Molecular Recognition

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Translation of Mutarotation into Induced Circular Dichroism Signals through Helix Inversion of Host Polymers

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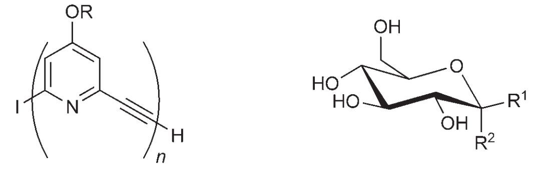
One of the most exciting and challenging topics in molecular recognition is the development of artificial host molecules that recognize saccharides in aqueous protic media through the formation of hydrogen bonds.[1,2] We recently designed and synthesized water-soluble *meta*-ethynylpyridine polymers such as **1** (Scheme 1)[3] which spontaneously form helical structures in protic media through intramolecular solvophobic interactions.[3,4] This organization forces the pyridine N atoms to be positioned on the inside of the helix. In the resulting pore, saccharides interact with the polymer through the formation of hydrogen bonds between the OH groups of the saccharide and the pyridine N atoms of the polymer, even in 100% protic media.[5] The association could be clearly detected by the appearance of induced circular dichroism (ICD)[6] signals in the absorptive region of the polymer. However, among the monosaccharides examined in this investigation, glucose exhibited weak ICD effects. This observation confused us because octyl β-D-glucopyranoside induced intense CD signals on association with **2**, a lipophilic analogue of **1**, in less polar solvents.[7]



1 : R = $(C_2H_4O)_8CH_3$
2 : R = $n C_4H_9$

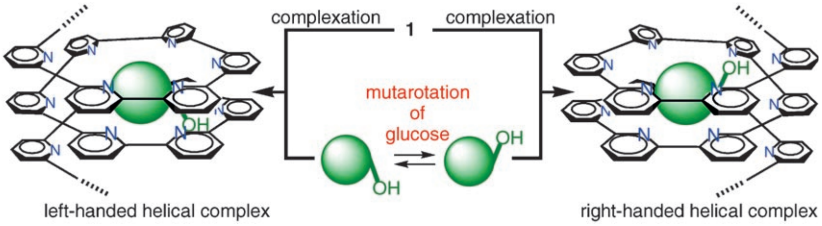
α-D-glucose : R^1 = H, R^2 = OH
β-D-glucose : R^1 = OH, R^2 = H
octyl β-D-glucopyranoside : R^1 = O*n*Oct, R^2 = H

Scheme 1. Structure of poly(*meta*-ethynylpyridine)s and saccharides.

Detailed investigations on this phenomenon elucidated that helix inversion[8] occurs in polymer **1** as a result of anomerization of β-glucose to α-glucose and vice versa (Scheme 2). In other words, each anomer of glucose caused the polymer to bias a single-handed helix in the opposite sense. Therefore, the ICD effects should be virtually cancelled out by the existence of both the right- and left-handed helices from an equilibrium mixture of α/β-glucose (ca. 1/1). This finding means that real-time information concerning the mutarotation of glucose is translated into ICD signals of the polymer through recognition-induced chirality transfer from the small molecules to the supramolecular architectures.

As mentioned above, a mixture of the water-soluble polymer **1** with D-glucose in MeOH/water (10:1) showed only a weak ICD band around 337 nm.[3] We also observed that the ICD effects could be reversed by changing the solvent composition. Figure 1a shows the CD spectra for **1** with D-glucose in MeOH/water mixtures of various ratios after the solutions had been allowed to stand over 48 h to reach the equilibrium state. A weak negative ICD was observed around 337 nm in a MeOH/water mixture of 10:1. However, the ICD effects weakened when the fraction of water was increased, and almost disappeared in a MeOH/water mixture of 8:1. Further increasing the water fraction (up to MeOH/water 5:1) resulted in positive ICD signals appearing in the same wavelength region instead. In the case of **2** with octyl β-D-glucopyranoside, the sign of the ICD effects remained unchanged regardless of the solvents used, although the ellipticity varied. There is a critical difference between D-glucose and octyl β-D-glucopyranoside: the former undergoes mutarotation in solutions and the latter does not.[9] Therefore, we speculated that the curious ICD behaviors of **1** may result from the mutarotation of D-glucose, and actually, that the α/β ratio of D-glucose varied with the solvent composition (see the Supporting Information), with each anomer biasing the helicity of the complex in an opposite sense according to the observed ICD effects.

To demonstrate this hypothesis the time dependence of the ICD effects was studied for **1** with anomerically pure



Scheme 2. Helix inversion of the complex formed between poly(*meta*-ethynylpyridine) **1** and D-glucose induced by mutarotation of D-glucose. Side chains are omitted for clarity.

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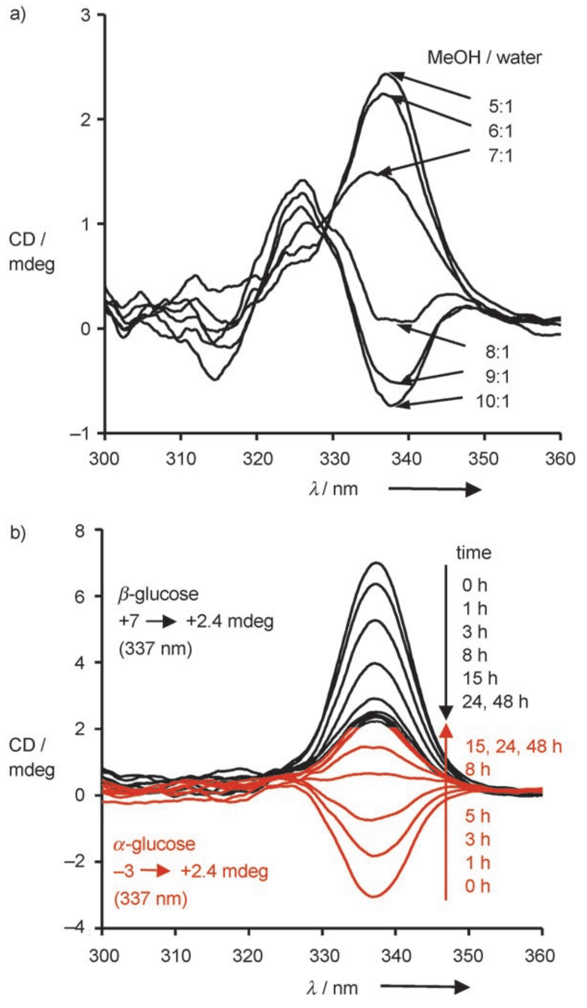

Figure 1. a) ICD signals of the mixture of **1** and D-glucose in mixed MeOH/water solvents of various ratios. Conditions: **1** (1.0×10^{-3} M, monomer unit concentration), D-glucose (0.30 M), MeOH/water = 5:1 to 10:1 (v/v), 25 °C, light path length = 1 mm. The sample solutions were analyzed after standing for over 48 h to bring them to the equilibrium state. b) Time dependence of the ICD effects for the mixture of **1** and α- or β-D-glucose. Conditions: **1** (1.0×10^{-3} M, monomer unit concentration), α- or β-D-glucose (0.30 M), MeOH/water = 5:1, 25 °C, light path length = 1 mm, time course = 0–48 h.

glucose. Crystalline α-D-glucose[10] was added to a solution of **1** (1.0×10^{-3} M, monomer unit concentration) in MeOH/water (5:1) and the CD spectrum was measured over time (Figure 1 b). A rather strong negative ICD signal appeared around 337 nm just after the addition of the α-D-glucose (at 0 h). The signal then began to weaken over time and seemed almost to disappear after 5 h. After that, the ICD signal reappeared with a positive sign in the same wavelength region and reached the equilibrium state after approximately 24 h. The value of the final ellipticity was +2.4 mdeg (after 48 h), identical to that obtained from a mixture of anomers (Figure 1 a) under the same solvent composition. A similar experiment was also carried out using β-D-glucose.[10] In this case, a strong ICD effect was first observed with a positive sign around 337 nm. The reversal of the ICD signs in the initial states (α-D-glucose: negative, β-D-glucose: positive) indicates that each anomer of glucose biases the helical sense of the complexes in an opposite manner despite the only difference being the C1 configuration of the glucose.[11] The ICD signal for **1** with β-D-glucose weakened over time and reached the equilibrium with at the same ellipticity value of +2.4 mdeg after 24 h.[12]

However, we had to rule out the possibility that the weakening of the ICD effects might be due to the collapse of CD-active helical complexes. Thus, the UV/Vis spectral change for the complexation was monitored under the same conditions as the CD measurement. When D-glucose was added to a solution of **1** in MeOH/water, a small hypochromic effect was immediately observed around 323 nm (see the Supporting Information). This hypochromism would suggest that the interaction with glucose caused **1** to become a more rigid structure, which induces a more efficient intramolecular π-stacking interaction. After that, unlike the case for the CD measurements, the UV/Vis spectrum scarcely changed its shape over 48 h. This finding means that the initially formed complex is stable at least over the course of the measurement, even though **1** can reversibly reform its helicity.

^{13}C NMR studies gave additional support for the mutarotation-induced inversion of the helix formed with **1**. The molar percentages of α- and β-D-glucose can be calculated from the sum of the integrated intensities of the signals for the C1–C5 carbon atoms of each anomer.[13,14] The ^{13}C NMR spectrum of β-D-glucose (0.30 M) in the presence of **1** (1.0×10^{-3} M, monomer unit concentration) in MeOH/CD$_3$OH/H$_2$O (6.35:2.00:1.65, this ratio corresponds to that of MeOH/water = 5:1) just after dissolving crystals of β-D-glucose is shown in the Supporting Information. In this solvent, β-D-glucose gradually anomerized and reached the α/β equilibrium state (α/β 44:56) after about 24 h (see the Supporting Information). When the percentage of β-D-glucose was plotted against time, the time transition curve for the ellipticity measured at 337 nm (θ_{337}) in the CD observation overlapped well (Figure 2). In a similar manner, the time

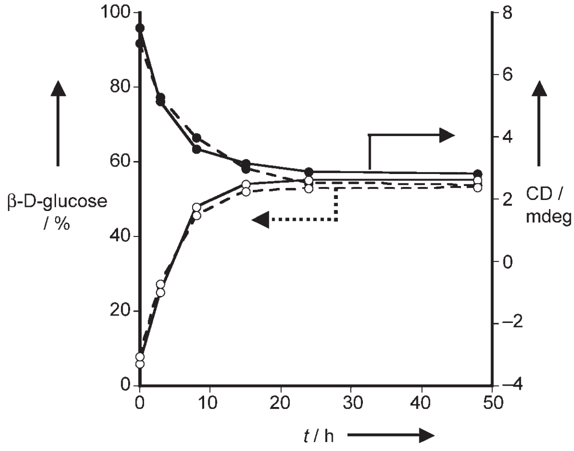

Figure 2. Time-transition of the percentage of the β-D-anomer estimated from the ^{13}C NMR spectrum (broken line) and that of the ellipticity at 337 nm in the CD measurement (solid line) by using α-D-glucose (○) or β-D-glucose (●) initially. Conditions: **1** (1.0×10^{-3} M, monomer unit concentration), α- or β-D-glucose (0.30 M), MeOH/CD$_3$OH/H$_2$O = 6.35:2.00:1.65 for ^{13}C NMR spectroscopy, MeOH/H$_2$O = 5:1 for CD measurements, 25 °C, light path length = 1 mm.

transition curves with α-D-glucose plotted from ^{13}C NMR and CD measurements also coincide well with each other.[12] Thus, the time-dependence for the ICD changes are directly dominated by the mutarotation of glucose: the association/dissociation between **1** and glucose and the helix inversion must be faster processes than that of mutarotation of glucose.[15] Furthermore, the time-dependence of the ICD effects was observed in the cases of mannose and allose (see the Supporting Information).

In summary, CD and ^{13}C NMR studies have revealed that the stereochemical information of anomers is translated to the helical sense of the host polymer **1**, with local chemical process in the small molecules inducing large mechanical motion of the supramolecules. This finding can be applied to the real-time monitoring of the mutarotation of saccharides through the ICD signals of helical polymers.

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[10] We used commercial reagents of 96% purity grade for α-D-glucose, and 97% purity grade for β-D-glucose.

[11] Association constants of **1** with anomerically pure α- and β-D-glucose were too small to be estimated (see the Supporting Information).

[12] A similar time dependence of the ICD effects for the mixture of **1** with α- or β-D-glucose was also demonstrated in MeOH/water (10:1; see the Supporting Information).

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[14] The T_1 values for C1–C5 of α- and β-D-glucose were almost equal (see the Supporting Information).

[15] It is possible that **1** can affect the kinetics and/or thermodynamics of mutarotation. However, no meaningful effect was observed, probably because the glucose was used in too great an excess.