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Synthesis of Lipo-Glycopolymer Amphiphiles by Nitroxide-Mediated Living Free-Radical Polymerization

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ABSTRACT: The nitroxide-mediated living free-radical polymerization of 1,2,5,6-di(iso-propylidene)-D-glucose-2-propenoate was achieved in dimethylformamide at 105 °C with an α-hydrido alkoxyamine initiator functionalized with a lipophilic *N,N*-di(octa-decyl)amine group. The kinetics of the polymerization were investigated, and the mechanism was shown to be a living process allowing, after hydrolysis, controlled molecular weight, low-polydispersity lipo-glycopolymers to be prepared. The amphiphilic character of the macromolecule could be altered by either the exchange of the alkoxyamine at the chain end with hydrogen or the preparation of copolymers with lipophilic monomers such as *N,N*-di(octadecyl)acrylamide. The surface and membrane-forming properties of these novel lipopolymers demonstrate their amphiphilic character. © 2002 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 40: 3379–3391, 2002

Keywords: living radical; nitroxide; lipopolymers; glycopolymers; block copolymers; biomacromolecules; amphiphiles; bioengineering

INTRODUCTION

In vivo saccharide recognition at lipid membrane surfaces plays an important role in virus infection, fertilization, and immunological protection systems.[1–3] Therefore, synthetic lipo-glycopolymers have been applied as model systems for the basic understanding of these saccharide recognition processes. Furthermore, lipo-glycopolymers are promising candidates for engineering substrate-supported biomembranes,[4–6] which show great promise as sensor devices, drug-delivery systems, and so forth. For a greater understanding of the structure–property relationships of these systems, well-defined synthetic lipo-glycopolymers are highly desirable. However, the high degree of functionality and the reactive nature of the sugar units present along the polymer backbone have precluded the ready availability of lipo-glycopolymers with controlled macromolecular structures by traditional living polymerization techniques.[7–14]

In an attempt to overcome the challenges typically associated with living procedures such as anionic polymerization, the field of living free-radical polymerization has been developed and is attracting significant attention.[15–28] One of the most desirable features of living free-radical procedures is their compatibility with functional groups and the facile synthesis of functionalized initiators. This permits tailored polymer chains

with active functional groups such as surface attachment sites and self-assembling units to be accurately placed at various sites along the polymeric backbone. These advantages are particularly important for highly functionalized synthetic biomacromolecules[29,30] such as glycopolymers, for which the growing importance of well-defined glycopolymers in many biotechnology applications has prompted a range of synthetic investigations by living free-radical procedures.[31–37] A noteworthy recent example is the design and synthesis of biotin chain-terminated glycopolymers for surface glycoengineering. The incorporation of a single biotin group at the chain end allows the fabrication of patterned glycosurface arrays with streptavidin binding.[38] In this work, we describe the synthesis of well-defined amphiphilic lipo-glycopolymers by nitroxide-mediated procedures in which the amphiphilic character is controlled and varied by the appropriate selection of monomers and initiating groups. Such control affords synthetic lipo-glycopolymers that mimic the glycocalix in a natural cell membrane and may lead to greater performance and biocompatibility.

RESULTS AND DISCUSSION

Initiators for nitroxide-mediated living free-radical polymerizations have recently been developed that allow the polymerization of a wide variety of monomer families. For example, acrylate-, acrylamide-, and acrylonitrile-based monomers can now be polymerized with accurate control over molecular weights and with polydispersities as low as 1.06.[39,40] These systems are based on α-hydrido nitroxides and have the added advantage of the facile introduction of functional groups into the initiator structure with standard organic synthesis techniques.[41,42] For applications as biomimetic membranes, an amphiphilic copolymer with a head group that resembles a membrane lipid is required. The N,N-di(octadecyl)amine (DODA)-substituted alkoxyamine initiator 2,2,5-trimethyl-3-{1-[4′-di(octadecyl)aminomethyl]phenylethoxy}-4-phenyl-3-azahexane (**1**) was, therefore, prepared from the chloromethyl derivative 2,2,5-trimethyl-3-[1-(4′-chloromethyl)phenylethoxy]-4-phenyl-3-azahexane (**2**; Scheme 1). The DODA chain end was chosen as a lipid analogue because it has been shown to form a stable monolayer with the lipid dimyristoylphosphatidylcholine, if attached to a hydrophilic polymer.[43] Glycopolymers with DODA head groups are, therefore, promising candidates for the preparation of polymer-supported membranes containing both lipo-glycopolymers and free lipids.

As the relatively hydrophobic nature of the dioctadecyl-substituted alkoxyamine initiator (**1**) may affect its ability to control the polymerization of hydrophilic monomers, the initiating ability of **1** was first examined with N,N-dimethylacrylamide as a model. Therefore, a solution of the lipid-functionalized alkoxyamine (**1**) and 125 equiv of N,N-dimethylacrylamide was heated at 125°C for 12 h in the presence of 0.05 equiv of the corresponding nitroxide (**3**) to afford the chain-end-functionalized poly(N,N-dimethylacrylamide) [**4**; number-average molecular weight (M_n) = 11,000, polydispersity index (PDI) = 1.15] in an 86% yield (Table 1).

One result of living free-radical procedures is the presence of a dormant group, an alkoxyamine in the case of nitroxide-mediated systems, at the propagating chain end. Because this relatively hydrophobic group may alter the hydrophilic–hydrophobic behavior of these lipo-glycopolymers, conditions for its removal were investigated with the dimethylacrylamide-based homopolymers (**4**). Under reducing conditions, the replacement of the alkoxyamine chain end with hydrogen was examined by the reaction of **4** with 10.0 molar equiv of (n-Bu)$_3$SnH at a variety of different temperatures and reaction times to maximize the extent of exchange and to minimize changes in the polymer structure. From ^{1}H NMR and gel permeation chromatography (GPC) analyses, it was shown that reaction temperatures below 80°C were insufficient to completely remove the alkoxyamine chain end in a reasonable period of time without appreciable broadening of the GPC trace. However, increasing the reaction temperature to 105°C for 12 h allowed 100% removal of the alkoxyamine chain ends to give the H-terminated derivative **5** (Scheme 2). Equally important, there was no detectable change in the molecular weight or PDI on reduction of the alkoxyamine chain end, indicating that the polymer backbone was not altered during the reaction.

The polymerization of D-glucose-2-propenoate, whose hydroxyl groups were protected by isopropylidene groups [1,2,5,6-di(isopropylidene)-D-glucose-2-propenoate (**6**)], was, therefore, initially conducted at 125°C under argon in the presence of **1** and 0.05% of the corresponding nitroxide (**3**). However, the sugar residue was observed to undergo partial decomposition at these elevated temperatures and prolonged reaction times.[44] To
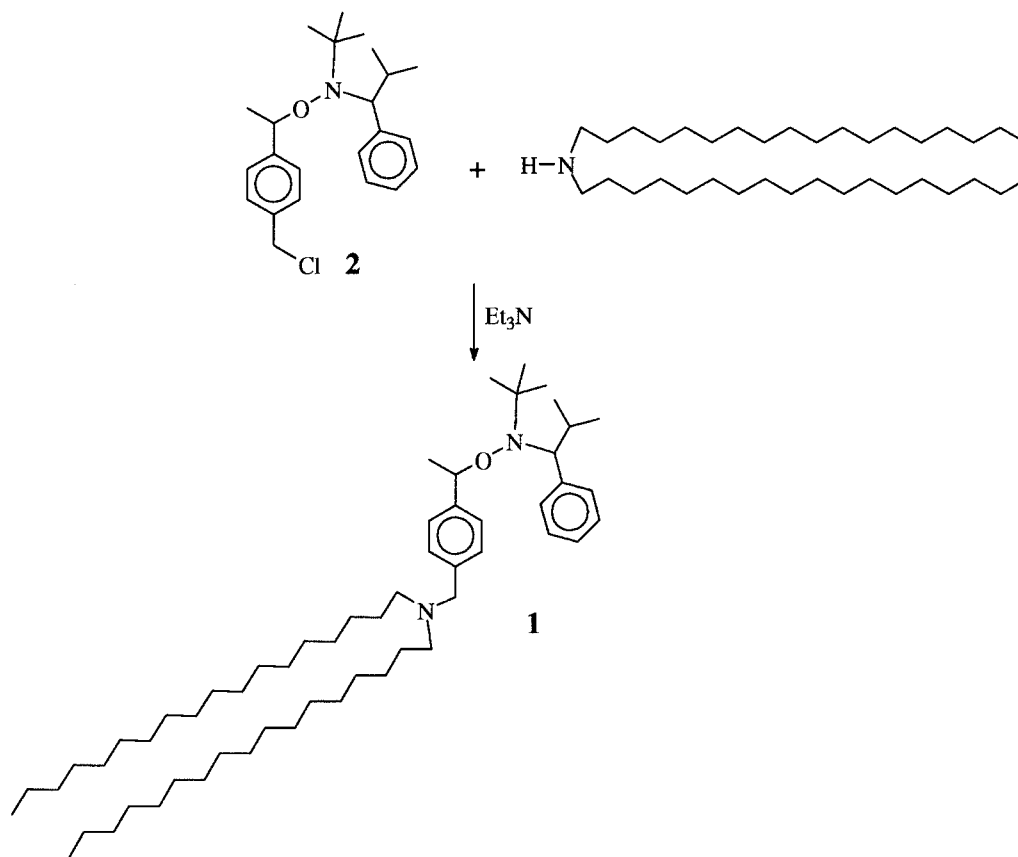
Scheme 1. Synthesis of the *N,N*-di(octadecyl)amino-substituted alkoxyamine initiator (**1**).

overcome these difficulties, the living free-radical polymerization was performed at a lower temperature (105 °C), and because of the high viscosity of **6** in the melt at 105 °C, a solvent (*N,N*-dimethylformamide (DMF)) was used. The choice of DMF was governed by the insolubility of poly(α-D-glucofuranose-1,2,5,6-di(isopropylidene)-2-propenoate) (**7**) in traditional solvents for nitroxide-mediated living free-radical procedures such as chlorobenzene or xylenes (Scheme 3).

**Table 1.** Molecular Weight and Polydispersity of **5**

Sample	M_n (theor.)[a]	M_n (exp)[b]	PDI
5-LP1	2,900	2,800	1.08
5-LP2	5,000	5,000	1.11
5-LP3	6,000	5,800	1.10
5-LP4	7,900	7,600	1.13
5-LP5	10,800	11,000	1.15

[a] Theoretical molecular weight determined by the multiplication of DP by the conversion percentage.
[b] Experimental molecular weight determined by ¹H NMR.

To confirm the living nature of the polymerization at 105 °C, kinetics for the polymerization of **6** in the presence of **1** were investigated for the theoretical degrees of polymerization (DPs) of 30 and 60 at 100% conversion. As can be seen in Figure 1, the relationship between $\ln([S]_0/[S]_t)$[45] and time is linear for both molecular weights, indicating that no detectable amount of termination is occurring and that the polymerizations are living at this reduced temperature in the presence of the solvent. As a result, the evolution of the molecular weight for the lipo-glycopolymer **7** with conversion is linear (Fig. 2), and the polydispersity in each case varies between 1.06 and 1.20 (Fig. 3).

It should, however, be noted that an increase in the amount of the solvent (DMF) to greater than 30 wt % leads to a decrease in the rate of polymerization and an associated increase in the polydispersity. As expected, the level of control in these studies was greater than for the initiating system based on di-*t*-butyl nitroxide with dicumyl
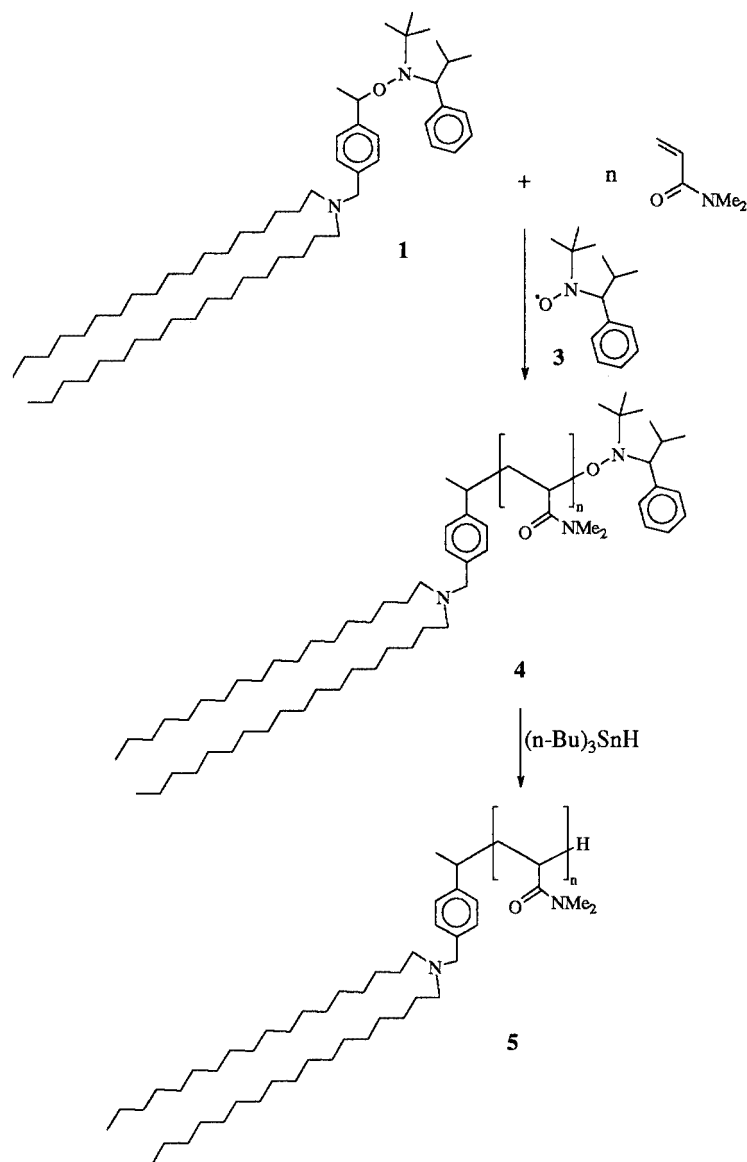
**Scheme 2.** Synthesis of *N,N*-di(octadecyl)amino-terminated poly(*N,N*-dimethylacryl-amide) (**5**).

peroxide as an accelerator,[46] for which only low conversions were obtained (5–50%) and polydispersities were relatively high (1.20–1.99).

Removal of the alkoxyamine chain end from the protected lipo-glycopolymer **7** was found to be a facile reaction under the conditions previously defined to give the H-terminated derivative poly(1,2,5,6-di(isopropylidene)-D-glucofuranose-2-propenoate) (**8**), which was subsequently deprotected by a reaction with trifluoroacetic acid to give the desired lipo-glycopolymer poly(α-D-glucopyranose-2-propenoate) (**9**) with no detectable loss of sugar units via hydrolysis of the secondary

ester linkage to the backbone (Scheme 4). The advantage of living free-radical conditions for the preparation of **9** is evidenced by the presence of a single di(octadecyl)amino unit at one chain end and the ability to easily alter the amphiphilic nature of the polymer by accurate control of the DP of the backbone.

Lipo-Glycocopolymers

A second strategy for the preparation of amphiphilic lipo-glycopolymers and their incorporation into a lipid bilayer is the synthesis of a co-
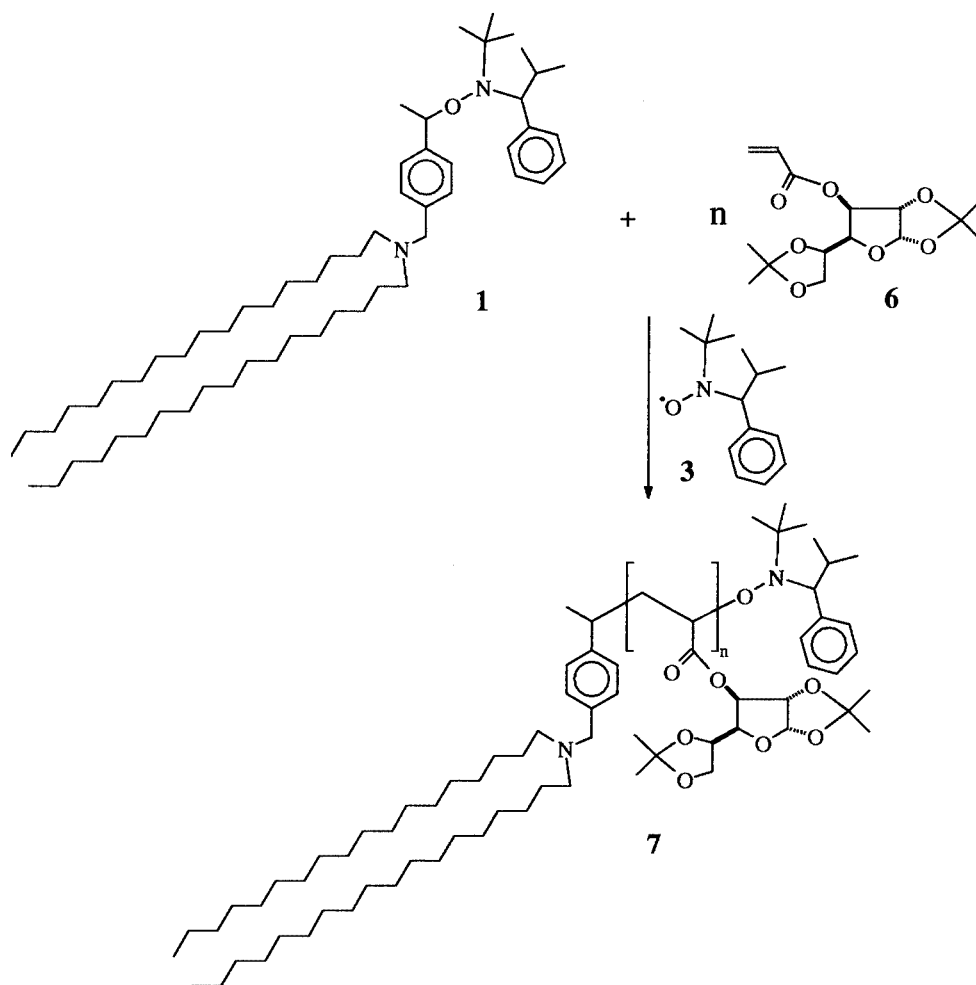
Scheme 3. Polymerization of 1,2,5,6-di(isopropylidene)-D-glucose-2-propenoate (**6**).

polymer with lipid-functionalized repeat units. In this scenario, the polymer would potentially have multiple incorporation sites in the lipid bilayer in contrast to the single site for the chain-end-functionalized derivative (**9**). With a strategy similar to that described previously, it was envisaged that the lipid-based monomer would be an acrylamide derivative and the polar glycomonomer would be acrylate-based. As a result, the lipo-glycopolymer would be an acrylate–acrylamide copolymer. For an understanding of the synthesis of these novel acrylate–acrylamide copolymers, the nitroxide-mediated living free-radical copolymerization of *t*-butylacrylate and *N,N*-dimethylacrylamide was initially examined as a model system. With 2,2,5-trimethyl-3-(1-phenylethoxy)-4-phenyl-3-azahexane (**10**) as an initiator, in the presence of 0.05 equiv of the corresponding nitroxide (**3**), mixtures of *t*-butylacrylate and *N,N*-dimethylacrylamide were heated at 125 °C, with

the kinetics of polymerization and characteristics of the final product being evaluated. As can be seen in Table 2, in the presence of the α-hydrido alkoxyamine initiating system, the copolymerization of acrylates and acrylamides leads to a copolymer with controlled molecular weights and low polydispersities (PDI = 1.10–1.20) at all comonomer ratios. A further kinetic analysis of the copolymerization confirmed the living nature of this copolymerization system.

The extension of these results to mixtures of **6** and *N,N*-di(octadecyl)acrylamide (**11**) proved to be facile when the polymerizations were again conducted at 105 °C in 30 wt % DMF for 40 h. Under these conditions, living polymerizations were observed for **6/11** monomer ratios of 85/15, 80/20, 75/25, 70/30, and 65/35, and conversions of 70–80% were typically obtained (Table 3). The exchange of the initiator end group with hydrogen and the deprotection of the protected sugar mono-
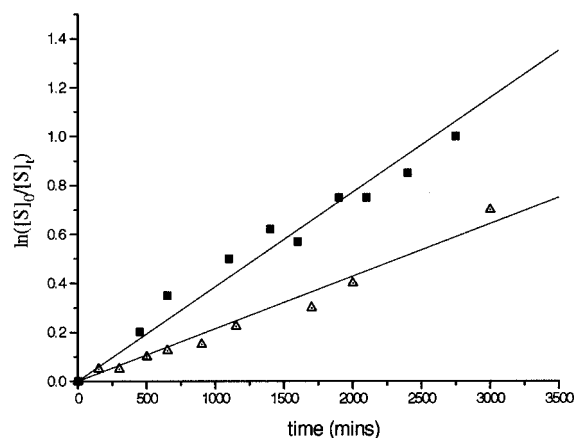
Figure 1. Kinetic investigation of the polymerization of **6** [(■) 30 and (△) 60 equiv] in DMF with 1.0 equiv of **1** and 0.05 equiv of **3** at 105 °C in DMF. $[S]_0$ = monomer concentration at $t = 0$; $[S]_t$ = monomer concentration at time t (determined by GPC).

mers were performed in analogy to the chain-end-functionalized lipo-glycohomopolymers to give the desired lipo-glycocopolymers (**12**; Scheme 5).

In contrast to the lipo-glycohomopolymer **9**, which contains one hydrophilic block and one hydrophobic block, the copolymers are composed of many hydrophobic and hydrophilic units within the same molecule. For example, the 85/15 copolymer with $M_n = 14,000$ has approximately 6 di-(octadecyl) units along the backbone, as confirmed by ^{1}H NMR spectroscopy, whereas the 65/35 copolymer has approximately 14 hydrophobic lipid units along the backbone. The influence
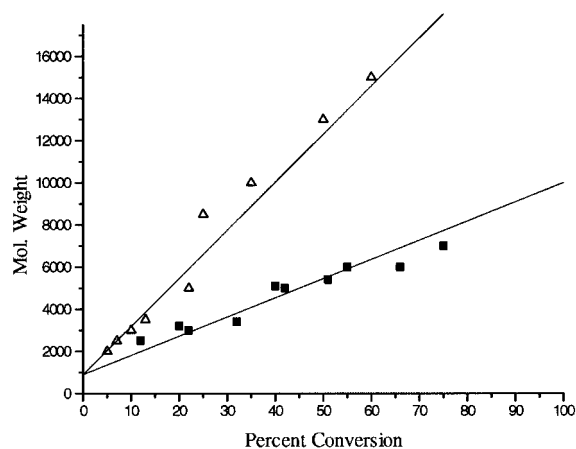
of these additional lipophilic units on the physical properties of these copolymers is immediately obvious when we examine their solubility properties. As the incorporation of the di(octadecyl) monomer increases from 15 to 35 mol %, the copolymers become soluble in chloroform and insoluble in methanol; for example, **12**-15 with 15 mol % incorporation is soluble in methanol and insoluble in chloroform, whereas **12**-35 with 35 mol % lipophilic di(octadecyl) comonomer (**11**) incorporated is insoluble in methanol but readily dissolves in chloroform and dichloromethane.

Conformational Behavior at the Air–Water Interface

For amphiphilic copolymers to be used for engineering biomembranes supported on solid substrates, a thorough understanding of the surface activity and the ability to form monolayers from these materials is required. To address these issues, we conducted a preliminary study of the behavior of these surface-active amphiphiles at the air–water interface in an effort to understand the relationship between the molecular structure and monolayer properties. Additionally, these materials are interesting because the high level of structural control permits the testing of scaling theories of grafted polymers for short chain lengths.[47–51]

For these preliminary studies, the DODA-terminated poly(N,N-dimethylacrylamide)s (**5**) were

Figure 2. Molecular weight (M_n) as a function of the conversion for the polymerization of **6** [(■) 30 and (△) 60 equiv] in DMF with 1.0 equiv of **1** and 0.05 equiv of **3** at 105 °C.
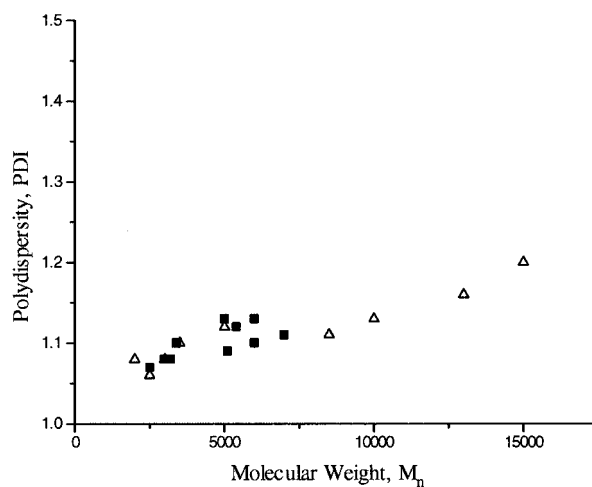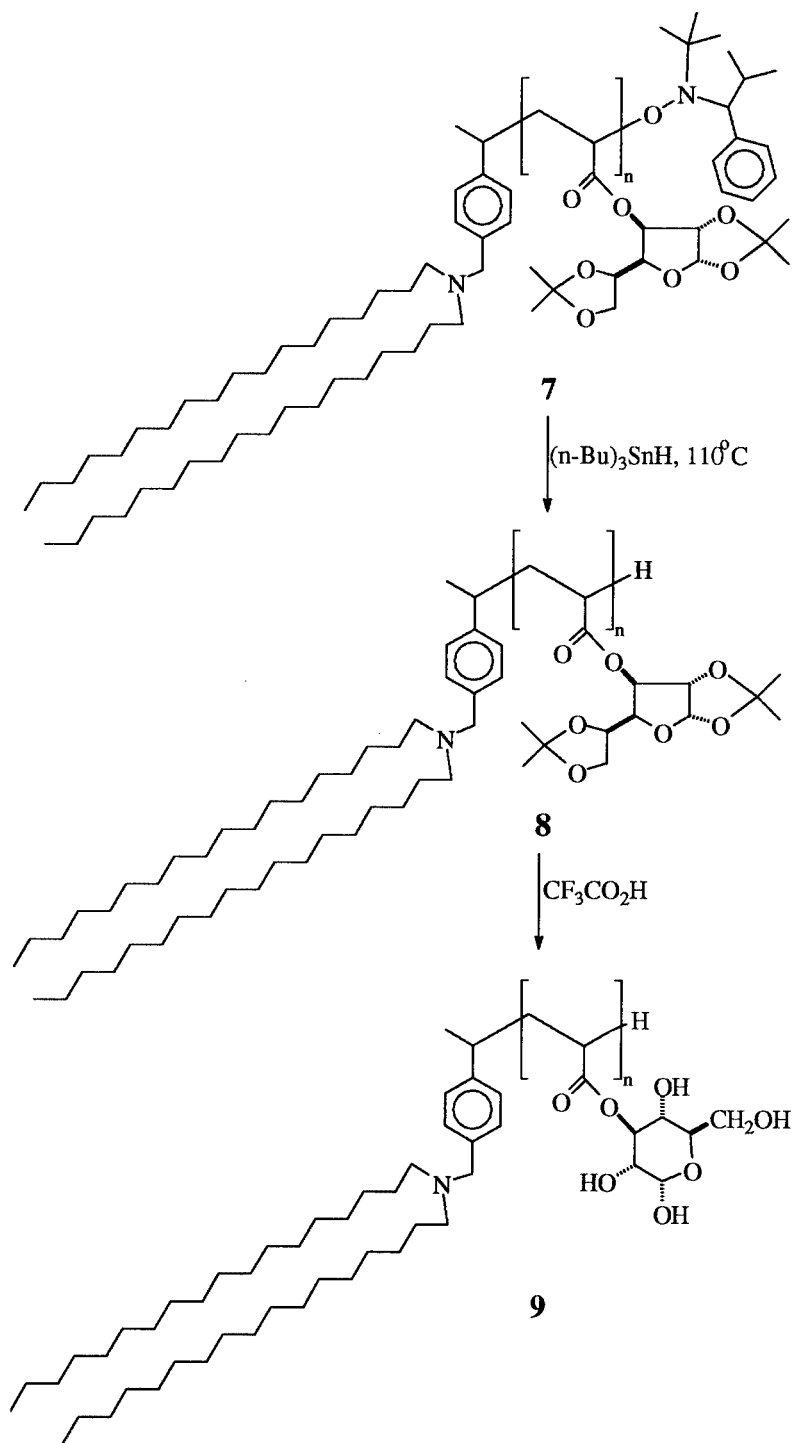

Figure 3. Polydispersity as a function of the molecular weight (M_n) for the polymerization of **6** [(■) 30 and (△) 60 equiv] in 30 wt % DMF with 1.0 equiv of **1** and 0.05 equiv of **3** at 105 °C.

Scheme 4. Preparation of an amphiphilic lipo-glycopolymer (**9**).

employed, and the amphiphilic character of these materials were varied by an examination of different DPs for the poly(*N,N*-dimethylacrylamide) backbone. With film-balance measurements, the π–A isotherms for **5** were examined at 28 °C and in each case revealed that the amphiphilic copol-

ymers (**5**) were surface-active and formed stable Langmuir monolayers (Fig. 4).

Another interesting feature of the π–A isotherms is the regular variation in the molecular area (A_p) with the molecular weight. The isotherms are shifted from **5**-LP1 to **5**-LP5 to pro-

Table 2. Molecular Weight and Polydispersity (GPC) for the Bulk Copolymerization of *t*-Butylacrylate (TBA) and *N,N*-Dimethylacrylamide (DMA) in the Presence of **1** and **3** (0.05 equiv) at 120 °C

TBA/DMA Ratio	M_n (theor.)[a]	M_n (exp.)[b]	PDI[c]
98/2	19,000	19,000	1.10
95/5	17,000	16,500	1.14
90/10	16,500	17,000	1.15
75/25	15,000	14,500	1.14
50/50	13,500	12,500	1.16

[a] Theoretical molecular weight determined by the multiplication of DP by the conversion percentage.
[b] Experimental molecular weight determined by ^{1}H NMR.
[c] Determined by GPC.

gressively larger areas because of the increase in the repulsive interactions between the polymers with greater DPs. This correlates with the water-soluble block adopting a pancakelike structure, and this pancake limiting area (A_p), obtained by the customary extrapolation of the pancake region in the compression isotherm to $\pi = 0$, varies linearly with DP (Fig. 5). The area per monomer, given by the slope of the limiting area versus DP, can then be calculated, and for the poly(*N,N*-dimethylacrylamide) series (**5**), this amounts to an area per *N,N*-dimethylacrylamide repeat unit of 36 ± 2 Å^2. In comparison, monolayers of polystyrene-*b*-poly(ethylene oxide) diblock copolymers at the air–water interface give an area per ethylene oxide repeat unit of 27 Å^2.[52,53] As a result, repeat units of the ethylene oxide chain lead to a slightly more compact structure in the pancake regime than for *N,N*-dimethylacrylamide repeat units. Future work will investigate the Langmuir behavior of the lipo-glycopolymers **9** and **12** and their ability to stabilize lipid bilayers.

CONCLUSIONS

Well-defined amphiphilic lipo-glycopolymers that may serve as the integral part of tethered bilayer membrane systems have been prepared by nitroxide-mediated living free-radical procedures. The structural control afforded by this living procedure permits the placement of the hydrophobic lipid functionality, DODA, at the chain end or along the glycopolymer backbone. Significantly, the use of second-generation nitroxides, such as **3**, allows the temperature of the polymerization mixture (30 wt % DMF) to be reduced to 105 °C,

thereby reducing the decomposition of the glycomonomer and still maintaining a reasonable rate of reaction. A preliminary examination of the π–A isotherms of these amphiphilic polymers at the air–water interface demonstrated surface activity and the ability to form stable Langmuir films with accurate control over the molecular area.

EXPERIMENTAL

General

All reactions were run under N_2 unless noted. *N,N*-Dimethylacrylamide and *t*-butylacrylate were distilled from calcium hydride. Commercial Merck plates coated with GF254 silica gel (0.25 mm thick) were used for analytical thin-layer chromatography (TLC). The silica gel used for flash chromatography was Merck Kieselgel 600 (230–400 mesh). NMR spectroscopy was conducted on a Bruker ACF 250 with CDCl$_3$, CD$_2$Cl$_2$, or D$_2$O as a solvent and with the internal solvent peak as a reference. GPC was carried out on a Waters chromatograph (four Waters Styragel HR columns in series: HR1, HR2, HR4, and HR5E) connected to a Waters 410 differential refractometer with tetrahydrofuran (THF) as the carrier solvent. IR spectra were recorded in a CD$_2$Cl$_2$ solution or as a KBr pellet.

2,2,5-Trimethyl-3-{1-[4′-di(octadecyl)aminomethyl]-phenylethoxy}-4-phenyl-3-azahexane (1)

To a solution of 2,2,5-trimethyl-3-[1-(4′-chloromethyl)phenylethoxy]-4-phenyl-3-azahexane (**2**; 2.00 g, 5.36 mmol)[39,40] in CHCl$_3$ (60 mL), DODA (11.0 g, 21.1 mmol) was added, and the reaction

Table 3. Polydispersity (GPC) and Molecular Weight for the Copolymerization of **6** and **11** with **1** (1 equiv) and **3** (0.05 equiv) at 105 °C in 30 wt % DMF for 40 h

Sample	**6/11** Ratio	M_n (theor.)[a]	M_n (exp.)[b]	PDI[c]
12–15	85/15	13,500	14,000	1.17
12–20	80/20	14,000	13,500	1.16
12–25	75/25	14,500	14,000	1.19
12–30	70/30	15,000	14,500	1.13
12–35	65/35	15,500	16,000	1.10

[a] Theoretical molecular weight determined by the multiplication of DP by the conversion percentage.
[b] Experimental molecular weight determined by ^{1}H NMR.
[c] Determined by GPC.
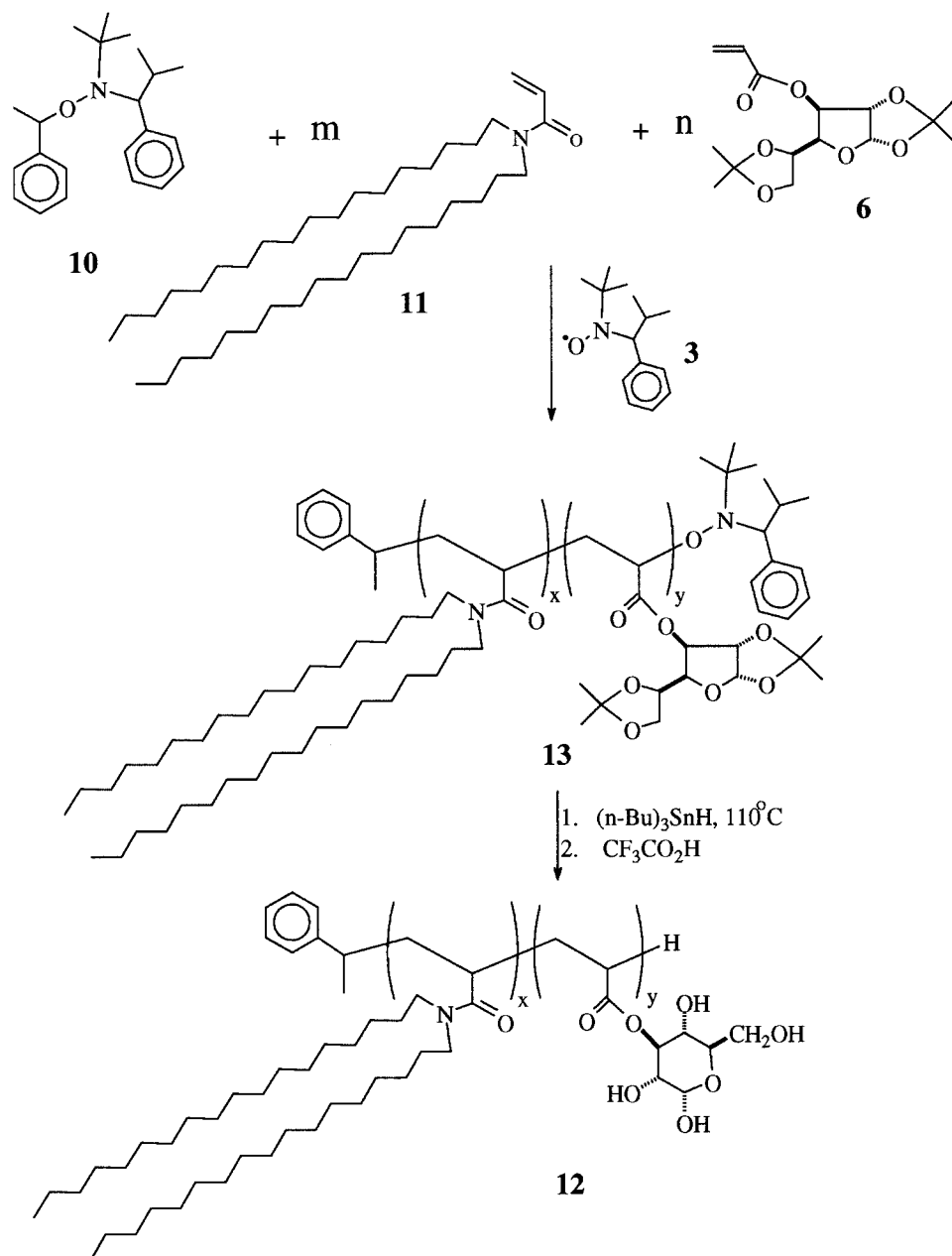
Scheme 5. Synthesis of a lipo-glycopolymer (**12**).

mixture was stirred at 60 °C for 24 h. Afterward, the white precipitate of amine hydrochloride was filtered off, the reaction solution was evaporated to dryness, and the crude product was purified by flash chromatography, eluting with 10/1 hexane/diethyl ether gradually increasing to 3/1 hexane/diethyl ether. The desired di(octadecyl)-functionalized alkoxyamine (**1**) was obtained as a yellow oil (4.51 g, 98% yield).

IR (CH$_2$Cl$_2$): 2924, 2852, 1652 cm^{-1}. ^{1}H NMR (250 MHz, CDCl$_3$, two diastereomers, δ): 7.26–6.95 (m, 9H), 4.67, 4.72 (d of q, J = 7.5 Hz, 1H), 3.34 (d, J = 11 Hz, 2H), 3.09, 3.22 (d of d, J = 11 Hz, 1H), 2.18–2.15 (m, 4H), 1.45–1.02 (m, 89H). ^{13}C NMR (63 MHz, CDCl$_3$): 131.0, 128.6, 127.3, 127.1, 126.8, 126.0, 53.8, 31.9, 29.7–27.0 (set of singlets), 22.7, 14.1.

1,2,5,6-Di(isopropylidene)-D-glucose-2-propenoate (6)

The sugar-based monomer was prepared by a slight modification of the method described by
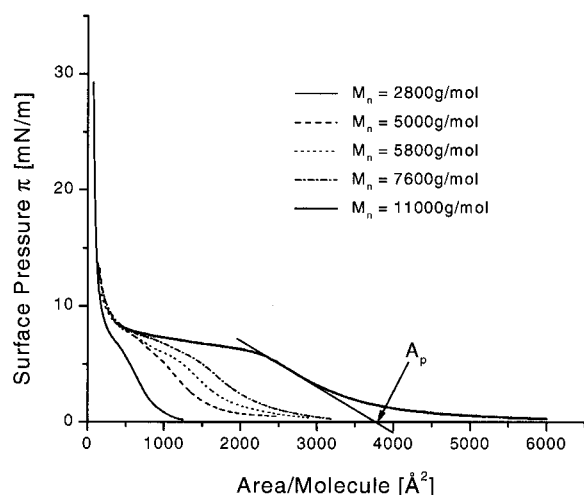
Figure 4. π–A compression isotherms of **5** at 28 °C with the determination of A_p for **5**-LP5.

Ouchi et al.[44] To a solution of 1,2,5,6-di(isopropylidene)-D-glucofuranose (25.0 g, 96.0 mmol) in acetone (125 mL) was added aqueous sodium hydroxide (25 mL, 5 N), and the reaction mixture was stirred for 30 min at room temperature under nitrogen. Acryloyl chloride (27.8 g, 308 mmol) was then added dropwise under stirring with cooling (ice bath) followed by additional stirring at 0 °C for 3 h. Water (250 mL) was added, and the reaction mixture was extracted with chloroform (3 × 150 mL); the combined organic layers were washed with a 0.01 M Na_2CO_3 solution until neutral, which was followed by water (3 × 250 mL), dried with Na_2SO_4, and concentrated *in vacuo* to give the crude compound **6** as a colorless, viscous liquid. It was purified by flash chromatography, eluting with 10/1 hexane/ethyl acetate gradually increasing to 1/1, and was obtained as a white solid (10.6 g, 35% yield; 1/1 hexane/ethyl acetate TLC, molybdenum stain, R_f, retention factor = 0.72). Analytical data corresponded to those previously reported.[44]

General Procedure for α-D-Glucofuranose-1,2,5,6-di(isopropylidene)-2-propenoate Polymerization (7)

The alkoxyamine **1** (126 mg, 0.147 mmol), the corresponding nitroxide **3** (1.30 mg, 0.0059 mmol), **6** (2.67 g, 8.50 mmol), and DMF (1.09 g, 14.9 mmol) were degassed by three freeze–thaw cycles, sealed under argon, and heated at 105 °C for 40 h. The reaction mixture was then dissolved in 2 mL of THF and precipitated into a 20/3 mixture of MeOH and H_2O (2 × 60 mL). The precip-

itate was then collected by vacuum filtration and dried to give the desired compound **7** as a slightly yellow solid (1.55 g, 58% yield).

M_n: 9000 g/mol. PDI: 1.17. IR (CH_2Cl_2): 2991, 2924, 2852, 1735 cm^{-1}. ^{1}H NMR (250 MHz, CD_2Cl_2): 5.69 (br, s), 5.47 (br, s), 4.94 (br, s), 4.28 (br, s), 3.96 (br, s), 3.77 (br, s; integration ratio of the five signals between 5.69 and 3.77: 1/1/1/2/1), 2.22 (br, s), 2.04 (br, s), 1.42–0.69 (br, multiplets). ^{13}C NMR (63 MHz, $CDCl_3$, δ): 165.8, 112.6, 109.8, 105.5, 83.5 79.8, 77.0, 72.1, 67.2, 32.3, 31.0, 30.0–25.7 (set of singlets), 23.0, 14.2, 13.8, 10.3.

General Procedure for the Exchange of the Alkoxyamine Chain End with Hydrogen

Poly[1,2,5,6-di(isopropylidene)-D-glucofuranose-2-propenoate] (**7**; 1.20 g, 0.133 mmol) and tributyltin hydride (720 mg, 2.67 mmol) were dissolved in 50 mL of anhydrous toluene and heated at 105 °C for 5 h. The solvent was evaporated, and the crude product was dissolved in 2 mL of THF and precipitated into a 10/1 mixture of MeOH and H_2O (60 mL). The precipitate was then collected by vacuum filtration and dried to give the desired poly[1,2,5,6-di(isopropylidene)-D-glucofuranose-2-propenoate] (**8**) as a slightly yellow solid (1.03 g, 86% yield, M_n = 9000 g/mol, PDI = 1.17). IR (CH_2Cl_2), ^{1}H NMR (250 MHz, CD_2Cl_2), and ^{13}C NMR (63 MHz, $CDCl_3$) were similar to those for **7** minus the minor resonances for the alkoxyamine chain end.

General Hydrolysis Procedure: Preparation of Poly(α-D-glucopyranose-2-propenoate) (9)

8 containing a hydrogen end group (1.03 g, 0.114 mmol) was dissolved in 9/1 trifluoroacetic acid/
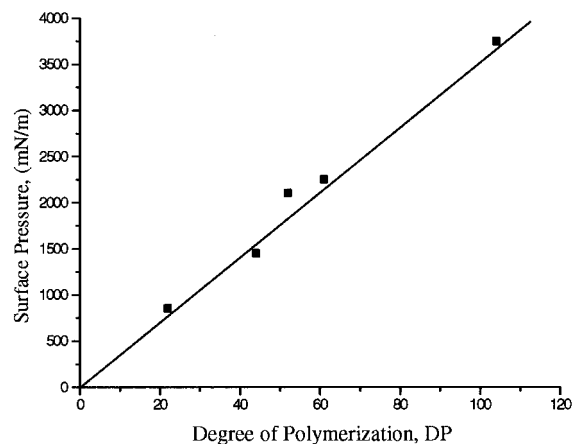

Figure 5. A_p versus DP for **5** at 28 °C.

water (7.2 g) and stirred at room temperature under nitrogen for 30 min [for the *N,N*-di(octadecyl)acrylamide/1,2,5,6-di(isopropylidene)-D-glucofuranose-2-propenoate copolymers (**12**-15, **12**-20, **12**-25, **12**-30, and **12**-35], 10 mL of THF was added to dissolve the polymer). Then, 50 mL of anhydrous toluene was added and removed at room temperature with high vacuum (3×), and this was followed by drying of the white solid under high vacuum. **9** was obtained as a white solid (0.71 g, 92% yield).

IR (CH_2Cl_2): 3456, 2931, 1789, 1729, 1681 cm^{-1}. ^1H NMR (250 MHz, D_2O, δ): 5.61 (br, s), 5.10 (br, s), 4.73–4.57 (br, m), 4.16 (br, s), 3.79–3.35 (br, m), 2.63 (br, s), 1.44–0.73 (br, m).

General Procedure for the Copolymerization of *N,N*-Dimethylacrylamide and *t*-Butylacrylate

A mixture of **1** (32.7 mg, 0.101 mmol), the corresponding nitroxide **3** (1.1 mg, 0.0051 mmol), *N,N*-dimethylacrylamide (0.0782 g, 0.789 mmol), and *t*-butylacrylate (1.92 g, 15.0 mmol) was degassed with three freeze–thaw cycles, sealed under argon, and heated at 105 °C for 36 h. The reaction mixture was then dissolved in CH_2Cl_2 (3 mL) and precipitated into a 10/1 mixture of MeOH and H_2O (100 mL). The precipitate was collected by vacuum filtration and dried to give the desired 1/19 *N,N*-dimethylacrylamide/*t*-butylacrylate copolymer as a white solid (1.62 g, 80% yield).

M_n: 16,000 g/mol. PDI: 1.25. IR (CH_2Cl_2): 2976, 2934, 1724, 1647 cm^{-1}. ^1H NMR (250 MHz, acetone) 3.09 (br, s), 2.89 (br, s), 2.29 (br, s), 1.84 (br, s), 1.49 (br, s; the *N,N*-dimethylacrylamide/*t*-butylacrylate ratio in the copolymer was determined by ^1H NMR to be 1/19). ^{13}C NMR (63 MHz, $CDCl_3$, δ): 174.1, 164.9, 80.3, 42.4, 42.0, 28.1.

N,N-Di(octadecyl)acrylamide (11)

To a solution of DODA (34.08 g, 65.29 mmol) in $CHCl_3$ (500 mL) was added an aqueous KOH solution (19 mL of a 20 wt % solution) at room temperature, and the mixture was stirred at room temperature for 20 min. A solution of acryloyl chloride (8.27 g, 91.4 mmol) in $CHCl_3$ (30 mL) was added dropwise at 0 °C, and stirring continued for 2.5 h at 0 °C. The reaction mixture was then washed with 0.01 M Na_2CO_3 until neutral, which was followed by water (3 × 250 mL), was dried with Na_2SO_4, and was concentrated *in vacuo* to give **11** as a waxy solid. The crude product was then redissolved in THF and precipitated with

MeOH to give **11** as a white solid (35.9 g, 95% yield).

IR (CH_2Cl_2): 2924, 2852, 1652, 1616 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, δ): 6.47, 6.54 (d of d, *J* = 9 Hz), 6.27, 6.33 (d of d, *J* = 2 Hz), 5.59, 5.63 (d of d, *J* = 2 Hz), 3.35–3.21 (m, 4H), 1.52 (s, 4H), 1.29–0.81 (m, 60H), 0.84 (*t*, *J* = 7.5 Hz, 6H). ^{13}C NMR (63 MHz, $CDCl_3$, δ): 165.7, 128.0, 127.1, 48.1, 46.7, 31.9, 29.7–27.1 (set of singlets), 22.7, 14.1. ELEM. ANAL. Calcd. for $C_{39}H_{77}NO$: C, 81.3%; H, 13.4%; N, 2.43%. Found: C, 81.0%; H, 13.5%; N, 2.35%.

General Procedure for the Preparation of *N,N*-Di(octadecyl)acrylamide/1,2,5,6-Di(isopropylidene)-D-glucofuranose-2-propenoate Copolymers (13)

A mixture of the alkoxyamine **10** (104.3 mg, 0.0122 mmol), the corresponding nitroxide **3** (1.3 mg, 0.608 µmol), **11** (1.14 g, 1.98 mmol), **6** (1.86 g, 5.92 mmol), and DMF (1.23 g, 16.8 mmol) were degassed with three freeze–thaw cycles, sealed under argon, and heated at 105 °C for 40 h. The reaction mixture was then dissolved in THF (20 mL) and precipitated by the addition of MeOH. The precipitate was collected by vacuum filtration and dried to give the desired copolymer **13** as a white solid (1.60 g, 55% yield).

M_n: 13,800 g/mol. PDI: 1.20. IR (CH_2Cl_2): 2986, 2919, 2852, 1740, 1636 cm^{-1}. ^1H NMR (250 MHz, CD_2Cl_2): 5.69 (br, s), 4.94 (br, s), 4.28 (br, s), 3.96 (br, s), 3.77 (br, s), 2.16 (br, s), 1.39–1.06 (br, multiplet), 0.68 (br, s). ^{13}C NMR (63 MHz, $CDCl_3$, δ): 165.2, 113.3, 110.0, 109.4, 105.6, 83.0 79.9 77.4, 72.1, 66.9, 32.4, 32.0, 30.1, 29.7, 26.9, 23.0, 14.2.

The removal of the alkoxyamine end group and hydrolysis to give the lipo-glycocopolymer **12** were accomplished with the general procedures previously defined.

Film Balance Measurements

The isotherm measurements were conducted with a 50 cm × 15 cm symmetric-compression KSV-5000 Langmuir–Blodgett trough (KSV, Helsinki, Finland). Deionized water, purified with the Milli-Q system (Millipore Corp.), was used as a subphase and held constant at 28 °C within 0.1 °C. Solutions of 0.5–1 mg/mL of **5** in high performance liquid chromatography (HPLC)-grade chloroform were prepared for spreading. The solution was added dropwise onto the water surface with the help of a microsyringe. After a 15-min

waiting period for solvent evaporation, the barriers were compressed at 5 mm/min. The Wilhelmy plate method allowed the measurement of the surface pressure with an experimental error of approximately 0.1 mN/m. For the hysteresis experiments, the compression and expansion rates of the barriers were identical (5 mm/min). The barriers were allowed to reach their starting positions before further compression and expansion cycles were performed. During the area relaxation experiments, the surface pressure was held constant after the film had been compressed to the target value, and the change in the film area was measured. A new film was spread for each isotherm and relaxation experiment.

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45. $[S]_0$ = concentration of the sugar monomer **6** at time $t = 0$; $[S]_t$ = concentration of the sugar monomer **6** at time t.

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