

Diaza-18-crown-6-based Sugar Receptor Bearing Two Boronic Acids. Possible Communication between Bound Sugars and Metal Cations

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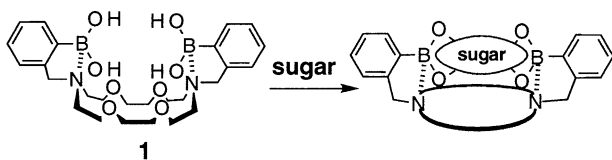
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(Received February 22, 1995)

A novel diaza-18-crown-6-based sugar receptor (**1**) bearing two boronic acids has been developed. In **1** boronic acids in the side arms and a metal cation bound to the crown cavity competitively interact as Lewis acids with amines. It was shown that sugars and metal cations can "communicate" each other in an allosteric manner.

Several groups are now keen on molecular design of artificial sugar interfaces based on boronic acid functions.¹⁻⁹ Boronic acids have a merit and a demerit, however: they can rapidly and reversibly form complexes with diol groups in sugars in an aqueous system but such complexation occurs significantly only in basic pH region because cyclic boronate esters are stabilized only in a sp³-hybridized boron atom and OH⁻ is indispensable for this. It was shown later that boronic acids bearing an appropriate intramolecular amine can bind sugars even in neutral pH region for the boron atom has been changed to sp³-hybridization through the B...N interaction.^{9,10} By using this concept several reading-out-type sugar interfaces have successfully been developed.⁹

The purpose of the present study is to design a new sugar receptor in which a sugar-binding site and a metal-binding site "communicate" each other. This system should be useful as a metal-controllable sugar receptor or a sugar-controllable metal receptor. We designed compound **1**: one can expect for **1** that boronic acids in the side arms and a metal cation bound to the crown cavity competitively interact as Lewis acids with two nitrogens in diaza-18-crown-6.



Compound **1** was synthesized from *o*-bromomethylphenylboronic acid and 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane in acetonitrile in the presence of K₂CO₃: yield 71%, mp. 291.6 - 293.2 °C. The product was identified by IR and ¹H NMR spectroscopic evidence.¹¹

Firstly, we estimated pK_a values for amines and boronic acids by using both photometric and potentiometric titrations. To avoid the possible metal-crown interaction we used choline OH⁻ as base. The pH-dependent change in the absorption spectra was observed. Although the absorption band at around 270 nm decreases monotonously, the change is apparently biphasic. From a plot of pH vs. A₂₇₂ (Figure 1A) we obtained three pK_a values: pK_{aN1} 4.87, pK_{aN2} 6.77 and pK_{aB} 12.2. Two equivalents of choline OH⁻ were consumed at pH 3 - 8 and at pH 8 - 11, respectively. Judging from our previous studies,⁹ they are assigned to first and second deprotonation of amines and dissociation of boronic acids.

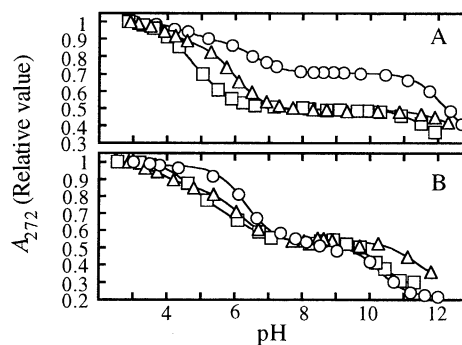
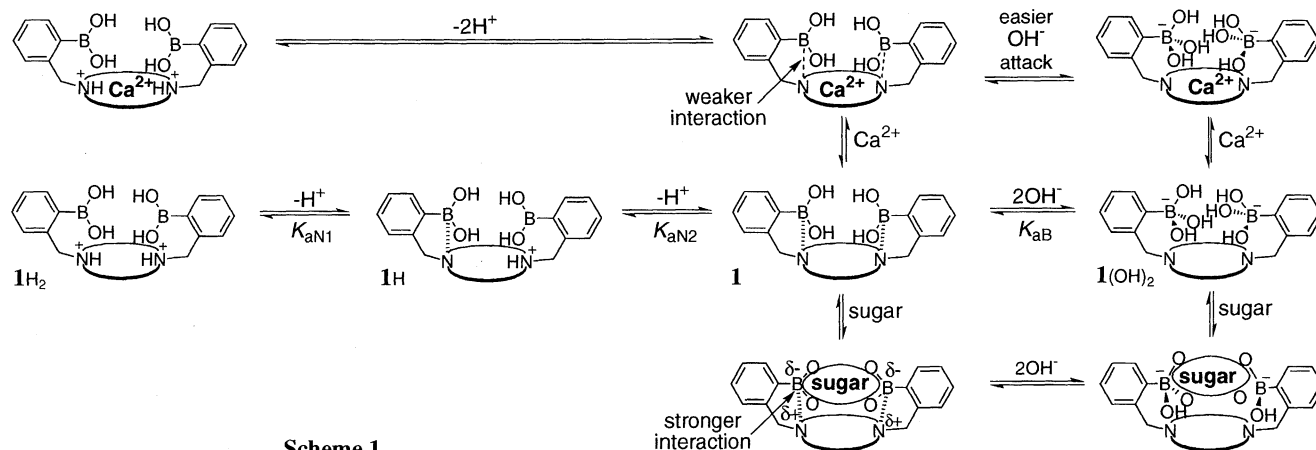


Figure 1. Plot of A₂₇₂ vs. pH. A: without Ca²⁺, B: with Ca²⁺ (added as perchlorate, 3.4 × 10⁻³ mol dm⁻³), (O) no sugar, (□) D-fructose (3.4 × 10⁻² mol dm⁻³), (Δ) D-glucose (3.4 × 10⁻² mol dm⁻³), [1] = 3.4 × 10⁻⁴ mol dm⁻³ in methanol - water 9:1 containing 0.05 M choline.

In the presence of sugars (3.4 × 10⁻² mol dm⁻³) the pK_{aN1} and the pK_{aN2} shifted to lower pH (pK_{aN1} 4.47 for D-fructose and 3.97 for D-glucose and pK_{aN2} 5.56 for D-fructose and 6.01 for D-glucose) whereas the pK_{aB} is affected only to smaller extent (pK_{aB} 11.6 for D-fructose and 12.1 for D-glucose). The finding indicates that sugar-boronic acid complexation, which makes the acidity of the boron atom stronger,^{2,9} facilitates dissociation of the nitrogen protons through the B...N interaction.

The plots for A₂₇₂ vs. [sugar] are shown in Figure 2. Here, one can consider that **1** forms a 1:1 complex with D-fructose or D-glucose for several reasons: that is, (i) the exciton coupling in CD spectroscopy, which appears only when two boronic acids are rigidified by ring closure with a monosaccharide,⁵ is observed (Figure 3), (ii) the Benesi-Hildebrand equation made from the data in Figure 2 assuming the formation of a 1:1 complex features a good linear relationship, and (iii) the association constants thus determined (K_{ass} = 2.6 × 10³ dm³ mol⁻¹ for D-fructose and 7 × 10⁴ dm³ mol⁻¹ for D-glucose) are much greater than those for the corresponding monoboronic acid (*o*-dimethylaminomethylphenylboronic acid): K_{ass} = 1.0 × 10³ dm³ mol⁻¹ for D-fructose and 6.3 × 10³ dm³ mol⁻¹ for D-glucose.

When Ca²⁺ was added, pK_a's of two amines became equal because the stabilization of second N⁺-H through an intramolecular hydrogen bond was disappeared by bound Ca²⁺. Thus, we obtained two pK_a values (pK_{aN} 6.33 and pK_{aB} 10.3; Figure 1B). Ca²⁺ competes with the boronic acids for the nitrogens, *i.e.*, the B...N interaction is weakened by the Ca²⁺...N interaction, so the pK_{aN} shifts to higher pH. Similarly, in dissociation of the boronic acids (*i.e.*, OH⁻ attack on the boron atom) the B...N interaction is weakened because of the Ca²⁺...N interaction, so that the pK_{aB} is lowered. Thus, the foregoing complexation processes are



Scheme 1.

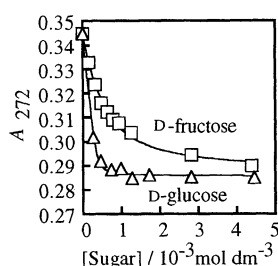


Figure 2. Plot of A_{272} vs. concentration of sugar: pH 8.5, $[1] = 3.4 \times 10^{-4} \text{ mol dm}^{-3}$.

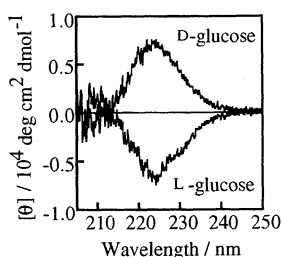


Figure 3. CD spectra of **1** ($9.1 \times 10^{-4} \text{ mol dm}^{-3}$) in the presence of D- and L- glucose ($6.4 \times 10^{-4} \text{ mol dm}^{-3}$): pH 8.5.

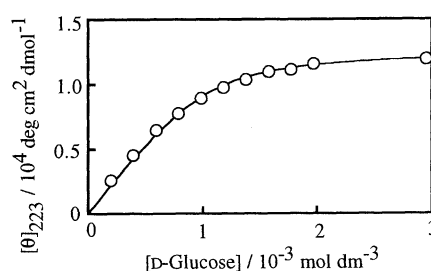


Figure 4. Plot of $[\theta]_{223}$ vs. [D-glucose] in the presence of Ca^{2+} ($2.0 \times 10^{-2} \text{ mol dm}^{-3}$): pH 8.5, $[1] = 1.0 \times 10^{-3} \text{ mol dm}^{-3}$.

summarized as in Scheme 1.

When sugar and Ca^{2+} coexist, as seen from Figure 1B, the $\text{p}K_{\text{a}}$'s of two amines split into two and the both $\text{p}K_{\text{aN}1}$ and $\text{p}K_{\text{aN}2}$ shift to lower pH region ($\text{p}K_{\text{aN}1}$ 4.70 for D-fructose and 3.82 for D-glucose and $\text{p}K_{\text{aN}2}$ 6.23 for D-fructose and 6.14 for D-glucose) whereas the $\text{p}K_{\text{aB}}$ scarcely changes ($\text{p}K_{\text{B}}$ 10.3 for D-fructose and 11.3 for D-glucose). Since the acidity of the boronic acid is strengthened by sugar complexation,^{2,9} the shift of $\text{p}K_{\text{aN}1}$ and $\text{p}K_{\text{aN}2}$ is attributable to the strengthened B...N interaction. On the other hand, the minor change in the $\text{p}K_{\text{aB}}$ implies that Ca^{2+} does not contribute to the boronic acid dissociation step: that is, the sugar-enhanced acidity has made the boronic acids more advantageous in the competitive interaction with the nitrogens. At present, we cannot explain why $\text{p}K_{\text{a}}$'s of two amines become different in the presence of both Ca^{2+} and sugar. Further study has to be carried out to answer the question.

As A_{272} was not affected by added sugars in the presence of Ca^{2+} (Figure 1B), the association constant for D-glucose in the presence of Ca^{2+} could be determined from the plot for $[\theta]_{223}$ vs. [D-glucose] shown in Figure 4. The smaller association constant ($K_{\text{ass}} = 1.1 \times 10^4 \text{ dm}^3 \text{ mol}^{-1}$) strongly supports that the Ca^{2+} bound to the crown cavity competes with boronic acids for the nitrogens.

In conclusion, the present study showed a novel example for the design of artificial sugar receptors in which sugar and Ca^{2+} interact with the binding-sites competitively. The influence of

other mono- and disaccharides and other metal cations is extensively being studied in this laboratory.

References and Notes

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- IR (KBr) 3304 (O-H) and 1376 cm^{-1} (B-O); ^1H NMR (CD_3OD) $\delta = 3.23$ (8H, t, $J = 5$ Hz, $\text{NCH}_2\text{CH}_2\text{O}$), 3.63 (8H, s, $\text{OCH}_2\text{CH}_2\text{O}$), 3.80 (8H, t, $J = 5$ Hz, $\text{NCH}_2\text{CH}_2\text{O}$), 4.22 (4H, s, CH_2Ar), and 7.15-7.65 (8H, m, aromatic).