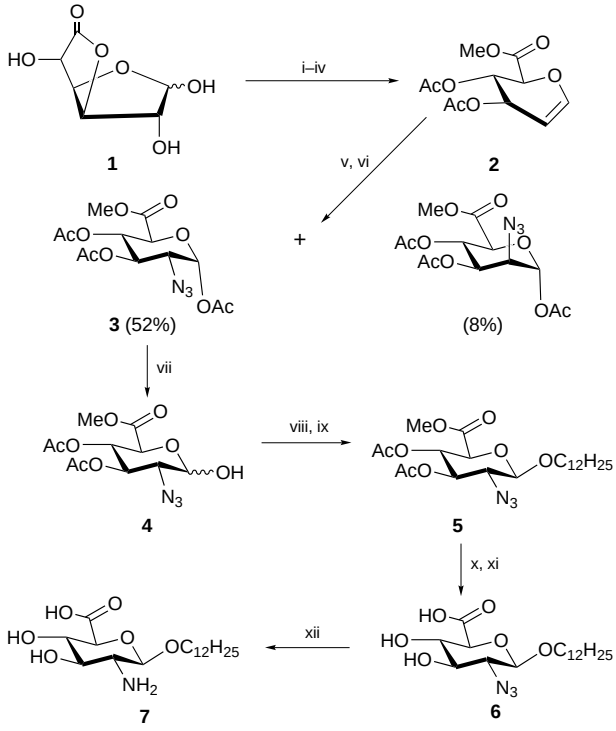
Amphiphilic poly(sugar amino acid)s: a novel class of glycoclusters for supramolecular materials[1]

Shin-Ichiro Nishimura,*† Shinnosuke Nomura and Kuriko Yamada

Laboratory for Bio-Macromolecular Chemistry, Division of Biological Sciences, Graduate School of Science, Hokkaido University, Sapporo 060, Japan

A poly(sugar amino acid) having self-assembling properties was efficiently synthesised by simple polymerisation of 1-*O*-dodecyl-2-amino-2-deoxy-β-D-glucopyranosiduronic acid 7 derived from D-glucofuranurono-6,3-lactone as the key starting material.

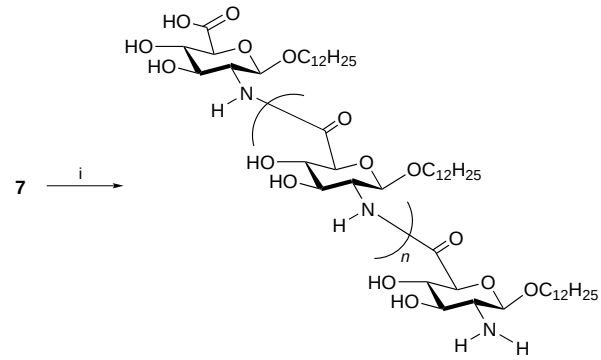
The growing importance of glycoconjugates in biology[2] and the emergence of libraries[3] for the construction of glycodrugs prompted us to design and synthesise a series of carbohydrate analogues and glycomimetics.[4] Carbopeptoids[5] (peptide-bond linked carbohydrates) are also potential candidates for functional glycomimetics having interesting biological activity as carbohydrate or peptide mimetics. Sugar amino acids (SAAs)[6,7] and their derivatives are important synthons for the preparation of a series of carbopeptoids.[8] One of the synthetic SAAs has been incorporated into a cyclic peptide with the β-turn motif of somatostatin containing Phe-Trp-Lys-Thr.[9] Poly(sugar amino acid)s [poly (SAA)s],[10] peptide-bond linked polysaccharide mimetics (polyamides[11]) derived from the SAAs, are regarded as one of the potential starting points for the synthesis of a novel class of biocompatible and/or biodegradable materials. As part of our ongoing efforts in designing artificial glycoclusters with specific functions,[12] we report herein the first synthesis of poly(sugar amino acid)s able to self-assemble to form stable monomolecular layers using the readily available D-glucofuranurono-6,3-lactone **1** ($194 per 1 kg, Aldrich Chemical Company, Inc.) as a key starting material.



Scheme 1 *Reagents and conditions*: i, NaOH, MeOH; ii, Ac_2O, C_5H_5N; iii, HBr–AcOH; iv, Zn, AcONa, $CuSO_4$, 60% from **1**; v, NaN_3 (1.4 equiv.), $Ce(NO_3)_6(NH_4)_2$ (2.3 equiv.), MeCN, −15 °C, 20 h; vi, NaOAc (3 equiv.), AcOH, 100 °C, 1 h, 52% from **2**; vii, $BnNH_2$ (1.5 equiv.), THF, 20 °C, 3 h, 99%; viii, DAST (1.2 equiv.), THF, −20 °C, 15 min; ix, $C_{12}H_{25}OH$ (2.0 equiv.), Cp_2ZrCl_2 (2.5 equiv.), $AgClO_4$ (5.0 equiv.), C_6H_6, 4 Å molecular sieves, 25 °C, 16 h, 45% from **4**; x, NaOMe (0.2 equiv.), MeOH, 25 °C, 1.5 h; xi, 1 M NaOH (aq.) (1.0 equiv.), MeOH, 25 °C, 3 h, then 1 M HCl (aq.) (pH 3), 79% from **5**; xii, Pd–C, H_2 gas, MeOH, 25 °C, 48 h, 55%

For the construction of the amphiphilic poly(sugar amino acid) we designed a D-glucosaminuronic acid derivative **7** as an amphiphilic SAA monomer. Scheme 1 summarises the synthetic route to the target compound **7** starting from **1**. Thus, manipulation of **1** by a known sequence afforded glucal derivative **2** in large quantities.[13] The latter compound was then converted to 2-azido derivative **3**, under standard conditions for the azidonitration of glucals,[14] in 52% overall yield.‡ Removal of the C-1 acetyl group of **3** was accomplished *via* treatment with benzylamine to afford hemiacetal **4** in quantitative yield. Fluorination of the 1-OH group of **4** with DAST, followed by direct glycosylation with dodecan-1-ol in the presence of Cp_2ZrCl_2–silver perchlorate (1 : 2) in benzene gave β-glycoside **5** in 45% yield from **4**.‡§ Successive treatment of **5** with NaOMe–MeOH and aq. NaOH afforded intermediate **6** in 79% overall yield.¶ Hydrogenolysis of **6** over Pd–C gave amphiphilic SAA monomer **7** in 55% yield.‡

Polymerisation of monomer **7** having two unprotected hydroxy groups at the C-3 and C-4 positions proceeded smoothly using diphenylphosphoryl azide (DPPA) according to the published procedure[15] and gave new poly(SAA) in 72% yield (Scheme 2).‖ The molecular weight of the poly(SAA) was estimated to be in the range 700–4500 (DP = 2–13) by the MALDI-TOF mass spectrum.‖ This polymer forms a stable monolayer *via* spreading of a dilute DMSO–$CHCl_3$ solution on a pure water surface. The surface pressure–area diagram shows a steep increase of the surface pressure at around 1.8 nm^2 per molecule [Fig. 1(*a*)]. This indicates that the poly(SAA) molecules are closely packed. Upon further compression the monolayer collapses, at 50 mN m^{-1}. On the other hand, compound **7**, the repeating unit of this polymeric amphiphile, exhibited a poor ability to form a monomolecular layer,



Scheme 2 *Reagents and conditions*: i, $Ph_2P(O)N_3$ (2.3 equiv.), Et_3N (2.3 equiv.), DMSO, 25 °C, 15 h, 72%

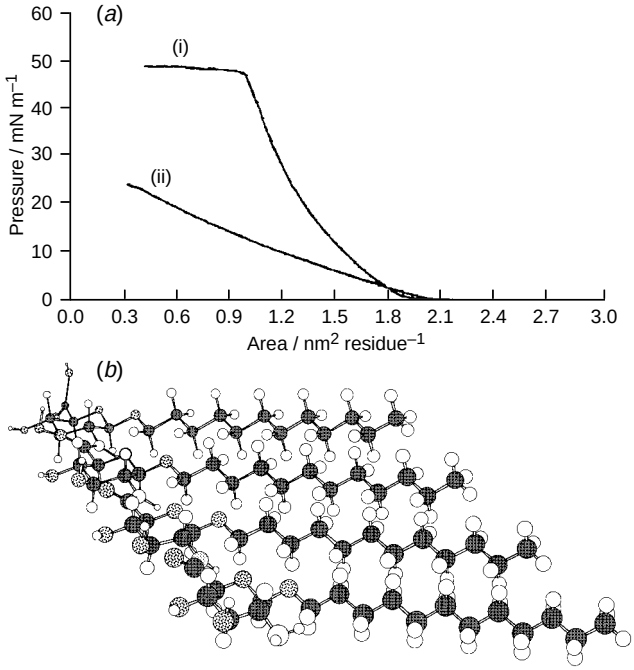


Fig. 1 (*a*) Surface pressure–area isotherms of (i) poly(SAA) and (ii) monomer **7**. (*b*) Possible molecular arrangements of the amphiphilic poly(SAA).

suggesting that the stable peptide bond-type linkages of poly(SAA) are efficient triggers for control of the orientation of the hydrophilic sugar head groups and the hydrophobic alkyl tails, as indicated in the possible molecular arrangements of the polymer [Fig. 1(*b*)]. It should also be noted that the highly ordered structure of the amphiphilic poly(SAA) will favour further chemical and/or enzymatic modification of the two hydroxy groups at the C-3 and C-4 positions. The versatility of the synthetic strategy using poly(SAAs) as 'scaffolds' allows monolayers to be applied to a variety of novel supramolecular materials[16] having specific molecular recognition sites, such as galactose and sialic acid residues.

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Notes and References

† E-mail: nishimura@polymer.sci.hokudai.ac.jp

‡ *Selected data* for **3**: $\delta_H(CDCl_3)$ 6.37 (d, 1 H, *J* 3.7, H-1), 5.51 (t, 1 H, *J* 9.8, H-4), 5.20 (t, 1 H, *J* 9.8, H-3), 4.37 (d, 1 H, *J* 10.3, H-5), 3.75 (s, 3 H, Me), 3.69 (dd, 1 H, *J* 11.0 and 10.2, H-2), 2.21, 2.12 and 2.05 (each s, 3 H, MeCO). For **5**: $\delta_H(CDCl_3)$ 5.12 (t, 1 H, *J* 9.8, H-4), 5.02 (t, 1 H, *J* 10.2, H-3), 4.41 (d, 1 H, *J* 8.1, H-1), 3.98 (d, 1 H, *J* 9.9, H-5), 3.95 and 3.58 (each q, 1 H, *J* 6.5, OCH_2), 3.75 (s, 3 H, Me), 3.56 (dd, 1 H, *J* 9.4 and 9.2, H-2), 2.09 and 2.01 (each s, 3 H, MeCO) 1.64–1.26 (m, 20 H, CH_2), 0.88 (t, 3 H, *J* 7.0, CH_3). For **7**: $\delta_H([^2H_6]DMSO)$ 5.75 (br s, 2 H, NH_2), 4.30 (d, 1 H, *J* 8.0, H-1), 3.72 and 3.40 (each q, 1 H, *J* 6.5, OCH_2) 3.56 (t, 1 H, *J* 10.0, H-4), 3.49 (t, 1 H, *J* 10.0, H-3), 3.34 (d, 1 H, *J* 9.8, H-5), 3.20 (q, 1 H, *J* 9.8, H-2), 1.56 and 1.23 (m, 20 H, CH_2), 0.84 (t, 3 H, *J* 7.9, CH_3).

§ Glycosyl fluoride derived from **4** was directly employed for the glycosidation reaction without further chromatographic purification owing to its unstable nature.

¶ The versatility of compound **6** as a carboxyl component for the synthesis of the sequential poly(SAAs) should also be noted, and some examples will be reported shortly.

‖ *Polymerisation* of **7**: To a solution of **7** (100 mg, 0.277 mmol) in Me_2SO (5 ml) was added DPPA (137 μl, 0.637 mmol) and Et_3N (89 μl, 0.637 mmol). The mixture was stirred at room temp. for 15 h. The precipitate obtained by addition of EtOH–Et_2O (1 : 1) was collected and dried over P_2O_5 under reduced pressure to give the poly(SAA); ν_{max}/cm^{-1} 3350, 2930, 2850, 1660 and 1545; δ_H ($[^2H_6]$DMSO) 4.48 (br d, 1 H, *J* 8, H-1), 3.85–3.35 (br m, H-2, 3, 4, 5 and OCH_2), 1.55 and 1.22 (m, 20 H, CH_2), 0.85 (br t, 3 H, CH_3). *m/z* 727.9, 1071.4, 1414.9, 1758.3, 2101.8, 2445.25, 2788.7, 3132.2, 3475.7, 3819.1, 4162.6 and 4506.0.

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