and ^{13}C NMR spectra (in CDCl$_3$-d_1, DMF-d_7) showed that no signals ascribed to the acetal protecting groups remained, but all other characteristic resonances of the intact deprotected sugar bound through an ester linkage to the backbone were present. FT-IR spectra showed a broad absorption band characteristic of OH groups (3415 cm^{-1}) without absorptions assigned to a carboxylic acid.† These facts clearly indicated the exclusive removal of the acetal protecting group. The deprotected polymers were soluble to varying degrees in dimethyl sulfoxide, dimethylformamide, chloroform, slightly soluble in water, THF at room temperature, and insoluble in hexane and pentane.

Table 2 Preparation of poly(macromonomer)s by repetitive ROMP[a]

	poly(**3**)				poly(**4**)				
Run no.	NBE/**a** or **b** (m/n)[b]	$M_{n(GPC)}$[c] × 10^{-4}	Catalyst (equiv.[d]/k)	Time/h	$M_{n(calcd)}$[e] × 10^{-4}	$M_{n(GPC)}$[c] × 10^{-4}	M_w/M_n[c]	DP_n[f]	Yield[g]/%
7	NBE/**a** (25/25)	1.58	**A2** (10)	1.5	11.95	4.50[h]	1.08	—[h]	98
8	NBE/**a** (25/25)	1.58	**B** (10)	1.0	11.95	1.27	1.70	—	95
9	NBE/**a** (25/25)	1.58	**A3** (5)	2.0	5.98	8.18	1.15	5.2	98
10	NBE/**a** (20/20)	1.28	**A3** (10)	2.0	9.72	11.76	1.07	9.2	96
11	NBE/**a** (20/20)	1.28	**A3** (5)	2.0	4.83	5.87	1.09	4.6	97
12	NBE/**a** (20/20)	1.28	**A3** (3)	1.0	2.89	3.99	1.19	3.1	97
13	NBE/**b** (20/30)	1.02	**A3** (10)	2.0	11.72	14.33	1.22	10.2	97
14	NBE/**b** (20/20)	1.40	**A3** (10)	2.0	8.42	8.42	1.12	8.3	96

[a] Conditions: Toluene (2.0 g) at 25 °C. [b] Starting feedstock ratio shown in Table 1. [c] Calculated from GPC data. [d] Ratio of macromonomer to initiator (see Scheme 1). [e] Calculated from initial feedstock ratios. [f] Calculated from GPC data. [g] Isolated yield. [h] Mixture of macromonomer and oligomeric-(macromonomer), *i.e.* dimers or trimers.



Scheme 2

We have shown that precise control of both main and side chain in the new class of amphiphilic poly(macromonomer)s containing sugars is possible for the first time by the present repetitive ROMP procedure. Since this present approach should introduce a new possibility to prepare various kinds of amphiphilic nano arrangements containing sugars, unique properties such as both strong and specific affinities based on protein–carbohydrate interactions will be thus expected. We are currently exploring other possibilities to prepare another series of amphiphilic nano architectures containing sugars by a combination of this approach with our 'grafting to' approach, and these results will be presented in the near future.

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