DOI: 10.1002/chem.200700291

Precise Synthesis of Poly(macromonomer)s Containing Sugars by Repetitive ROMP and Their Attachments to Poly(ethylene glycol): Synthesis, TEM Analysis and Their Properties as Amphiphilic Block Fragments

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Abstract: Various poly(macromonomer)s (PMMs) have been prepared by a repeating ring opening metathesis polymerization (ROMP) technique using the well-defined molybdenum initiators of the type, [Mo(CHCMe$_2$Ph)(NAr)(OR)$_2$] with OR = OCMe$_3$, OCMeC(CF$_3$)$_2$; Ar = 2,6-*i*Pr$_2$C$_6$H$_3$, 2,6-Me$_2$C$_6$H$_3$. The synthetic strategy is based on the polymerization of norbornene and its derivatives affording di- and triblock side chains bearing sugars (mannose, galactose, glucose etc.), linked via O- (ester), and glycosidase resistant C- (isoxazoline) glycosides. The efficient placement of norbornene units on the side chain termini and their conversion into PMMs, facilitated by the Mo alkylidenes, proceeded in a living manner with the quantitative initiation. The methodology was applied to prepare poly(macromonomer)-*graft*-PEG [PEG: poly(ethylene glycol)], by the attachment of a pseudo phenol terminus on the PMM main chain to PEG-Ms$_2$ [MsO(CH$_2$CH$_2$O)$_n$Ms, Ms = MeSO$_2$] using a "grafting to" approach. Removal of the acetal protecting groups from the sugar coating of a variety of supramolecular structures including PMMs, linear amphiphilic block copolymers (ABC) and a PMM-*graft*-PEGby using trifluroacetic acid/water (9:1), and suspension in water, prompted the spontaneous formation of spherical architectures by self-assembly of the amphiphilic PMMs as observed by transmission electron microscopy (TEM). The ability to uptake the hydrophobic dye (Nile Red) into the micellar cores of a variety of amphiphilic polymeric fragments is a significant step towards the production of sugar-coated nanospheres for cell-targeting biomimetic applications.

Keywords: metathesis · micelles · molybdenum · polymerization · ring-opening polymerization

Introduction

Amphiphilic block copolymers (ABCs), which consist of hydrophilic and hydrophobic parts in the polymer molecules, have generated considerable attention lately due to their ability to exhibit unique structures and properties such as the formation of a diverse range of micellar aggregates (e.g. spheres, vesicles, rods, lamellae) in solution or bulk (in both aqueous and hydrophobic media).[1,2] The ability to control the properties by varying the initial blocks (hydrophilic/hydrophobic) results in the formation of various well defined microstructures and nano-rchitectures. Several variations on copolymer topology have thus been investigated including linear,[3] double hydrophilic block copolymers,[4] miktoarm,[5] graft,[6] dendrons,[7] and poly(macromonomer)s.[8] The use of polymeric micelles as nano-vehicles is effective due to the core–shell architecture leading to the protection of an active agent in the core by the polymer shell, and has thus been recently exploited for the encapsulation of gold particles,[9] hydrophilic biofunctional materials (e.g. carboxyfluoroceine),[10] hydrophobic anti-inflammatory agents,[11] chemotherapeutics,[12] and for other pharmaceutical applications.[13,14] The ability of ABCs as delivery agents arises from their unique chemical structure, in which the hydrophobic core segment serves as a reservoir for hydrophobic substances upon micellisation; the micelles may be loaded by chem-

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ical, physical, or electrostatic means depending on the specific core-forming block and solubilizer. Currently, research has been focused towards the preparation of micelles which are responsive to environmental change, with notable successes using external stimuli such as pH,[14a,15] temperature,[16] IR[17] and UV light[18] for implementing programmed functions that respond to signatures in vivo.

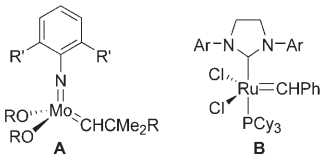
Poly(macromonomer)s (PMMs) containing ABCs in the side chain are of particular interest, not only due to the axisymmetric distribution of side chains from the central polymer backbone, but also because they should exhibit interesting (spherical, cylindrical, star and worm-like) morphologies in bulk and solution which are dependant on the tunable composition of the side chain and backbone.[19] ABCs containing carbohydrates have been previously prepared for cellular specific targeting[20] and have been shown to recognize certain cell surface lectins. The preparation of amphiphilic PMMs bearing carbohydrates has potential for improved targeting, recognition and modulation of cell surface processes. The increased density of the sugar functions and the ability to mediate protein–carbohydrate interactions in three dimensions should reveal improved properties compared with those of the corresponding monovalent or linear polyvalent displays of carbohydrates as previously reported.[21] There have been several reports concerning the synthesis of PMMs by radical,[22] anionic,[23] metallocene catalysis,[24] although we previously demonstrated the preparation of amphiphilic PMMs via repetitive ring opening metathesis polymerization (ROMP).[25] This technique allows the precise control of the polymerization of the side chain and the macromonomer to complete conversion.[25] We have recently expanded this strategy to incorporate carbohydrates.[26] This approach is facilitated by the precise placement and manipulation of end group functionality and for this purpose the molybdenum–alkylidenes prepared by Schrock[27] are proven to be powerful tools as they facilitate living polymerizations and enable access to precise polyvalent arrangements containing a variety of functionality.[3a,28–30]

We previously demonstrated that ABCs could be prepared by the attachment of polyethylene glycol (PEG) to ROMP diblock copolymers by a "grafting to" approach[3a] because hybrid "pegylated" materials have a wide applicability in materials science, medicine, and biotechnology. Polymers and surfaces functionalized with PEG have shown enhanced biocompatibility due to its low toxicity as well as its ability to minimize protein absorption to surfaces and have thus been adopted for use as the hydrophilic segment (shell region) in micelle formation,[31] and for improving biocompatibility with foreign materials.[32] The ability to precisely place a masked phenol terminus on the PMM main chain during the termination process can in principle be applied to the polymerization of a macromonomer. The subsequent manipulation of this functionality suggests the possibility of preparing a PMM-*graft*-PEG block copolymer, which illustrates a powerful method of placing different functionalities in amphiphilic polymeric architectures as well as the possibility for further end group functionalization of the PEG chains for targeting or recognition chemistry. Therefore, we herein report that PMMs can be prepared with varying amphiphilic diblock side chain lengths containing a variety of pendant sugar residues (galactose, mannose, ribonic-γ-lactone, and xylose), and that the degree of polymerization of the main chain (DP_n) proceeds in a living manner. We also demonstrate that an amphiphilic star-coil diblock copolymer can be prepared in a precisely controlled manner by attachment of the PMM to poly(ethylene glycol) using a "grafting to" approach.

Results and Discussion

Synthesis and polymerization of norbornene macromonomers bearing ester linked carbohydrates, poly(3a–b): The repetitive ROMP approach using well-defined molybdenum–alkylidene initiators of type [Mo(CHCMe$_2$Ph)(NAr)(OR)$_2$] (**A**, see below) has been adopted,[25,26] because this technique enables precise control and complete conversion of the polymerization in both the side and main chains due to the fact that the ROMP proceeds in a living manner with quantitative initiation. The accurate placement, manipulation of end group functionality (as illustrated by the preparation of the macromonomer poly(**3**) in Scheme 1) are thus possible.

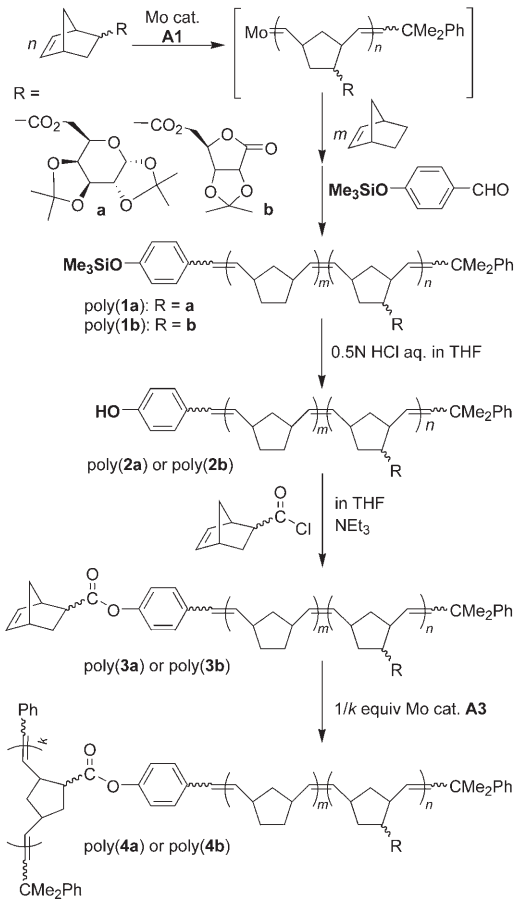
The approach encompasses the following three key steps that are required for their preparation: i) exclusive end-capping of block ROMP copolymer with TMS ($SiMe_3$) protected 4-hydroxy-benzaldehyde; ii) removal of the TMS protection from the terminus,[26,29] and iii) efficient preparation of the macromonomer by esterification of the OH group at the terminus with norbornene carboxylic acid chloride. Norbornene derivatives containing acetal protected galactose (**a**) or ribose (**b**) were chosen, because the synthesis and purification procedures for these monomers were already established by us.[3a,26,29] [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



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

Ar = 2,4,6-Me$_3$C$_6$H$_2$, Cy = cyclohexyl

ability to prepare the multi-block copolymers in a precise manner.[27–29] 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$_3$SiO-C$_6$H$_4$CHO (Scheme 1).[33] The M_n values for the resultant copolymers were dependent on the initial feedstock ratio. The M_w/M_n values were low in all cases (M_w/M_n = 1.10–



Scheme 1. Preparation of poly(macromonomer)s using the molybdenum initiators (**A1**–**A3**). Detailed preparation procedures for poly(**3a**,**b**) are given in the Supporting Information.

1.20),[33] which suggests that the polymerization proceeded in a living manner.[27–29] The TMS group in the polymer termini could be cleanly hydrolyzed using 0.5 M HCl aqueous solution in THF to afford poly(**2**) in high yields (>95%)[33] without any notable changes in the M_n values obtained by gel-permeation chromatography (GPC) as well as without any cleavage of the acetal protecting groups.[26,33] The reaction of poly(**2**) with norbornene carboxyllic acid chloride (1.5 equiv) in THF in the presence of NEt_3 afforded the macromonomer, poly(**3a**,**b**), in high yield (>97%).[33] The monomers were confirmed by the key resonances in the ^1H and ^{13}C NMR spectra.[25,26,33] The macromonomers were thus prepared with different diblock side chain combinations by varying the molar ratios of NBE and **a** or **b**. The flexibility of this strategy is highlighted with the preparation of a triblock side chain incorporating NBE and the two carbohydrate derivatives (Table 1). The presence of signals attributable to the polymerizable end group in the ^1H NMR spectra (at δ 6.87, 6.27, 6.04 ppm) and the ^{13}C NMR spectra (at δ 137.7, 135.4, 134.7 ppm) illustrated the placement of a norbornene terminus on the diblock copolymer.[33] As shown in Table 1,[33] the M_n values obtained by GPC were in good correlation with those calculated, and the values were also close to those estimated by the ^1H NMR spectra (the integration of olefinic signals of the NBE versus those of the internal polymer chain).

We communicated previously that [Mo(CHCMe$_2$Ph)(N-2,6-*i*Pr$_2$C$_6$H$_3$){OCMe(CF$_3$)$_2$}$_2$] (**A2**) and the Grubbs ruthenium carbene of [Ru(CHPh)(Cl)$_2$(IMesH$_2$)(PCy$_3$)] (**B**, IMesH$_2$ = 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene)[34] (see above) were unsuitable for the complete conversion of the macromonomers poly(**3a**,**b**).[26] Although the ROMP of macromonomer containing poly(NBE) by **A2** took place with complete conversion,[25] the ROMP for poly(**3a**) afforded a mixture consisting of the trimer, tetramer and poly(**3a**) {conditions: [poly(**3a**)]/[**A2**] = 10:1, Table 1, run 1}, probably a result of the insufficient reactivity toward the norbornenyl olefins in poly(**3a**,**b**) under these conditions. The same experiment with initiator (**B**) gave a polymer with a decreased M_n value as well as with increased M_w/M_n value (run 2), suggesting that the metathesis (degradation) with internal olefins took place instead of ROMP.[35]

Table 1. Preparation of poly(macromonomer)s (PMMs) by repetitive ROMP.[a]

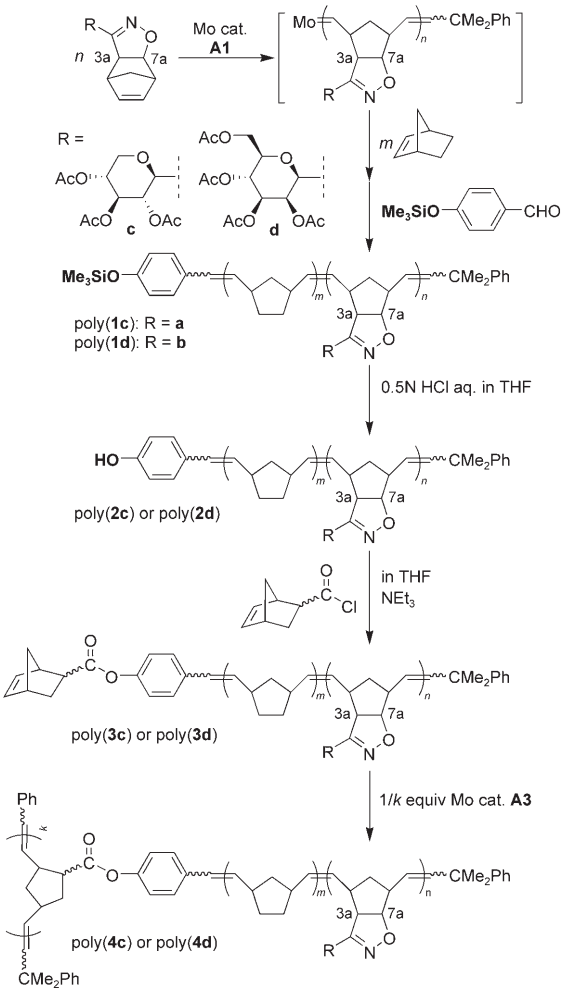
Run	poly(**3**)					Cat.	*t*	poly(**4**),PMMs				
	monomer feed ratios in poly(**3**)[b]	$M_{n(GPC)}$[c] $\times10^{-4}$	$M_{n(calcd)}$[d] $\times10^{-4}$	$M_{n(NMR)}$[e] $\times10^{-4}$	M_w/M_n[c]	[equiv k^{-1}][f]	[h]	$M_{n(calcd)}$[d] $\times10^{-4}$	$M_{n(GPC)}$[c] $\times10^{-4}$	M_w/M_n[c]	DP_n[g]	Yield[h] [%]
1	NBE_{25}-*b*-$\mathbf{a}_{25}$	1.58	1.18	1.24	1.1	**A2** (10)	1.5	11.95	4.50[i]	1.08	–	98
2	NBE_{25}-*b*-$\mathbf{a}_{25}$	1.58	1.18	1.24	1.10	**B** (10)	1.0	11.95	1.27	1.70	–	95
3	NBE_{25}-*b*-$\mathbf{a}_{25}$	1.58	1.18	1.24	1.1	**A3** (5)	2.0	5.98	8.18	1.15	5.2	98
4	NBE_{25}-*b*-$\mathbf{a}_{25}$	1.58	1.18	1.24	1.1	**A3** (10)	2.5	11.95	16.45	1.13	10.4	96
5	NBE_{20}-*b*-$\mathbf{a}_{20}$	1.28	0.95	1.02	1.11	**A3** (10)	2.0	9.72	11.76	1.07	9.2	96
6	NBE_{20}-*b*-$\mathbf{a}_{20}$	1.28	0.95	1.02	1.11	**A3** (5)	2.0	4.83	5.87	1.09	4.6	97
7	NBE_{20}-*b*-$\mathbf{a}_{20}$	1.28	0.95	1.02	1.11	**A3** (3)	1.0	2.89	3.99	1.19	3.1	97
8	NBE_{20}-*b*-$\mathbf{b}_{30}$	1.02	0.84	0.92	1.18	**A3** (10)	2.0	11.72	14.33	1.22	10.2	97
9	NBE_{10}-*b*-$\mathbf{a}_{20}$	1.18	0.85	0.94	1.12	**A3** (15)	3.0	12.77	20.04	1.07	17	>99
10	NBE_{10}-*b*-$\mathbf{a}_{20}$	1.18	0.85	0.94	1.12	**A3** (5)	2.0	4.27	5.74	1.17	4.9	98
11	NBE_{20}-*b*-$\mathbf{b}_{20}$	1.4	1.15	1.24	1.16	**A3** (10)	2.0	8.42	8.42	1.12	8.3	96
12	NBE_{20}-*b*-$\mathbf{b}_{20}$-*b*-$\mathbf{a}_{20}$	1.82	1.56	1.59	1.08	**A3** (10)	3.0	15.62	17.47	1.11	9.6	99

[a] Conditions: toluene (2.0 g) at 25 °C. [b] Starting feedstock ratio (repeating units per composition in the side chain corresponding to *m* and *n* in Scheme 1), and the detailed results for syntheses of poly(**3a**-**b**) are shown in the Supporting Information (Table S2-1). [c] Calculated from GPC data. [d] Calculated from initial feedstock ratios. [e] Estimated from ^1H NMR spectra. [f] Ratio of macromonomer to initiator (see Scheme 2). [g] Calculated from GPC data. [h] Isolated yield. [i] Mixture of macromonomer and oligo(macromonomer)s.

By contrast, the ROMP of macromonomers bearing galactose [poly(**3a**)] and ribose [poly(**3b**)] catalyzed by [Mo(CHCMe$_2$Ph)(N-2,6-Me$_2$C$_6$H$_3$)[OCMe(CF$_3$)$_2$]$_2$] (**A3**) proceeded to completion which was confirmed by the disappearance of the signals attributable to the NBE olefinic group as well as GPC trace (see Supporting Information). The reaction resulted in the PMMs poly(**4a**,**b**) with narrow molecular weight distributions (M_w/M_n = 1.07–1.22). Depending on the initial feedstock ratio of poly(**3a**)/**A3**, poly(**4a**)s with main chains with average degrees of polymerization (DP$_n$, estimated based on M_n values by GPC) were obtained in high yields in all cases (DP$_n$ = 3, 5 and 10, > 96 % yields, Table 1, runs 3–10). These results suggest that the ROMP of the macromonomer (**3a**,**b**) by **A3** proceeds in a living-like manner with high initiation efficiency. In an attempt to prepare the PMM with a longer main chain, the ROMP reaction of poly(**3a**) consisting of NBE$_{10}$-*b*-**a**$_{20}$ with **A3** (molar ratio 15:1) afforded poly(**4a**) with about 17 repeat units (run 9, estimated by GPC analysis) coupled with a unimodal molecular weight distribution (M_w/M_n = 1.07). Moreover, the complete conversion could be achieved in the ROMP reaction of the macromonomer containing the triblock copolymer of NBE$_{20}$-*b*-**b**$_{20}$-*b*-**a**$_{20}$. The GPC traces showed an increase in the M_n value from 1.82×10^4 for poly(**3b**,**a**) to 17.47×10^4 for the PMM, which corresponds to a main chain of approximately 10 units while maintaining a narrow unimodal distribution (M_w/M_n = 1.11, run 12); this illustrates the ability to produce a PMM with three different well defined blocks in the side chain.

Synthesis and polymerization of norbornene macromonomers containing glycosyl isoxazolines poly(3c,d): We recently reported that the in situ generation and subsequent cycloaddition of glycosyl nitrile oxides to norbornadiene (NBD) afforded monomeric isoxazolinonorbornenes bearing xylose, glucose and mannose residues in high yields;[36] also, that the ROMP of the norbornene derivatives containing acetyl-protected sugar residues initiated by [Ru(CHPh)(Cl)$_2$(PCy$_3$)$_2$] (Cy: cyclohexyl) and [Mo(CHCMe$_2$Ph)(N-2,6-*i*Pr$_2$C$_6$H$_3$)(O*t*Bu)$_2$] (**A1**) proceeded in a living manner with quantitative initiation, affording polymers with narrow molecular weight distributions (M_w/M_n = 1.11–1.35).[36] This facile method of the preparation of norbornenyl monomers is an alternative tool from the Diels–Alder or "tether" approaches, which afford polymerizable architectures containing a variety of functionality.[37] As previously reported, the isoxazolinonorbornenes bearing xylose (**c**), mannose (**d**) residues were found to be suitable for copolymerization with norbornene with **A1** at various compositions.[36] Preparation of the macromonomers poly(**3c**,**d**) could be achieved in the same manner for the galactose (**a**) and ribose (**b**) derivatives, as shown in Scheme 2.

According to Scheme 2, NBE and (**c**) were polymerized with **A1** in toluene in almost quantitative yields. The M_n values increased upon increasing the initial initiator/monomer molar ratios while maintaining narrow unimodal molecular weight distributions (M_w/M_n = 1.08–1.18),[33] indicative



Scheme 2. Preparation of glycosyl isoxazolino functionalized poly(macromonomer)s. Detailed preparation procedures for poly(**3c**,**d**) are shown in the Supporting Information.

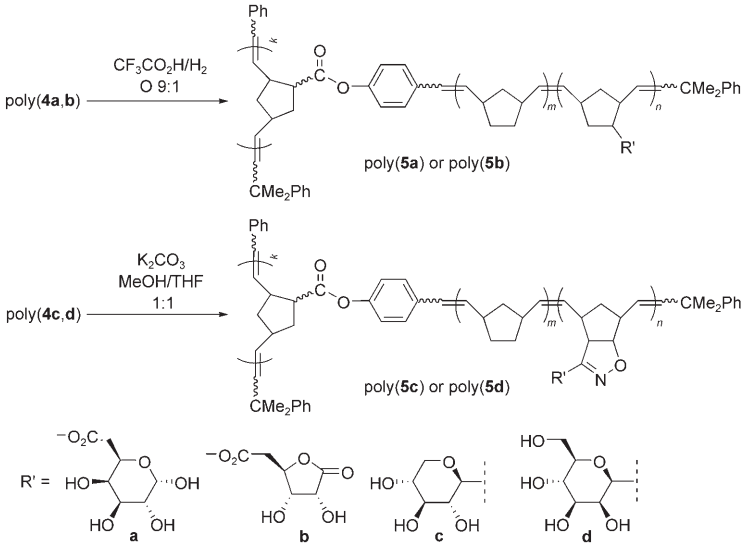
of a living system.[36] The hydrolysis of the phenol terminus protection (TMS) was effected under mild acidic conditions. The disappearance of the signal attributable to the SiMe$_3$ group without any other significant changes was observed in the NMR spectrum for the resultant poly(**2c**).[33] The macromonomer was thus prepared according to the same procedure described above in high yields (98 %), and the presence of the polymerizable NBE end group was confirmed in the both ^{1}H NMR (δ 6.46, 6.41, 5.91, 5.77 ppm) and the ^{13}C NMR spectrum (δ 135.8, 135.6, 134.9 ppm).[33] The macromonomer containing mannose residue, poly(**3d**), containing NBE$_m$-*b*-**d**$_n$ ($m=n$ = 20, 30), was also prepared in the same manner (Table 2). The polymerizations of the macromonomer based on NBE$_{20}$-*b*-d$_{20}$ in toluene [molar ratio of poly(**3d**)/**A3** 5,10] afforded poly(**4d**) in high yields (> 97 %, Table 2, runs 16–17). The resultant polymers possessed repeating units according to the initial molar ratio (DP$_n$ = 5.1 estimated by GPC, $M_n=6.42\times10^4$; DP$_n$ = 10.2, $M_n=12.92\times10^4$; poly(**3d**), $M_n=1.27\times10^4$, M_w/M_n 1.09) with narrow molecular weight distributions (M_w/M_n = 1.11 and 1.17, respectively). The polymerization of the macromonomer contain-

Table 2. Preparation of isoxazoline functionalized poly(macromonomer)s (PMMs) by repetitive ROMP.[a]

Run	poly(**3**) monomer feed ratios in poly(**3**)[b]	$M_{n(GPC)}$[c] $\times 10^{-4}$	$M_{n(calcd)}$[d] $\times 10^{-4}$	$M_{n(NMR)}$[e] $\times 10^{-4}$	M_w/M_n[c]	Cat. [equiv k^{-1}][f]	t [h]	poly(**4**), PMMs $M_{n(calcd)}$[d] $\times 10^{-4}$	$M_{n(GPC)}$[c] $\times 10^{-4}$	M_w/M_n[c]	DP_n[g]	yield[h] [%]
13	NBE_{20}-*b*-$\mathbf{c}_{20}$	1.08	1.00	1.02	1.15	**A3** (10)	2.0	10.2	11.32	1.16	10.5	98
14	NBE_{25}-*b*-$\mathbf{c}_{25}$	1.56	1.25	1.27	1.09	**A3** (5)	2.0	6.29	7.92	1.08	5.1	97
15	NBE_{25}-*b*-$\mathbf{c}_{25}$	1.56	1.25	1.27	1.09	**A3** (10)	2.0	12.52	16.71	1.19	10.7	98
16	NBE_{20}-*b*-$\mathbf{d}_{30}$	1.27	1.15	1.18	1.09	**A3** (5)	2.0	5.77	6.42	1.11	5.1	97
17	NBE_{20}-*b*-$\mathbf{d}_{30}$	1.27	1.15	1.18	1.09	**A3** (10)	2.0	11.52	12.92	1.17	10.2	98
18	NBE_{30}-*b*-$\mathbf{d}_{30}$	1.94	1.71	1.75	1.14	**A3** (5)	2.5	8.57	10.09	1.16	5.2	99

[a] Conditions: toluene (2.0 g) at 25 °C. [b] Starting feedstock ratio (repeating units/composition in the side chain corresponding to *m* and *n* in Scheme 2) and the detailed results for syntheses of poly(**3c**,**d**) are shown in the Supporting Information (Table S2-2). [c] Calculated from GPC data. [d] Calculated from initial feedstock ratios. [e] Estimated from ^{1}H NMR spectra. [f] Ratio of macromonomer to initiator (see Scheme 2). [g] Estimated from GPC data. [h] Isolated yield.

ing a larger side chain, NBE_{30}-*b*-$\mathbf{d}_{30}$, could also be completed [initial molar ratio of poly(**3d**)/**A3** = 5] to afford poly(**4d**) with the estimated DP_n [$DP_n = 5.2$, $M_n = 10.09 \times 10^4$), with a narrow molecular weight distribution ($M_w/M_n = 1.16$), although the reaction time was longer until completion (2.5 h, run 18). The polymerization of poly(**3c**) containing NBE_{20}-*b*-$\mathbf{c}_{20}$ [feedstock ratio of poly(**3c**)/**A3** = 10] afforded poly(**4c**) in high yield (98%) with an M_n value corresponding to a main chain of approximately 10 units, with a narrow molecular weight distribution ($M_n = 11.32 \times 10^4$, $M_n/M_w = 1.16$, Table 2, run 13). The complete conversion of the xylose-containing poly(**3c**) with a larger side chain, NBE_{25}-*b*-$\mathbf{c}_{25}$ ($M_n = 1.56 \times 10^4$), could also be achieved [initial molar ratio of poly(**3c**)/**A3** 5,10] affording the poly(**4c**)s in quantitative yield (>97%) with the identical repeat units estimated by the molar ratios ($DP_n = 5.1$, $M_n = 7.92 \times 10^4$; $DP_n = 10.7$, $M_n = 16.71 \times 10^4$, respectively) with narrow molecular weight distributions ($M_w/M_n = 1.08$–1.19, Table 2, runs 14–15). The ability to incorporate glycosyl isoxazolines into the backbone of poly(**4c**) is again demonstrative of the functional group tolerance of the Mo alkylidenes (**A1**–**3**).



Scheme 3. Deprotection of acetal, acetyl protecting groups in poly(macromonomer)s, poly(**4a**–**d**)s affording poly(**5a**–**d**)s.

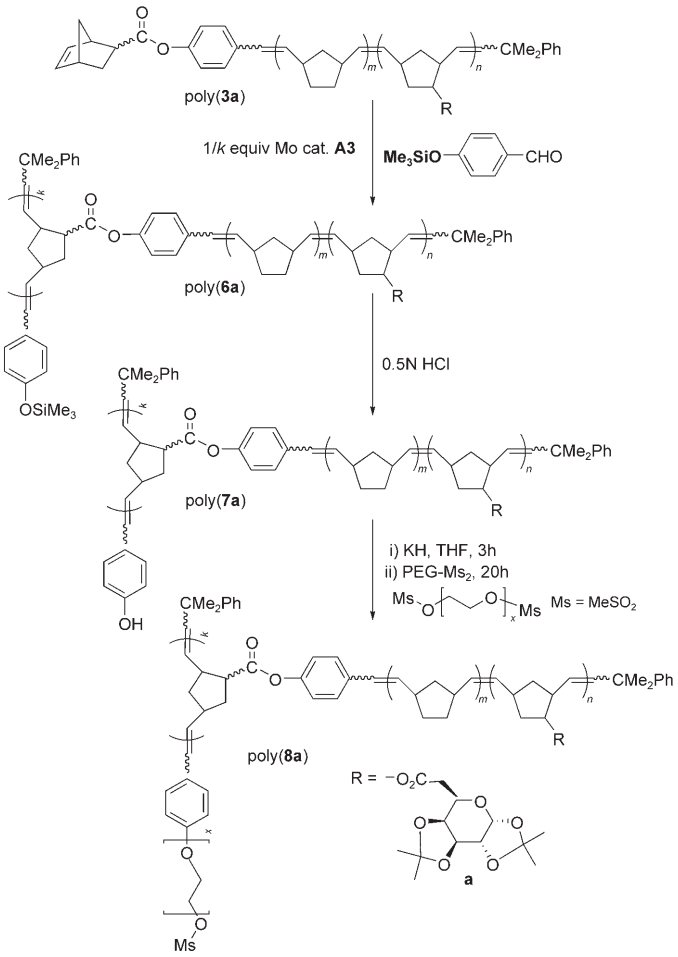
Deprotection of acetal and acetyl protecting group in sugars: The hydrolysis of the acetal protecting groups of carbohydrates in various polymeric architectures by stirring with CF_3CO_2H/H_2O 9:1 is a well established method (Scheme 3).[3a,26,29] The complete disappearance of the signals attributable to the acetal protecting groups, the presence of signals attributable to the deprotected moiety as well as to the polymeric scaffold were confirmed by both the ^{1}H and ^{13}C NMR spectra (in addition to the FTIR spectra). Moreover, since the isolated yields were high in all cases (typically >80%), it is thus clear that this protecting strategy is compatible with an array of topologies (Scheme 3).

In this report, we have extended the range of carbohydrates and linking functionalities to incorporate xylose and mannose isoxazolines as illustrated by poly(**4c**,**d**). Previously, 3,4-dipyranosyl-1,2,5-oxadiazole-2-oxides bearing free sugars were prepared in high yield (91%) by the deacetylization of the acetate protected analogues using an ammonia saturated methanolic solution (NH_3/MeOH).[38a] However, in this case we have investigated a related method of removing the acetate protection by stirring the PMM, poly(**4c**,**d**), in a solution of MeOH/THF 1:1 with sodium carbonate and quenching the reaction under acidic conditions (Scheme 3)[36] (see Experimental Section for full details). The resultant deprotected PMMs, poly(**5c**,**d**), were afforded in high yield (83–86%). Disappearance of the corresponding resonances in both ^{1}H and ^{13}C NMR spectra [at δ_H 2.09–2.00 ($4 \times COCH_3$); δ_C 170.6, 170.1, 169.6, 169.5 ($4 \times COCH_3$) and 20.8, 20.7 ppm ($4 \times COCH_3$)] and an absorption band in the FTIR spectrum [at $\tilde{\nu}$ 1628–1705 cm^{-1} (C=O)] attributable to

the acetyl protecting groups, whereas the observation of all other characteristic signals for the intact deprotected mannose residues fused to the PMM through isoxazoline linkages [^{1}H NMR: δ = 3.28 (H-3a), 4.76 (H-3a); ^{13}C NMR: δ = 51.5 (C-3a), 90.7 (C-7a), 159.9 ppm (C=N)], coupled with the presence of stretches in the IR spectrum [between $\tilde{\nu}$ 1497–1589 (C=N), 1647, 1686, 1695 (C=O, side chain ester linkage), and 3669–3815 cm^{-1} (OH)], suggested that the deprotection occurred without removal of the sugars from the side chains.[39]

Synthesis of poly(macromonomer)-*block*-PEG amphiphilic macrostructures: The synthetic route adopted in this work for the preparation of PMMs demonstrates the ability for a precise placement and manipulation of the end group functionality. It was postulated that the scope of this method could be extended by terminating the polymerization of the macromonomer with a $SiMe_3$ group (TMS) protected 4-hydroxybenzaldehyde [$Me_3SiOC_6H_4CHO$], thus placing a masked phenol terminus on the main chain potentially allowing further manipulation. Previously, various amphiphilic architectures were prepared by the potassium hydride mediated attachment of poly(ethylene glycol) (PEG) to hydrophobic ROMP polymers bearing a phenolic end group,[3a] prompting the investigation of a new polymeric amphiphilic macrostructure, which could be achieved in the same manner using the phenol chain end of a PMM.

Our extended strategy entails the preparation of a PMM as described above except that the polymerization of the macromonomer was quenched with the 4-Me_3SiO-C_6H_4CHO in this case to afford poly(**6a**) as shown in Scheme 4. In the same manner as described earlier, the TMS protection was cleanly removed under mildly acidic conditions, which was accompanied by the absence of the peak attributable to the $Si(CH_3)_3$ group in the ^{1}H NMR spectrum at δ 0.25 ppm. No significant decrease in the M_n values from poly(**6a**) to poly(**7a**) (from 5.91×10^4 to 5.85×10^4) was observed while maintaining a narrow molecular weight distribution (M_w/M_n = 1.09, Table 3, runs 20–21). The phenol terminus was used for the KH-mediated attachment to methane sulfonyl protected poly(ethylene glycol) [PEG-Ms_2, $MsO(CH_2CH_2O)_nMs$, Ms = $MeSO_2$], prepared by the treatment of PEG with methane sulfonyl chloride, as PEG attached polymer architectures have previously been used as potential candidates for investigation as drug delivery agents.[31] The preparation of an ether linkage through



Scheme 4. Preparation of poly(macromonomer)-*graft*-PEG, poly(**8**).

$PEGMs_2$ would also be suitable for this approach.[40] Thus, two PEGs with different molecular weights [M_n = 2200 (PEG_{47}) and 4600 (PEG_{110}), M_w/M_n = 1.03] were investigated as the hydrophilic segment in the preparation of PMM-*block*-PEG amphiphilic architectures. The attachment of (PEG_{47}) to poly(**7**) afforded poly(**8**) (yield 82%), and the M_n value measured by GPC revealed an increase from 5.85×10^4 to 6.11×10^4 (run 20), with a resultant narrow unimodal dispersity (M_w/M_n = 1.08). The analogous reaction with (PEG_{110}) resulted in poly(**8**) in a similarly high yield (85%) with an increase in molecular weight ($M_n = 6.40\times10^4$, run 21) as well as with a unimodal molecular weight distri-

Table 3. Preparation of poly(macromonomer)-*block*-(PEG), poly(**8**).[a]

Run	poly(**3**)/**A3**	poly(**6**)					poly(**7**)			PEG	poly(**8**)				
	[equiv][b]	$M_{n(calcd)}$[c] $\times10^{-4}$	$M_{n(GPC)}$[d] $\times10^{-4}$	M_w/M_n[d]	DP$_n$[e]	yield [%]	$M_{n(GPC)}$[d] $\times10^{-4}$	M_w/M_n[d]	yield [%]	M_n	$M_{n(GPC)}$[d] $\times10^{-4}$	$M_{n(calcd)}$[c] $\times10^{-4}$	$M_{n(NMR)}$[g] $\times10^{-4}$	M_w/M_n[d]	yield[h] [%]
19	3:1	2.88	3.91	1.15	3.1	98	3.89	1.11	99	4600	4.77	3.33	3.43	1.12	87
20	5:1	4.78	5.91	1.12	4.6	97	5.85	1.09	98	2200	6.11	4.99	5.07	1.08	82
21	5:1	4.78	5.91	1.12	4.6	97	5.85	1.09	99	4600	6.40	5.23	5.29	1.11	85

[a] Based on MM (macromonomer) poly[$(NBE)_{20}$-*b*-(**2a**)$_{20}$]; $M_{n(GPC)} = 1.28\times10^4$, M_w/M_n = 1.11 (runs 5–7, Table 1).[33] [b] **A3** = $F_6(Me_2)$ ratio of macromonomer to initiator. [c] Calculated from initial feedstock ratios. [d] GPC data in THF versus polystyrene standards. [e] Estimated from GPC data. [f] Isolated yield. [g] Estimated from ^{1}H NMR spectra. [h] Isolated yield.

bution ($M_w/M_n = 1.11$). These results clearly illustrate a facile method of preparing amphiphilic architectures by the careful manipulation of the end groups of PMMs.

Preparation and TEM observation of polymeric micelles derived from poly(5a), poly(8a) and poly(9a): The self-assembly of polymers based on various topologies has generated substantial interest on account of the variety of nanostructures formed,[1,2] however, PMMs prepared via ROMP traditionally possess main chains with low DPs, and thus have received little attention concerning their aggregation behaviors and measurement via surface microscopic techniques.[25,26,41] Amphiphilic polymeric architectures containing well defined hydrophobic and hydrophilic segments form micelles in aqueous conditions when the water content is equivalent to a given critical mass concentration (CMC).[42] These architectures have been previously observed using surface microscopic techniques.[1,2,3e,f,9a,12,14e,15d,18,22d,24a,43] We herein report that nanospheres could be prepared by the aggregation of polymers with varying topologies: i) PMM-*block*-PEG [poly(**8a**)]; ii) linear amphiphilic block copolymers [ABCs, poly(**9a**)], and iii) PMMs after removal of acetal protecting group [poly(**5a**)]; their dimensions measured using TEM (Table 4). Linear ABCs were known to be effective for the preparation of micelles.[11,13c,14,15a,c,16a,18] Therefore, a triblock linear ABC (NBE_{20}-*b*-$\mathbf{a}_{20}$)-*b*-PEG_{110} [poly(**9a**), Table 4, run 22] was prepared in an analogous manner to that reported previously,[3a] and was investigated for its potential to form micelles (see Supporting Information for full experimental details). Briefly, a solution of poly(**9a**) (0.05 mg per mL THF) was added into deionized water. The formed micelles, indicated by an increase in the solution viscosity, were quenched. After removal of THF, the sample was subjected to TEM and from the resulting micrographs (Figure 1a–c), core–shell structures were clearly visible, with prominent hydrophobic centers evident, due to the more sterically bulky "rod-type" poly(NBE) based segment, in comparison to the "coil-type" PEG blocks. These micelles have a diameter of $d_{TEM} = 231.3 \pm 17.60$ nm, corresponding to a circumference of 727 nm (Table 4, run 22). The diameters of the core and shell were 107.3 ± 13.8 nm and 123.9 ± 15.1 nm, respectively, the core occupying 44% of the micelle on average, which is excellent compared with the 40% calculated (see the Supporting Information for full analysis).[44,45] In a similar manner, poly(**8a**), PMM-*block*-PEG (Tables 3 and 4, run 20) aggregated to form spherical micelles as observed by TEM (Figure 2), revealing spherical aggregates with a diam-

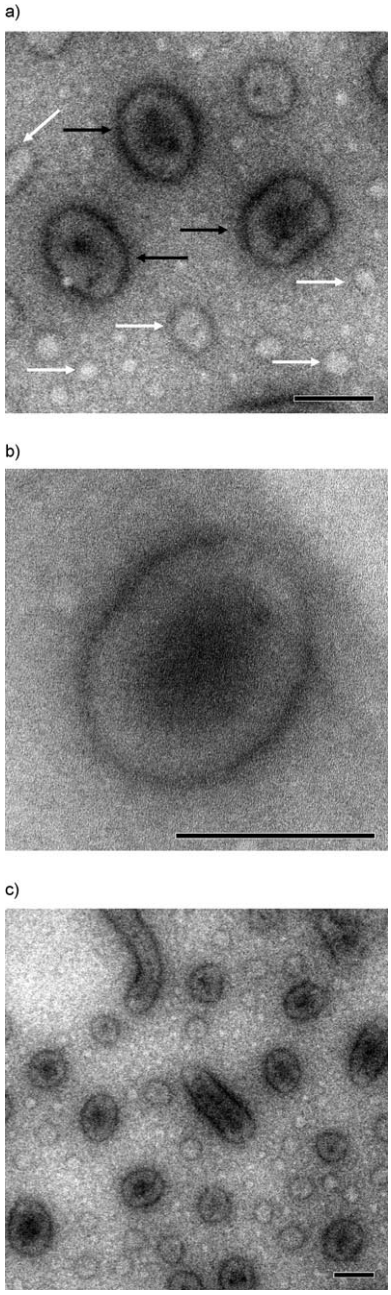


Figure 1. TEM images of the spherical aggregates (black arrow) derived from the linear ABC, (NBE_{20}-*b*-$\mathbf{a}_{20}$)-*b*-PEG_{110} [poly(**9a**), Table 4, run 22] at a concentration of 0.05 mg per mL THF at varying magnification. Bar equivalent to 200 nm. White bright circles (white arrow) would be a TEM artifact formed after rapid evaporation of THF droplet (containing trace amount of 2,6-tBu_2-4-MeC_6H_2OH) in vacuo on copper grid covered with a perforated polymer film and coated with carbon.[46]

Table 4. TEM measurement of micelles derived from poly(**5a**), poly(**8a**) and poly(**9a**).

Run	Figure	poly(***n***)s	Description	Topology	micelle diameter[a] d_{TEM} [nm][44]	Micelle diameter SEM[b] d_{TEM} [nm][44]	Micelle circumference[c] c_{TEM} [nm][44]
5	7	poly(**5a**)	$(NBE_{20}$-*b*-$\mathbf{a}_{20})_{10}$	PMM	126.4 ± 4.5	1.01	397
20	5	poly(**8a**)	$(NBE_{20}$-*b*-$\mathbf{a}_{20})_5$-PEG_{110}	PMM-*b*-PEG	148.5 ± 7.2	1.61	467
22	4	poly(**9a**)[d]	NBE_{20}-*b*-$\mathbf{a}_{20}$-*b*-PEG_{110}	linear ABC	231.3 ± 17.6	3.94	727

[a] Isolated micelle diameter standard deviation (SD) was calculated from 20 measurements. [b] Standard error of the mean ($SD/\sqrt{n}$). [c] Isolated micelle circumference (πd), was estimated from 20 measurements. [d] GPC data for linear ABC poly(**9a**): $M_n = 1.89 \times 10^4$, $M_w/M_n = 1.13$.[3a]

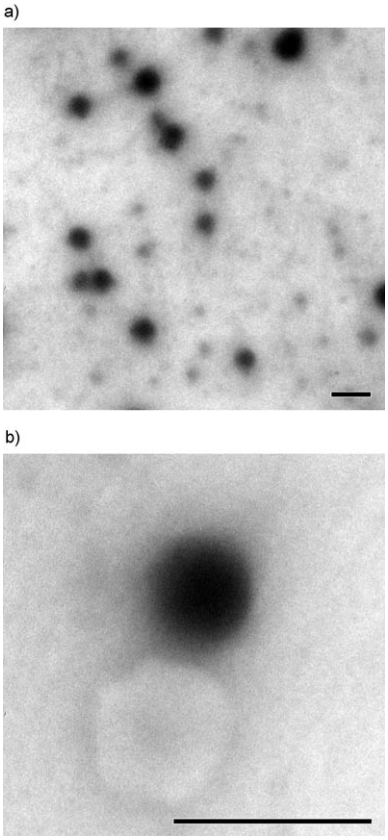


Figure 2. TEM images of spherical aggregates of poly(NBE_{20}-*b*-$\mathbf{a}_{20})_5$-*b*-PEG_{110} [poly(**8a**), Tables 3 and 4, run 20] at a concentration of 0.05 mg per mL THF at varying magnification. Scale bar: 200 nm.

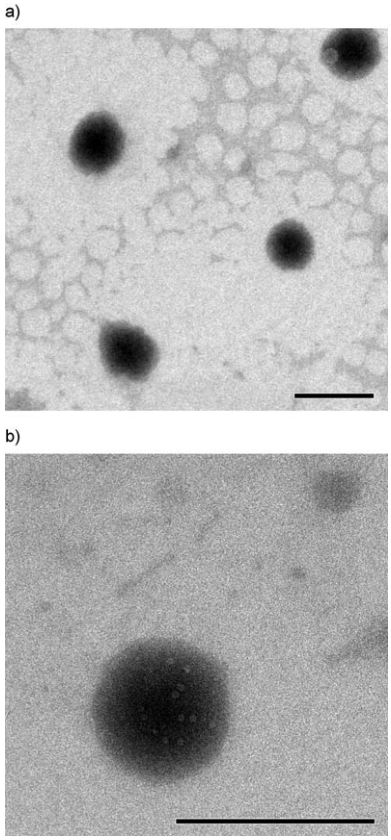


Figure 3. TEM images of the spherical aggregates derived from poly-(NBE_{20}-*b*-$\mathbf{a}_{20})_{10}$ [poly(**5a**), after deprotection of acetal of sample in run 5, Tables 1 and 4] at a concentration of 10–4 mg per mL THF at varying magnification. Scale bar: 200 nm.

eter, $d_{TEM} = 148.5 \pm 7.2$ nm, corresponding to a circumference of approximately 467 nm (run 20). These well defined micelles are smaller in size compared with the corresponding PEG-based ABC, poly(**9a**), which can be explained by the more facile packing of the linear chains into the hydrophobic center in comparison to the bulky core-forming PMM of poly(**8a**).

Intelligent materials derived from aggregated nanostructures,[47] which are responsive to external stimuli[14a,15a,16–18] or solvent environment[48] are important for interesting applications such as nanowires or biomimetic macromolecules. The internal polymeric components are rendered incompatible upon the triggering of functionality resulting in a structural change allowing for tunable properties. Upon removal of the acetal protecting groups, the resulting poly(**5a**) (Table 4, run 5) possessed a clearly defined amphiphilic structure. A sample was prepared for TEM analysis by suspension of a dilute solution of poly(**5a**) (10^{-4} mg per mL DMF) in deionized water (see the Supporting Information for full experimental details). The resulting micrographs (Figure 3) depict the aggregation into uniform nanospheres with diameters of 126.4 ± 4.5 nm, corresponding to a circumference of 397 nm (the support sheet is visible as a poorly contrasted web structure in the background of Figure 3, right). The aggregation mechanism is explained by the formation of an outer shell consisting of a galactose functionalized block with a core comprised of hydrophobic poly(NBE) blocks and the main chains (see Supporting Information). This clearly demonstrates that through the facile manipulation of the polymer functionality pre-aggregation well defined coil-like or spherical aggregates can be prepared. In summary, we have demonstrated that spherical micelles were assembled from various ROMP-based amphiphilic polymeric fragments, poly(**5a**), poly(**8a**) and poly(**9a**) in water. The ability to precisely control the polymerization in each topological synthesis (as demonstrated above), suggests that size control of the resultant nanoparticles should be expected. In combination with the ability to target specific cells[49] with the sugar coating of these micelles we believe that the present contribution will demonstrate a new class of nanoparticles for potential drug delivery purposes.

Encapsulation of a dye (Nile Red) using amphiphilic polymeric architectures: The encapsulation of the dye, Nile Red (a fluorescence probe), was previously demonstrated as a successful drug mimic to probe the potential of aggregates derived from ABCs as drug delivery agents.[17] This method entails the uptake of the dye by the polymeric aggregate at the CMC. The observation of an increase in fluorescence emission intensity coupled with a blue shift in the UV and

fluorescence emission spectra gave evidence that the dye was residing in the hydrophobic core. We herein thus focus on the encapsulation of the dye, Nile Red, using two ABCs with different architectures: i) the deprotected PMM, poly-(**5a**), and ii) a linear ABC, poly(**9a**).

The micelles were formed in all cases as previously described[18] (see the Supporting Information for full experimental procedure) by adding deionized water into a THF solution of the polymer (0.05 mg mL^{-1}) containing Nile Red (6% wt.), with stirring for 30 minutes. The micelle was then quenched by adding a four-fold amount of deionized water and the mixture was heated at 60 °C to remove all traces of THF. The formation of the encapsulation of Nile Red was monitored by a color change from bright orange to pink.[18] In an attempt to perform initial investigations to determine whether the various polymeric fragments could encapsulate the dye or not, a series of samples were taken before and after encapsulation. In summary (Figure 4), excitation of the

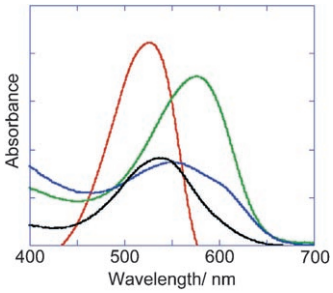


Figure 4. UV spectra of the hydrophobic dye Nile Red and the dye encapsulated micelles derived from poly(**5a**), and poly(**9a**). Nile Red in THF ——; Nile Red in THF/water ——; dye encapsulated in micelle derived from poly(**5**) ——; dye encapsulated in micelle derived from poly(**9**) ——.

hydrophobic Nile Red in THF with 540 nm light reveals an absorption maximum at 527 nm which red shifts to 576 nm on addition of water. The initial encapsulation experiment was performed with poly(**5a**) [see the Supporting Information for the proposed encapsulation mechanism]. From the UV spectrum the absence of the peak attributed to the dye, in addition to the blue shifted absorption maxima, $\lambda_{max} =$ 542 nm, suggested that the dye resided in the hydrophobic poly(NBE) core.

In a similar manner, encapsulation of the dye with the micelle prepared from poly(**9a**) revealed a spectrum with an absorption maximum at 551 nm, which is attributable to the micelle encapsulated dye. A shoulder was also observed at $\lambda = 605$ nm, which was attributed to the aggregated dye in close proximity to the micellar core. The photophysical properties of charge transfer dyes (such as Nile Red) are significantly dependant on the polarity of the solvent. Accordingly, these dyes should red-shift with increasing polarity. However, the spectrum of Nile Red encapsulated by the micelles derived from the present polymers, blue-shifted to a shorter wavelength by about 25 nm or more when compared with the spectrum of Nile Red alone in the mixed solvent of THF and water; this suggests that dyes were residing in the hydrophobic nonpolar micellar cores.[17,18]

Figure 5 depicts the fluorescence emission spectra of the micellar solution with encapsulated Nile Red derived from poly(**5a**) and poly(**9a**). Excitation of the dye, dissolved in THF at 540 nm, exhibited an emission band with a maximum peak of 590 nm, which on addition of water is shifted to 647 nm. The encapsulation of the dye with a polymeric micelle derived from poly(**5a**) results in the fluorescence emission centered at a wavelength of 639 nm without any trace of the signal at 647 nm. On the other hand, with the micelles derived from poly(**9a**), the fluorescence emission of Nile Red is very weak and a little red shifted to 650 nm, which is presumably a result of energy transfer to the aggregated dye acting as an energy trapping and quenching site.

In summary, the encapsulation of hydrophobic dyes is possible in the cores of micelles derived from the various amphiphilic fragments as revealed by UV and fluorescence emission spectroscopy. The incorporation of a wide range of hydrophobic molecules (e.g. drugs) into the nanospheres is thus possible for potential applications as cell targeting drug delivery agents.

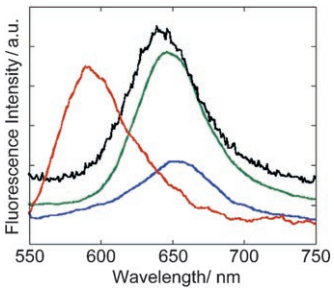


Figure 5. Fluorescence emission spectra of the hydrophobic dye Nile Red and the dye encapsulated micelles derived from poly(**5a**), and poly(**9a**). Nile Red in THF ——; Nile Red in THF/water ——; dye encapsulated in micelle derived from poly(**5**) ——; dye encapsulated in micelle derived from poly(**9**) ——.

Conclusion

Poly(macromonomer)s (PMMs) bearing a variety of carbohydrate residues (galactose, glucose, ribose and xylose) have been prepared by using a repeat ROMP technique. Regulating the initial feedstock ratio of initiator to the comonomers and macromonomers accurately controlled the side and main chain valencies. The flexibility of this synthesis was illustrated by the precise placement and manipulation of polymer termini described herein to prepare a new type of PMM-*block*-PEG amphiphilic architecture. The observation of micelles by TEM, which are derived from the suspension of a variety of amphiphilic topologies in aqueous media, and their ability to encapsulate a hydrophobic dye (Nile Red) are preliminary steps focused toward their function as delivery agents. In addition, the facile removal of the carbohydrate protecting groups suggests that the various sugar coated amphiphilic fragments have the potential for cell tar-

geting biomimetic applications. We are currently investigating the preparation of stimuli respondent amphiphilic nanostructures, which may be effective for the control of micelle degradation and will present these findings in the near future

Experimental Section

General: All chemicals used were of reagent grade and were purified by the standard purification procedures. Polymerization grade toluene was distilled from sodium/benzophenone, stored over sodium/potassium alloy in the drybox, and was then passed through an alumina short column prior to use. Anhydrous grade diethyl ether, dichloromethane, tetrahydrofuran (THF), and *n*-hexane (Kanto Kagaku Co. Ltd) were transferred into a bottle containing molecular sieves (mixture of 3 Å, 4 Å 1/16, and 13×1/16) in the drybox. The molybdenum initiators of the type $[(ArN)Mo(CHCMe_2Ph)(OR)_2]$ with Ar = 2,6-*i*Pr$_2$C$_6$H$_3$, R = *t*Bu (**A1**) or CMe(CF$_3$)$_2$ (**A2**); Ar = 2,6-Me$_2$C$_6$H$_3$, R = CMe(CF$_3$)$_2$ (**A3**),[50] and 5-norbornene carboxylic acid chloride[51] were prepared according to the literature; $[Ru(CHPh)(Cl)_2(IMesH_2)(PCy_3)]$ (**B**, IMesH$_2$ = 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene, Cy = cyclohexyl) was purchased from Aldrich and was used without further purification. The terminating agent 4-Me$_3$Si-C$_6$H$_4$CHO was prepared according to the previous report.[25] The detailed preparation procedures including identification for poly(**1**), poly(**2**), and poly(**3**) are shown in the Supporting Information.[33]

All experiments were carried out under a nitrogen atmosphere in a Vacuum Atmospheres drybox or using standard Schlenk techniques. All ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-LA400 spectrometer (^{1}H, 399.65 MHz; ^{13}C, 100.40 MHz), and were obtained in the solvent indicated at 25 °C, with all chemical shifts quoted in ppm and referenced to SiMe$_4$. HPLC grade THF (Wako Pure Chemical Industries, Inc.) was used for GPC and was degassed prior to use. GPC were performed at 40 °C on a Shimadzu SCL-10 A using a RID-10 A detector (Shimadzu Co. Ltd.) in THF (containing 0.03 wt % 2,6-di-*tert*-butyl-*p*-cresol, flow rate 1.0 mL min^{-1}). GPC columns (ShimPAC GPC-806, 804 and 802, 30 cm × 8.0 mmϕ) were calibrated versus polystyrene standard samples.

Transmission Electron Microscopy (TEM) measurements were made on thin films on an Okenshoji Co. Ltd. copper grid, which was covered with a perforated polymer film and coated with carbon on all sides (diameter 3 mm), at different concentrations of 10^{-1}, 10^{-2}, 10^{-3} and 10^{-4} mg mL^{-1} (THF). They were then analyzed with a JEOL JEM-3100FEF electron microscope (gun type: field emission) at an accelerate voltage of 300 kV, a column vacuum of 1.0×10^{-5} Pa and at a magnification of 20000×. All pictures were energy filtered TEM images, which were taken with an Omega energy filter for zero-loss images (cut inelastic scattered electrons). The temperature was set to 22 °C and the relative humidity was set to 50 %. Samples for measurements of the thin films of the micelles prepared by suspending THF solutions of poly(**5**), poly(**8**) and poly(**9**) into water were obtained by placing a droplet of the aqueous micellar solution onto a microgrid, and then drying in vacuo for 3 h prior to analysis.

UV spectra were recorded on a JASCO V-570 spectrophotometer and PL spectra were measured using a JASCO FP-6500 Fluorescence Spectrophotometer at an excitation wavelength (λ_{ex}) of 540 nm, using quartz cells (GL Sciences Inc. Japan, 10 mm) on samples taken directly from the reaction vessel used for the dye encapsulation experiments.

Preparation of poly(macromonomer)s (PMM)

Poly(4a): The conversion of the macromonomer poly(**3a**) to the PMM was carried out as reported earlier.[26] The typical procedure was as follows: Poly(**3a**) (80 mg, 10 equiv to the initiator **A3**) was dissolved in toluene (2.0 g) and $[Mo(CHCMe_2Ph)(N\text{-}2,6\text{-}Me_2C_6H_4)\{OCMe(CF_3)_2\}_2]$ (**A3**) in toluene (0.5 g) was added in one portion at room temperature. The mixture was stirred for the given time and the polymerization was terminated by the addition of benzaldehyde in excess amount. The solution was stirred for 1 h to ensure completion and then was poured into cold methanol to isolate poly(**4a**) as a white precipitate. Yield 96–98 %. ^{1}H NMR ($CDCl_3$): δ = 5.32–5.19 (br, 6H, olefinic H), 5.49 (brs), 4.58 (brs), 4.29–4.20 (brd), 3.97 (br, 7H, sugar group protons), 3.10–2.93 (brd), 2.76 (s), 2.40 (brs), 1.95–1.74 (br, 22H, protons of five-membered rings), 1.47, 1.41, 1.32, 1.30 ppm (4×brs, 12H, 4×CH$_3$); ^{13}C NMR ($CDCl_3$): δ = 174.4 (C=O), 134.8, 134.6, 133.9, 133.6–132.7, 129.5 (C=C), 109.5, 108.7 (2×CMe$_2$), 96.2, 76.7, 71.0–70.4, 65.8, 62.9 (sugar group), 45.7, 43.4–41.4, 38.6, 36.1, 32.9–32.2 (five-membered rings), 26.0, 25.0, 24.5 ppm (4×CH$_3$); FTIR (KBr disc): $\tilde{\nu}$ = 1744 cm^{-1} (brs, C=O).

Poly(4b): Preparation analogous to that described above afforded poly(**4b**) as a white precipitate. Yield 95–96 %. ^{1}H NMR ($CDCl_3$): δ = 5.36 (m), 5.31 (m), 5.29–5.20 (m), 5.14–5.13 (brd, 6H, olefinic H), 5.53 (brs), 4.79 (brs), 4.70–4.63 (brd), 4.29–4.01 (brm, 5H, sugar group protons), 2.81–2.72 (brm), 2.39 (brs), 2.35 (brs), 1.92–1.71 (br, 22H, protons of five-membered rings), 1.49, 1.41, 1.32, 1.30 ppm (4×brs, 6H, 2×CH$_3$); ^{13}C NMR ($CDCl_3$): δ = 174.3, 173.6, 172.9 (C=O), 132.9, 132.1, 131.7, 130.4, 128.6, 125.5 (C=C), 113.7, 108.9 (CMe$_2$), 100.7, 92.9, 81.3, 79.7, 75.4, 63.0 (sugar group), 49.2, 48.5, 47.0, 45.1, 43.1–41.4, 38.3, 36.6, 35.5, 32.2 (five-membered rings), 26.9, 25.7, 25.4 ppm (2×CH$_3$); FTIR (KBr disc): $\tilde{\nu}$ = 1746 cm^{-1} (brs, C=O).

Poly(4a,b): Preparation analogous to that described above afforded poly(**4a**,**b**) as a white precipitate. Yield 99 %. ^{1}H NMR ($CDCl_3$): δ = 5.37–5.18 (br, 8H, olefinic H), 5.49 (brs), 4.74–4.62 (m), 4.58 (brs), 4.28–4.20 (brd), 4.08 (br), 3.96 (brs, 12H, sugar group protons), 2.92 (br), 2.76 (br), 2.41 (br), 1.94–1.81 (br, 29H, protons of five-membered rings), 1.50, 1.46, 1.41, 1.36, 1.33, 1.29 ppm (6×brs, 6×CH$_3$, 18H); ^{13}C NMR ($CDCl_3$): δ = 174.6, 174.7, 173.6 (C=O), 154.6 (phenoxy), 132.9–129.3 (polymer olefinic carbons), 115.6, 109.5, 108.7 (3×CMe$_2$), 96.2, 79.7, 76.7, 75.2, 71.0, 70.7, 70.4, 65.9, 63.3–62.9, 60.4 (sugar group), 48.2, 45.7, 42.9, 39.7, 38.6, 35.8, 33.1, 32.2 (five-membered ring), 26.8, 26.0, 25.9, 25.0, 24.9, 24.5 ppm (6×CH$_3$).

Poly(4c): Preparation analogous to that described above afforded poly(**4c**) as a white precipitate. Yield 97–98 %. ^{1}H NMR ($CDCl_3$): δ = 5.61–5.22 (br, 6H, olefinic H), 4.93 (br, 1H, sugar group proton), 4.75 (m, 1H, H-7a), 4.29 (br), 4.18 (br), 3.83 (br), 3.33 (br, 5H, sugar group proton), 3.50 (br, H-3a, 1H), 2.98 (br), 2.79 (br), 2.43 (br), 2.18 (br), 1.78 (brm), 1.57 (brs), 1.36 (br), 1.04 (br, 22H, protons of five membered rings), 2.03–2.00 ppm (3×brs, 9H, 3×COCH$_3$); ^{13}C NMR ($CDCl_3$): δ = 170.7, 170.1, 169.7 (3×*C*OCH$_3$), 156.3 (C=N), 151.3 (phenoxy), 134.0–130.4 (olefinic carbons), 91.7 (C-7a), 73.8, 72.5, 69.6, 68.0, 66.6, 62.7 (sugar group carbons), 58.6 (C-3a), 50.5, 47.0, 43.3, 43.1, 42.7, 42.0, 40.1, 38.5, 38.3, 33.1, 32.2, 32.1, 30.8 (five membered rings), 20.8, 20.7 ppm (3×CO*C*H$_3$).

Poly(4d): Preparation analogous to that described above afforded poly(**4d**) as a white precipitate. Yield 97–99 %. ^{1}H NMR ($CDCl_3$): δ = 5.73–5.21 (br, 6H, olefinic H), 5.09 (br, 1H, sugar group proton), 4.72 (m, 1H, H-7a), 4.47 (br), 4.31 (br), 4.20–4.17 (br), 3.75 (br, 6H, sugar group protons), 3.49 (br, 1H, H-3a), 2.79 (br), 2.58 (br), 2.43 (br), 2.17 (br), 1.87–1.60 (m), 1.43 (brs), 1.04 (br, 22H, protons of five membered rings), 2.09–2.00 ppm (4×brs, 12H, 4×COCH$_3$); ^{13}C NMR ($CDCl_3$): δ = 170.6, 170.1, 169.6, 169.5 (4×*C*OCH$_3$), 155.5 (C=N), 150.9 (phenoxy), 133.8, 133.0, 131.2, 130.3 (olefinic and aromatic carbons), 90.8 (C-7a), 73.8, 72.1, 71.8, 67.9, 65.9, 62.7 (sugar group carbons), 58.6 (C-3a), 50.5, 46.9, 43.4, 43.1, 42.7, 42.0, 41.3, 38.6, 38.4, 33.1, 32.9, 32.2 (five membered rings), 20.8, 20.7 ppm (4×CO*C*H$_3$); FTIR (KBr disc): $\tilde{\nu}$ = 1628, 1637, 1657, 1686, 1705 (5×br, C=O), 1491, 1503, 1540, 1550, 1579 (5×br, C=N), 2318 (br), 3202 (br, alkyl), 3640, 3689, 3737, 3815, 3835, 3854, 3873, 3903 cm^{-1} (8×s, H$_2$O).

Hydrolysis of diisopropylidene (acetal) groups

Poly(5a): The general method of acetal deprotection was as follows:[3a,26,29] poly(**4a**) was added to a solution consisting of CF_3CO_2H/H_2O 9:1 v/v (1.01 mL) and the reaction stirred at room temperature for 15 minutes. The homogeneous pale blue solution was then poured dropwise into a vigorously stirred THF solution (≈70 mL) at 0 °C. The pale to white precipitate was collected by filtration, washed with THF, hexane and ether and then dried *in vacuo* to afford the deprotected PMM, poly(**5a**) as a white solid. Yield 91 %. ^{1}H NMR ([D$_6$]DMSO): δ = 7.38–7.10

(br d), 5.48–5.23 (br, olefinic H, 6H), 4.98 (br), 4.33 (br), 4.17 (br), 4.00 (br), 3.86 (br, sugar group protons, 11H), 2.97 (br), 2.57–2.36 (br d), 2.24 (br), 1.97 (br), 1.49 (br), 1.36 ppm (br, 22H, protons of five membered rings). FTIR (KBr disc): $\tilde{\nu}$ = 3421 (br, OH), 1729 cm^{-1} (br s, C=O).

Poly(5b): Preparation analogous to that described above afforded poly(**5b**) as a white precipitate. Yield 86%. ^{1}H NMR ([D$_6$]DMSO): δ = 7.27 (br d), 7.14 (br s), 5.89 (br s), 5.40–5.34 (br d), 5.11, 4.99, 4.89 (m), 5.55 (br s), 4.40–4.11 (br d), 3.58, 3.16 (m), 2.93–2.79 (br d, 7H, sugar group protons), 2.07–1.57 (m), 1.32–1.22 ppm (m, 22H, protons of five membered rings). FTIR (KBr disc): $\tilde{\nu}$ = 3417 (br, OH), 1724 cm^{-1} (br s, C=O).

Deacetylization

Poly(5c): The general method of acetal deprotection was as follows:[36,52] The protected poly(**4c**) (40 mg) was dissolved in MeOH/THF 1:1 (2 mL) and to this was added K_2CO_3 (20 mg) and the reaction stirred for 7–10 min. The mixture was then poured into a solution of THF/H_2O 1:1 (10 mL) containing 2 M HCl (1.76 mL). This was then allowed to stir for 30–60 min and then the solvents removed in vacuo. The resultant solid was washed with water and then with ethyl acetate and was dried in vacuo to afford the poly(**5c**) as a pale cream solid. Yield 83%. ^{1}H NMR ([D$_7$]DMF): δ = 6.94 (br), 6.86 (br), 5.67–5.48 (br, 6H, olefinic H), 4.80 (br, 1H, H-7a), 4.12 (br), 3.91 (br), 3.59–3.38 (br, 9H, sugar group protons), 2.61 (br, 1H, H-3a), 2.23 (br), 2.14 (br), 2.12 (br), 2.01 (br), 1.97 (br), 1.80 (br), 0.85–0.54 ppm (m, 22H, five membered rings).

Poly(5d): The removal of acetyl protecting groups was analogous to that described above, affording poly(**5d**) as a white precipitate. Yield 86%. ^{1}H NMR ([D$_7$]DMF): δ = 7.38–7.32 (m), 6.87 (br), 5.85–5.39 (br, 6H, olefinic H), 5.22 (br, 1H, sugar group proton), 4.76 (m, 1H, H-7a), 4.45–4.01 (br), 3.83 (br), 3.59 (br, 11H, sugar group protons), 3.28 (br, 1H, H-3a), 2.48 (br), 2.05–1.78 (br), 1.05 (br, 22H, protons of five membered rings); ^{13}C NMR ([D$_7$]DMF): δ = 159.9 (C=N), 133.6–130.1 (olefinic carbons), 128.7, 125.7 (olefinic end groups), 90.7 (C-7a), 82.6, 75.7, 72.2, 70.6, 68.2, 62.7, 60.0 (sugar group carbons), 51.5 (C-3a), 47.3, 43.5, 41.7, 38.9, 32.5, 32.1, 30.1 ppm (five membered rings); FTIR (KBr disc): $\tilde{\nu}$ = 1497, 1501, 1540, 1569, 1589 (5xbr, C=N), 1647, 1686, 1695 (3×s, C=O, side chain linkages), 2357 (br), 3028 (br, alkyl), 3669–3815 cm^{-1} (br, OH).

Placement of trimethyl silyl protected phenol on PMM terminus

Poly(6a): The typical procedure was as follows: Poly(**3a**) (80 mg, 3 equiv to the initiator **A3**) was dissolved in toluene (2.0 g), and [Mo(CHCMe$_2$Ph)(N-2,6-Me$_2$C$_6$H$_4$){OCMe(CF$_3$)$_2$}$_2$] (**A3**) in toluene (0.5 g) was added in one portion at room temperature. The mixture was stirred for the prescribed time, and the polymerization was terminated by the addition of 4-(CH$_3$)$_3$SiC$_6$H$_4$CHO in excess amount. The solution was stirred for 1 hour to ensure completion and the solvents removed in vacuo. The resulting brown tar was dissolved in the minimum amount of THF and was then poured into cold methanol affording a white precipitate. The product poly(**6a**) was collected by filtration and was dried in vacuo. Yield 97–98%. ^{1}H NMR (CDCl$_3$): δ = 5.34–5.21 (br, 6H, olefinic H), 5.51 (br s), 4.60 (br s), 4.30–4.23 (d), 3.99 (br, 7H sugar group protons), 3.11–2.96 (br d), 2.78 (s), 2.43 (br s), 1.97–1.77 (br), 1.05 (br, 22H, protons of five-membered rings), 1.53, 1.44, 1.33, 1.30 (4×br s, 12H, 4×CH$_3$), 0.25 ppm (s, 9H, Si(CH$_3$)$_3$); ^{13}C NMR (CDCl$_3$): δ = 174.5 (C=O), 134.6, 133.9, 133.0, 129.3, 128.0, 126.1, 125.6 (C=C), 109.5, 108.7 (2×CMe$_2$), 96.2, 76.7, 71.0–70.4, 65.9, 62.9 (sugar group), 45.8, 43.4–41.3, 38.4, 36.1, 32.9–32.2 (five-membered rings), 26.0, 25.6, 24.9, 24.5 ppm (4×CH$_3$).

Removal of TMS protection from PMM terminus

Poly(7a): The synthetic procedure for poly(**7a**) to prepare poly(**2**) by hydrolysis of the TMS group was according to the previous report.[3a,25,26] Into a rapidly stirred THF solution (5–10 mL) containing the copolymer was added 0.5 M HCl, one drop per 10 mg poly(**6a**), and the mixture stirred for 1 h at room temperature. The reaction solution was then added dropwise into methanol to isolate the end group deprotected copolymer, poly(**7a**) which was collected by filtration and dried in vacuo. Yield >99%. ^{1}H NMR (CDCl$_3$): δ = 5.58 (br), 5.39 (br), 5.37–5.17 (br, 6H, olefinic H), 5.51 (br s), 4.56 (br s), 4.29–4.20 (br d), 3.93 (br, 7H, sugar group protons), 2.96–2.76 (br d), 2.41 (br s), 1.86–1.74 (br, 22H, protons of five-membered ring), 1.47, 1.41, 1.34, 1.29 ppm (4×br s, 12H, 4×CH$_3$); ^{13}C NMR (CDCl$_3$): δ = 174.3 (C=O), 135.1–129.6 (olefinic carbons), 109.4, 108.7 (2×CMe$_2$), 96.4, 71.1–70.3, 67.9, 65.7, 62.8 (sugar group), 47.9, 45.8, 43.2–42.1, 38.6, 36.2, 32.9–32.2 (five-membered ring), 26.2, 25.6, 25.2, 24.7 ppm (4×CH$_3$).

Attachment of poly(ethylene glycol) to the PMM terminus

Poly(8a): A typical procedure for the attachment of PEG to the PMM, poly(**7a**) was according to the previous report[3a] as follows: Into a THF solution containing poly(**7a**) (1 equiv) was added KH (1.1 equiv), and the mixture stirred for 3 h at room temperature. A THF solution containing the PEG oligomer (1.8 equiv) was then added in one portion, and the mixture was stirred overnight. The reaction solvent was removed in vacuo, and the residual product was washed twice with hexane, then with diethyl ether, and finally with methanol to remove all traces of PEG. The resultant white solid was stirred in methanol for a further 2 h, and the PEG-*block*-PMM poly(**8a**) was collected by filtration and dried in vacuo. Yield 82–87%. ^{1}H NMR (CDCl$_3$): δ = 5.34–5.20 (br, 6H, olefinic H), 5.52 (br s), 4.60 (br s), 4.31–4.23 (br d), 4.00 (br, 7H, sugar group protons), 3.64 (br s, 4H, [O(CH$_2$)$_2$O]$_n$), 2.97 (br), 2.77 (br), 2.58 (br), 2.49 (br), 2.06–1.77 (br), 1.17 (br), 1.04 (br, 22H, protons of five-membered ring), 1.49, 1.44, 1.32, 1.30 ppm (4×br s, 12H, 4×CH$_3$); ^{13}C NMR (CDCl$_3$): δ = 175.8 (C=O), 162.1 (phenoxy), 133.9–131.3 (C=C), 109.6, 108.7 (2×CMe$_2$), 96.2, 71.1, 67.2, 66.0, 63.3 (sugar group), 70.5 ([O(CH$_2$)$_2$O]$_n$), 57.8, 49.3, 47.2, 43.6–40.9, 38.5, 36.6, 33.0–32.2 (five-membered ring), 26.0, 25.6, 25.0, 24.5 ppm (4×CH$_3$).

Linear the amphiphilic block copolymer (ABC)

Poly(9a): The preparation of the ABC poly(**9a**) based on poly[(NBE)$_{20}$-*b*-(**a**)$_{20}$-*b*-(PEG$_{47}$)] was performed as previously described,[3a] affording poly(**9a**) as a white solid. Yield 81%. ^{1}H NMR (CDCl$_3$): δ = 5.58 (br), 5.39 (br), 5.37–5.17 (br, olefinic H), 5.49 (br s), 4.58 (br s), 4.28–4.21 (br d), 3.97 (br, sugar group protons), 3.62 (br s, PEG H), 2.93–2.76 (br d), 2.40 (br s), 1.87–1.74 (br, protons of five-membered rings), 1.47 (br s), 1.41 (br s), 1.34 ppm (br s, 4×CH$_3$); ^{13}C NMR (CDCl$_3$): δ = 173.5 (carbonyl), 132.7–129.9 (olefinic carbon), 108.5, 107.7 (2×CMe$_2$), 95.2, 75.7, 70.9, 64.9, 61.9 (sugar group), 69.5 (PEG), 47.3, 44.7, 42.2, 41.0, 37.5, 32.0–31.3 (five-membered ring), 25.1, 23.9 ppm (2×CH$_3$). FTIR (KBr disc): $\tilde{\nu}$ = 1749 cm^{-1} (br s, carbonyl).

Acknowledgement

J.J.M. expresses his sincere thanks to the INOUE Foundation for Science for a postdoctoral fellowship, and to Tetsuharu Kawasaki (former graduate student, NAIST) for helpful discussion. J.J.M. and K.N. express their thanks to Professor Michiya Fujiki (NAIST) for helpful comments, and to Professor Giseop Kwak (Department of Polymer Science, Kyungpook National University, Korea) for helpful discussions and the experiments using UV/Vis and fluorescence emission spectra.

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[39] A referee pointed out that we could not eliminate a possibility of ester cleavage during acetyl deprotection. This is because the stretching band corresponding to C=O after the deprotection is somewhat broad (may suggest the possibility). In our previous report,[3a] we confirmed that the cyclic acetal in the sugar-containing ROMP polymers (consisting of norbornene and monomer **a**,**b**) grafted with PEG could be hydrolyzed using CF_3CO_2H/H_2O 9:1, and the M_n values for the corresponding deprotected analogues (estimated by ^{1}H NMR spectra for comparison with PEG protons) were very close to those calculated based on the initial molar ratios. We also reported[25] that deprotection of Si*t*BuMe$_2$ group in poly(macromonomer)s consisting of amphiphilic ring-opened ROMP block copolymers {consisting of ring-opened norbornene and (*cis*-2,3-*endo*-bis-

[(*tert*-butyldimethylsiloxy)methyl]norborn-5-ene) could be removed (conditions: CF_3CO_2H/H_2O, at RT for >12 h without cleaving the ester rinkage confirmed by MALDI-TOF mass spectrometry.[25] We believe that all side chains remain attached to the PMM main chain, although we have no GPC data on the deprotected poly(**5d**). It was, in fact, difficult to dissolve it in the NMR solvent [D_7]DMF, which would suggest a high molecular weight polyvalent array of "free" (unprotected) sugar residues, because the deacteylisation of the side chain linkages would result in the "release" of linear side chains (low M_W in comparison with the PMM), which would be freely soluble in the NMR solvent. Based on these facts, we could not confirm that the ester linkage in the side chain in poly(**4c**) and poly(**4d**) could not be cleaved under these deprotection conditions (K_2CO_3/MeOH). K.N. express his thank to a referee for pointing out this issue.

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[44] The dimensions of the formed aggregates: i) length l_{TEM}; ii) width w_{TEM}; iii) diameter d_{TEM}, and iv) circumference c_{TEM}; from poly(**4**), poly(**5**), poly(**8**) and poly(**9**) were measured using Gatan Digital Micrograph software and were averaged from 20 measurements. In each case the Mean, Standard Deviation and Standard Error of the Mean was calculated (See the Supporting Information for full details).

[45] The calculated dimensions i) length l_{TEM}; ii) width w_{TEM}; of the various polymeric architectures were estimated using M1, RHF/PM3D Spartan Pro '02 for Windows (Wavefunction Inc.), based on the following lengths: ring opened norbornene unit (5.99 Å); favored syndiotactic poly(NBE) 5-mer (27.79 Å); favored syndiotactic poly(NBE) 5-mer inclusive of CMe_2Ph terminus (34.37 Å) and a poly(ethylene glycol) 6-mer (18.92 Å).

[46] White, bright circles in Figure 2 (shown as white arrow) are TEM artifact due to THF droplet (containing trace amount of 2,6-tBu$_2$-4-MeC_6H_2OH) after rapid evaporation in vacuo on copper grid covered with a perforated polymer film and coated with carbon on all sides. We did not confirm reproducibility these figures (white circles) for size distributions as well as ratios between the micelles (shown as the black arrow) and the artifacts (shown as the white arrow).

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Received: February 21, 2007
Revised: June 5, 2007
Published online: July 31, 2007

