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Anion recognition by D-ribose-based receptors

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ABSTRACT

Anion recognition properties of D-ribose-based receptors α- and β-**1** were measured by ^{1}H NMR in $CDCl_3$ and MeCN-d_3. Receptor β-**1** showed effective binding with anions by cooperative hydrogen bonds of *cis*-diol. The anomeric isomer α-**1** is a less effective anion receptor which has similar *cis*-diol as a recognition site, indicating that the stereo configuration of the anomeric position is of significant influence on the anion recognition ability.

Anion recognition by neutral receptors has been developed in the last two decades aiming pharmaceutical and environmental applications.[1] In this regard, much effort has been devoted to the design and synthesis of the neutral anion receptors having multiple hydrogen-bonding sites. Although artificial anion receptors bearing NH groups of amide, urea, thiourea, and pyrrole have been greatly developed,[2] anion receptors bearing OH groups, in particular alcoholic hydroxy groups as hydrogen bond donors, have been rarely reported[3] in spite of the fact that these groups can be frequently found in the active sites of enzymes.[4] We and other groups explored that alcoholic hydroxy groups effectively act as hydrogen bond donors to recognize anionic species in organic solvents.[3] It is well known that saccharides (sugars and carbohydrates) ubiquitously exist in living organisms and consist of plural hydroxy groups those aligned orderly in the molecule.

In the active sites and binding sites of enzymes, saccharides are bound by main chain amide groups and side chains of amino acids by multiple hydrogen bondings.[5] In particular, hydroxy groups of saccharides are frequently recognized by carboxylate groups of Asp and Glu side chains. For instance, in the active site of ribokinase from *Escherichia coli*, two Asp and one Glu carboxylate groups can be found as hydrogen bond acceptor to recognize one D-ribose molecule as a substrate as shown in Figure 1.[6] It is worth noting that two hydroxy groups of the ribose at 2- and 3-positions cooperatively bind one anionic carboxylate residue of Asp_{16}. From the converse view of the host–guest system, D-ribose can be utilized as an anion receptor.

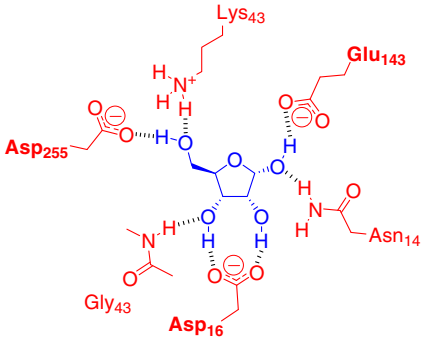

Figure 1. Schematic drawing of active site of ribokinase with D-ribose from *E. coli* generated from PDB data (1GQT).

However, saccharide-based anion receptors have been scarcely reported so far. Schneider and co-workers reported anion recognition properties of receptors based on hexoses such as D-glucose and D-galactose.[7] Kano et al. reported recognition of carboxylates by dextrins and cyclodextrins in DMSO-d_6.[8] Pentoses such as D-ribose easily form furanose ring which are structurally rigid due to five-membered ring by comparison with pyranoses such as D-glucose. However, to the best our knowledge, there is no report on pentose-based anion receptors.

In this Letter, we demonstrate the anion recognition properties of D-ribose-based receptors **1** (Scheme 1) and a significant influence of the anomeric configuration on the recognition process. Two hydroxy groups in the cis position are expected to recognize appropriate anionic species by cooperative hydrogen bonds as shown in the active site of ribokinase.

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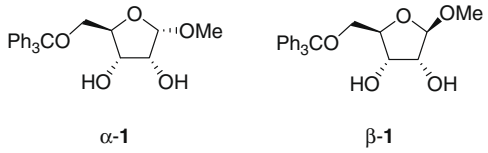

Scheme 1.

Receptors **1**, which are useful intermediates for the synthesis of ribose derivatives, were prepared by following a method in the literature.[9] The anomeric and 5-hydroxy groups were protected by methyl and trityl groups, respectively. Two anomers, α- and β-**1**, can be easily separated by silica gel column chromatography.

At room temperature, ^{1}H NMR spectra of both receptors **1** display well-resolved spectra and no concentration-dependent shifts were observed in 1.0×10^{-3}–1.0×10^{-2} mol dm^{-3} concentration ranges in $CDCl_3$. These results strongly indicate no dimerization or oligomerization of the receptors by intermolecular hydrogen bonds at least in our experimental concentration range. All ^{1}H NMR signals of receptors **1** have been fully characterized. The OH protons of β-**1** can be found at 2.22 and 2.47 ppm in the absence of guests in $CDCl_3$. These OH peaks showed large downfield shift upon the addition of Cl^- (tetrabutylammonium was used as a counter cation) indicating hydrogen bond formation of OH groups and Cl^- as shown in Figure 2. The association constant of β-**1** for Cl^- can be calculated to be 148 ± 21 mol^{-1} dm^3 by non-linear curve fitting analysis of the titration data.[10] Addition of AcO^- into a solution of β-**1** caused broadening of the OH signals, therefore the methine and methylene protons of the ribose ring were monitored and the association constant can be calculated to be 3380 ± 440 mol^{-1} dm^3 as shown in Figure 3. The stoichiometries of the complexation were confirmed by Job's plot analyses as shown in Figure 4. The maxima at mole fraction

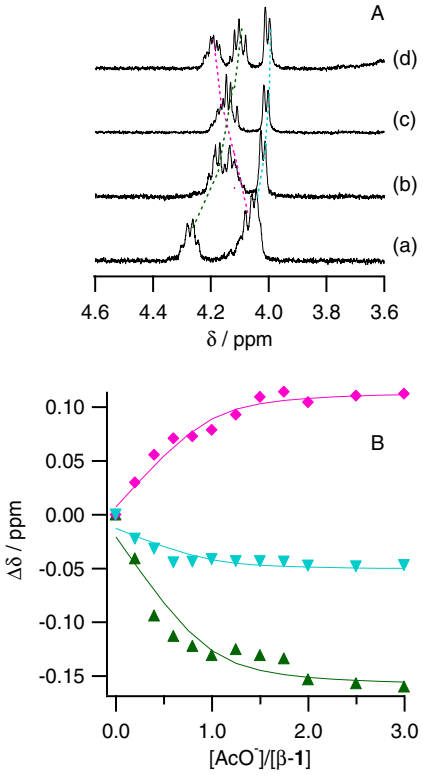

Figure 3. (A) Partial ^{1}H NMR spectra of β-**1** in the absence (a) and in the presence of 0.6 (b), 1.0 (c), and 3.0 equiv (d) of AcO^- in $CDCl_3$ at 298 K. [β-**1**] = 5.0×10^{-3} mol dm^{-3}. (B) Variation in the chemical shift of methine protons of β-**1** upon the addition of AcO^-.

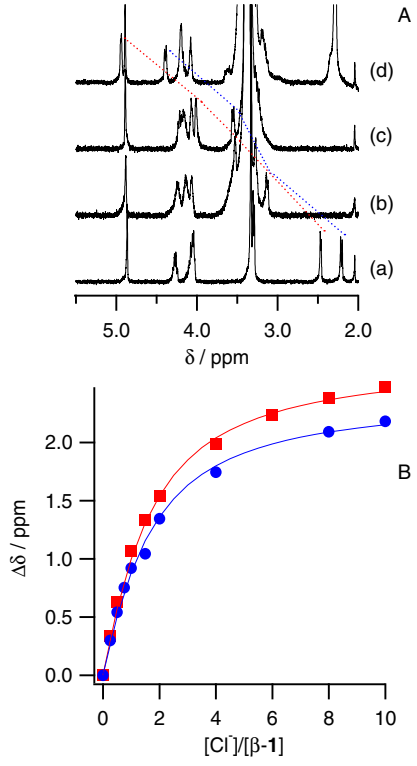

Figure 2. (A) Partial ^{1}H NMR spectra of β-**1** in the absence (a) and in the presence of 1.0 (b), 2.0 (c), and 10.0 equiv (d) of Cl^- in $CDCl_3$ at 298 K. [β-**1**] = 5.0×10^{-3} mol dm^{-3}. (B) Variation in the chemical shift of OH protons of β-**1** upon the addition of Cl^-.

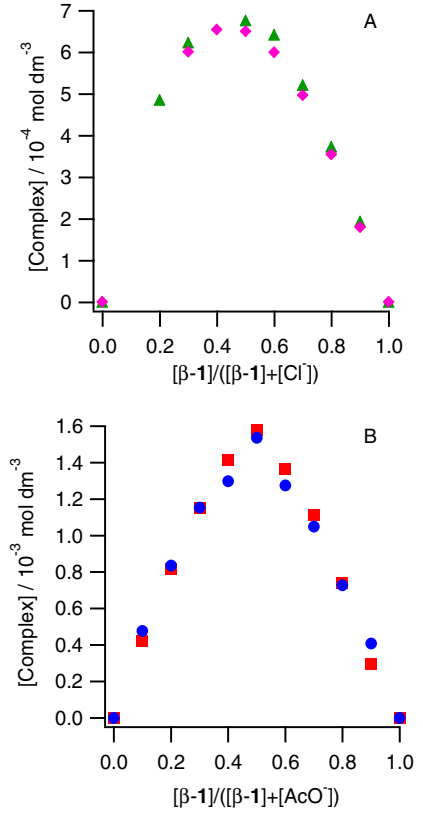

Figure 4. Job plots of β-**1** with Cl^- (A) and AcO^- (B) by 300 MHz ^{1}H NMR spectroscopy. [β-**1**] + [anion] = 5.0×10^{-3} mol dm^{-3} in $CDCl_3$.

Table 1
The association constants of receptors **1** in $CDCl_3$

	K_{11}[a]/mol^{-1} dm^3	
	α-**1**	β-**1**
AcO^-	71.8 ± 13.1	2450 ± 40
$H_2PO_4^-$	16.0 ± 0.6	2030 ± 320
Cl^-	6.7 ± 0.3	148 ± 21
Br^-	2.6 ± 0.1	36.8 ± 0.7

[a] Ref. 11.

0.5 indicate 1:1 complexation of β-**1** with Cl^- and AcO^- in $CDCl_3$. The association constants of β-**1** for $H_2PO_4^-$ and Br^- were also measured and reported as given in Table 1. The anion-binding ability of β-**1** was in the order of $AcO^- > H_2PO_4^- > Cl^- > Br^-$, which is consistent with the order of basicity of the anions. The association constant of β-**1** for Br^- (36.8 ± 0.7 mol^{-1} dm^3) is much higher than that obtained with partially protected D-glucose and D-galactose derivatives (1.9–9.6 mol^{-1} dm^3) in which two hydroxy groups were hydrogen bond donors.[7] The *cis*-diol of β-**1** could effectively associate with target anions.

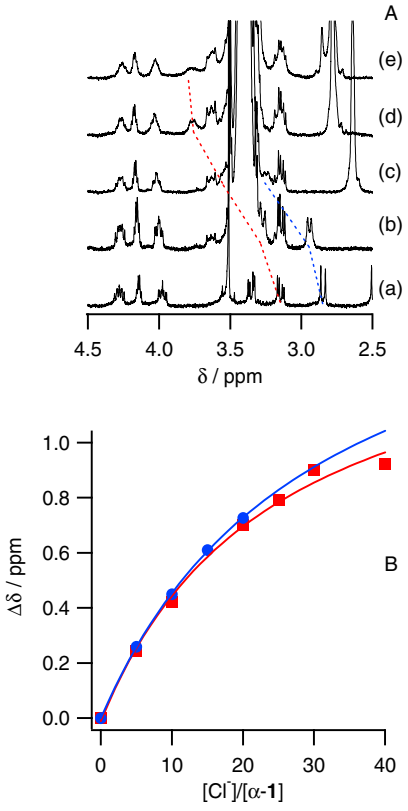

Figure 5. (A) Partial ^{1}H NMR spectra of α-**1** in the absence (a) and in the presence of 10 (b), 20 (c), 30 (d), and 40 equiv (e) of Cl^- in $CDCl_3$ at 298 K. [α-**1**] = 5.9 × 10^{-3} mol dm^{-3}. (B) Variation in the chemical shift of OH protons of α-**1** upon the addition of Cl^-.

Table 2
The association constants of receptors **1** in MeCN-d_3

	K_{11}[a]/mol^{-1} dm^3	
	α-**1**	β-**1**
AcO^-	149 ± 27	3380 ± 440
$H_2PO_4^-$	39.4 ± 1.6	459 ± 109
Cl^-	33.2 ± 1.5	235 ± 3
Br^-	6.5 ± 0.3	30.9 ± 7.3

[a] Ref. 11.

The OH signals of α-**1** were observed at 2.52 and 2.87 ppm in the absence of anions and these peaks showed downfield shift upon the addition of Cl^- anion in $CDCl_3$. However, it is very interesting that the calculated association constant is significantly smaller than that of β-**1** as shown in Figure 5. The similar trend is observed for all anions tested and the association constants of α-**1** were one or two order magnitude smaller than the corresponding ones of β-**1**. This may due to electrostatic and/or steric repulsion between the anomeric oxygen of α-**1** and the anions.

To evaluate the solvent effect on the recognition, titration experiments of receptors **1** were performed in MeCN-d_3 and the calculated association constants are collected in Table 2. The association constants in MeCN-d_3 show similar tendency in $CDCl_3$. The anion-binding abilities of receptors **1** are in the order of $AcO^- > H_2PO_4^- > Cl^- > Br^-$ in both anomers. In addition, the association constants of β-**1** are one order larger than those of α-**1** for all anions as observed in $CDCl_3$.

In conclusion, we have demonstrated that D-ribose-based receptors **1**, in particular β-**1**, show effective binding with anions by cooperative hydrogen bonds of *cis*-diol in $CDCl_3$ and MeCN-d_3. We have found that the stereo configuration of the anomeric position significantly affects anion recognition ability. Receptors **1** are quite simple, but the present results provide not only the ability of saccharide-based anion receptors but also insight of the role of saccharides in living organisms. It is noteworthy that saccharide-based receptors can exert chiral recognition due to the chiral environment of the recognition sites. Further functionalization such as an introduction of a fluorophore might provide promising candidate for various applications. Further studies on this line are in progress in our laboratory.

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11. A referee pointed out that small differences in small association constants are not real or relevant. However, we think that the association constants and the deviations shown in Tables 1 and 2 are sufficiently acceptable because these data were calculated from the independently duplicate or triplicate titration experiments.