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pH-dependent reversible polymers formed from cyclic sugar- and aromatic boronic acid-based bolaamphiphiles

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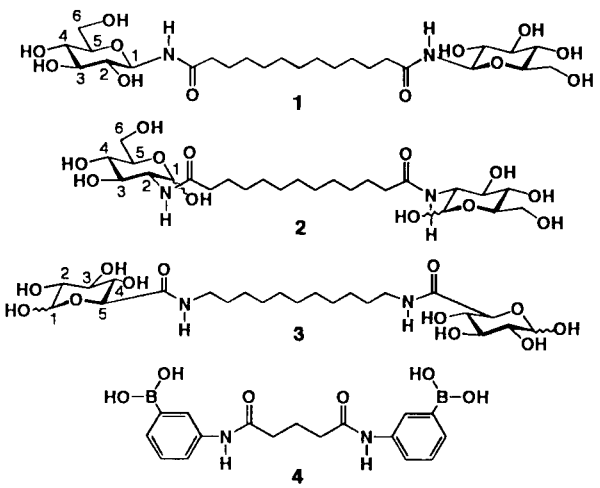
Glucuronamide-based bolaamphiphiles are found to form a reversible, linear polymolecular array, *via* a boronate ester linkage attached to the 1,2-positions of the pyranose or furanose ring, upon complexation with an aromatic boronic acid-based homologue in aqueous solutions.

Aromatic boronic acids form complexes with *cis* diol-type hydroxy groups of carbohydrates *via* ester-linkage formation.[1–3] In particular, Shinkai *et al*. have intensively developed new aspects on aqueous sugar sensing by employing aromatic boronic acids.[4] Even though there have been some arguments about the boronate structure in aqueous solutions,[5–7] the complexes should contain a furanose form of the glucose moiety.[8] Norrild and Eggert have confirmed by ^{1}H and ^{13}C NMR spectroscopy that monoboronic acids bind preferentially to the 1,2-position and secondly to the 3,5,6-position of α-D-glucofuranose in aqueous solutions.[3] We have so far investigated the self-assembling properties of 1-glucosamide (**1**)[9] and 2-glucosamide bolaamphiphiles (**2**)[10] in water. Although the former derivative **1** possesses free C-3, C-4 and C-6 hydroxy groups, it cannot convert into the furanose form. On the contrary, the latter homologue **2** possessing the same free hydroxy groups can rearrange to the furanose resulting in free C-3, C-5 and C-6 hydroxy groups. In line with this molecular design, we have newly synthesized a glucuronamide-based bolaamphiphile (**3**)† possessing free 1,2-diols available for ester formation with a boronic acid. Comparison of the complex formation between these three sugar-based bolaamphiphiles (**1**, **2** or **3**) and an aromatic boronic acid-based homologue **4**,† should provide further insight into the complex structures. Mikami and Shinkai are the first to prepare main-chain sugar-containing polymers *via* self-condensation with diboronic acid under nonaqueous conditions.[11] Advantageously, we are also able to solve a problem concerning the sequential head-to-tail irregularity of the cyclic sugar-containing polymer. Here we describe the pH-dependent, reversible polymolecular boronate complexation between glucuronamide- **3** and boronic acid-based bolaamphiphiles **4** in aqueous solutions.



The glucuronamide bolaamphiphile **3** was efficiently synthesized in 4 steps from commercially available glucuronic acid, in a similar manner to that reported by Falkowski *et al.*[12] The related derivatives, 1-glucosamide (**1**) and 2-glucosamide bolaamphiphiles **2** were prepared according to a published procedure.[10,13] The boronic acid-appended bolaamphiphile **4** was also synthesized in the same manner as described by Kimura *et al.*[14]

^{1}H NMR spectroscopy of **3** in DMSO-d_6 containing a trace amount of D_2O clearly displayed two sets of well-defined signals for the H-1 (δ 4.32 and 4.93), H-5 (δ 3.51 and 3.93) and hydroxy OH-1 protons (δ 6.52 and 6.82). The presence of these two sets of signals with an average integral ratio of 56 : 44 implies that the bolaamphiphile **3** exists as a mixture of α-(56%) and β-anomers (44%) in the solution. ^{1}H NMR spectra of **4** were measured in the weak acidic (pD = 3) and alkaline aqueous solutions (pD = 10–12). The aromatic proton regions of the obtained spectra displayed entirely different spectral patterns under each condition, suggesting that the sp^2-hybridized boron atom can convert completely into the sp^3 mode at pH values above 10.

In order to confirm the linear complex formation between the cyclic sugar- and boronic acid-based bolaamphiphiles, we employed ^{11}B NMR spectroscopy‡ since it is very sensitive to the spin state of the boron atom. Therefore, we can easily differentiate the neutral sp^2, anion sp^3 and coordinated sp^3 states of the aromatic boronic acid moiety in the bolaamphiphile. Actually, ^{11}B NMR spectra of the boronic acid bolaamphiphile **4** (0.1 M) displayed distinct chemical shifts for the boron atom under weak acidic and alkaline conditions [δ 11 and −16, respectively, Figs. 1(*a*) and 1(*b*)]. The addition of equimolar 1-glucosamide bolaamphiphile **1** induced no spectral change in the ^{11}B NMR of **4** [Fig. 1(*c*)]. Thus, the potent C-4 and C-6 hydroxy groups of **1** in the pyranose form proved inactive for the ester linkage formation, resulting in no polymer formation. In contrast to this spectral feature, two separate ^{11}B NMR signals (δ −11 and −16), with an integral ratio of 1 : 2, appeared for **4** coexisting with equimolar 2-glucosamide bolaamphiphile **2** [Fig. 1(*d*)]. The minor signal in intensity (*ca.* 33%) is compatible with the presence of a covalently attached sp^3-type boronic moiety. Considering no possibility of the pyranose form existing, this finding implies that either of the C-3, C-5 and C-6 hydroxy groups of the glucofuranose can participate in binding. For a linear non-strained polymolecular complex with **4** the 3,5,6-binding mode could be the more probable compared to the binding of monoboronic acids [Fig. 2(*a*)].[3] On the other hand, the glucuronamide derivative **3** with the free C-1 and C-2 hydroxy groups was found to produce covalently attached sp^3 hybridization, giving a polymolecular complex (*ca.* 70%) equilibrated with a small amount of free anions [*ca.* 30%, Fig. 1(*e*)]. Whether the complex structure is a pyranose or a furanose form cannot be concluded at present from any other NMR

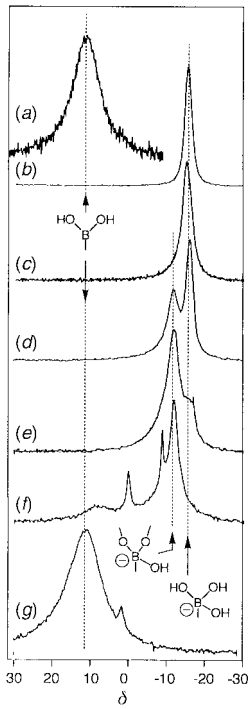


Fig. 1 ^{11}B NMR spectral change of the bolaamphiphiles **1**, **2** or **3** upon complexation with **4** (0.1 M, at 25 °C in D_2O/methanol-d_4 (6:4, *v/v*)). (*a*) **4** under weak acidic aqueous condition (pD = 3.0); (*b*) **4** under alkaline aqueous condition (pD = 12.7); a 1:1 mixture of (*c*) **1** and **4** (pD = 10.7); (*d*) **2** and **4** (pD = 10.3); (*e*) **3** and **4** (pD = 10.9); (*f*) **3** and **4** (pD = 6.4); (*g*) **3** and **4** (pD = 3.0).

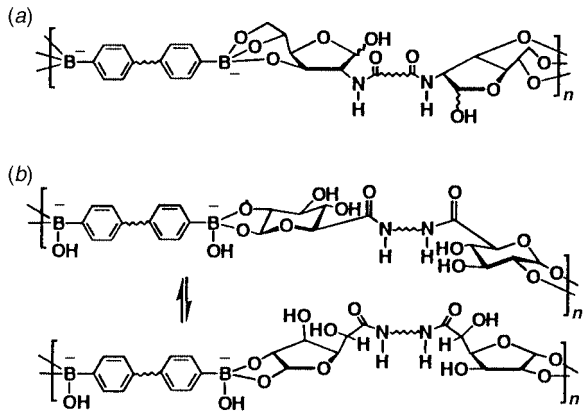


Fig. 2 Possible structures of the polymer main chains formed from (*a*) the mixture of **2** and **4**; (*b*) the mixture of **3** and **4**.

measurements including ^{13}C NMR [Fig. 2(*b*)]. Detailed structural analysis remains to be further investigated using single-head single-chain amphiphile models of **1**–**4**. It is well known that multiangle laser light scattering (MALLS)‡ detector measures, from the intensity of the scattering, the molar mass of biopolymers in solutions.[15] Especially, MALLS can provide a highly sensitive and useful method for the characterization of polysaccharides and protein oligomers. The weight-averaged molecular weight (M_w) for the present aqueous **3**·**4** polymer was evaulated by MALLS to be 2.04×10^6 g mol^{-1} at pD 10.8.

Dissociation of the boronate polymer complexes into each component **3** and **4** was investigated by neutralizing the solution with dilute hydrochloric acid. At neutral pH range (pD = 6.4), the ^{11}B NMR spectrum of the polymer indicated that a main signal (*ca.* 48%) attributable to the boronate complex still apears at δ −11 in addition to three minor signals at δ −8 (*ca.* 24%), 1 (*ca.* 13%) and 9 (*ca.* 15%), [Fig. 1(*f*)]. Complete dissociation of the polymer was achieved under weak acidic aqueous conditions (pD = 3). Namely, the decrease in the pH value of the aqueous solution from 11 to 3 resulted in a down-field shift of the main signal from δ −11 to 11 [Fig. 1(*g*)]. Thus, a reversible polymer formation and dissociation was realized depending on the pH conditions of the aqueous solutions. The monomers are connected to each other through identical cyclic sugar–boronate ester linkages, unike Mikami and Shinkai's cyclic sugar-containing polymer,[11] in a one-dimensional poly-molecular array. This kind of polymer system can be realized using both cyclic sugar- and boronic acid-based bola-form derivatives. In addition, the notably different features of **1** and **2** upon complexation with **4** gave unequivocal evidence for the participation of the furanose form of **2**.

Notes and references

† *Selected data* for **3**: yield 28%, mp 198–200 °C (decomp.), FAB mass (in glycerol) *m*/*z* 553 (M^+). ^{1}H NMR (in DMSO-d_6 plus one drop of D_2O at 25 °C) δ 1.24 (s, 16H, $CH_2(CH_2)_8CH_2$), 1.38 (dd, 4H, $CH_2(CH_2)_8CH_2$), 3.05 (m, 4H, CH_2CH_2NHCO), 2.90–3.45 (m, 8H, H-2, H-3, H-4), 3.51 (d, 0.96H, H-5(β)), 3.93 (d, 1.04H, 2H, H-5(α)), 4.32 (d, 0.88H, H-1(β)), 4.94 (d, 1.12H, H-1(α)), 6.52 (d, 2H, OH-1(β)), 6.82 (d, 2H, OH-1(α)) and 7.91 (dd, 2H, CH_2NHCO-). Anal. Calcd. for $C_{24}H_{44}O_{12}N_2$: C, 52.16; H, 8.03; N, 5.07. Found: C, 51.96; H, 8.07; N 4.83%. For **4**: yield 36%, mp 210 °C, ^{1}H NMR (in DMSO-d_6 at 25 °C) δ 1.98 (m, 2H, $CH_2CH_2CH_2$), 2.37 (t, 4H, CH_2CH_2CONH), 7.24, 7.46, 7.72, 7.85 (s, d, d, t, 8H, Ar-H), 7.97 (s, 4H, $B(OH)_2$) and 9.84 (s, 2H, CH_2CONH). Anal. Calcd. for $C_{17}H_{20}O_6N_2B_2$: C, 55.19; H, 5.45; N, 7.57. Found: C, 55.02; H, 5.48; N 7.36%.

‡ ^{1}H and ^{11}B NMR spectra were collected with a JEOL 600 Fourier transform spectrometer operating at 600.05 and 192.45 MHz, respectively. All solutions were prepared in a mixture of D_2O and methanol-d_4 (6:4 *v/v*) with the spectrometer locked onto D_2O. Each pH value of the solutions was adjusted with NaOD aqueous solutions.^{11}B NMR chemical shifts were measured relative to external $NaBF_4$. MALLS was measured using a Wyatt DAWN DSP, coupled with refractive index detectors operated in a microbatch mode.

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