Anomer-Selective Molecular Recognition of Free Amino Sugars with Simple Bisphosphonate Receptor Molecules

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Recently, we introduced xylylene bisphosphonates as a new class of selective artificial receptor molecules for 1,2- or 1,3-amino alcohols.[1] Now we found that these bisphosphonates represent highly efficient hosts for the complexation of amino sugars,[2] because they form cooperative hydrogen bonds between the phosphonates and their hydroxyl groups.[3] Contrary to most of the known synthetic sugar receptors with lipophilic *O*- or *S*-glycosidic substituents which must be examined in organic solvents, the bisphosphonates allow NMR titrations with free amino sugars in DMSO, methanol, or water. For α-D-glucosamine hydrochloride and **1**, we found 1:1-association constants in DMSO of 59 000 M^{-1} and in methanol of 630 M^{-1}. Even in water, weak binding is observed, indicated by a 0.1 ppm upfield shift of the C*H*N-proton. The complex geometry can be deduced from the NMR spectra. On phosphonate addition to glucosamine in DMSO, only the OH-1 and OH-3 protons are shifted downfield by ca. 1 ppm, whereas OH-4 and OH-6 remain untouched. Preorientation by the chelate between the phosphonates and the ammonium group obviously induces formation of two cooperative hydrogen bonds between the phosphonate and the hydroxyl groups adjacent to the NH_3^+-functionality (Figure 1). Recently it was suggested, that Nature uses a very similar binding motif, that is, the 1,2- and 1,3-amino alcohol moieties present in many aminoglycoside antibiotics recognize phosphodiesters (as present in RNA) by means of strong electrostatic as well as directed hydrogen bond interactions.[4]

To determine the degree of structure-selective recognition we examined four aminopyranoses and a synthetic open-chain amino sugar alcohol. None of these amino sugars carried any protecting groups which could have created differences in the steric demand of epimeric OH-groups. We performed NMR titrations in d_6-DMSO with anomeric mixtures of varying α,*β*-ratio (Figure 2).

The obtained binding curves had a distinct sigmoidal character for the weaker binding partner, whereas a relatively normal curve was found for the stronger one. This is typical for a system in which the receptor first binds preferentially to the guest with the higher binding constant. When saturation is reached, the NMR signals of the second guest begin to shift as usual (Figure 3).

For mannosamine and 6-aminodesoxyglucose, the experiments were complicated by a fast mutarotation catalyzed by the host compound.[5] Nevertheless, we could obtain quantitative results in all cases. To calculate both binding constants from one titration experiment, we used the competitive method described by

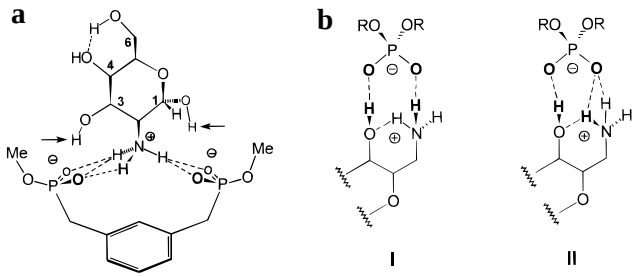

Figure 1. (a) Energy-minimized complex structure of α-D-glucosamine and bisphosphonate receptor molecule **1** according to force-field calculations; arrows indicate additional hydrogen bonding sites. (b) Two possible conformations of the 1,3-amino alcohol recognition motif by the RNA phosphodiester groups.[4]

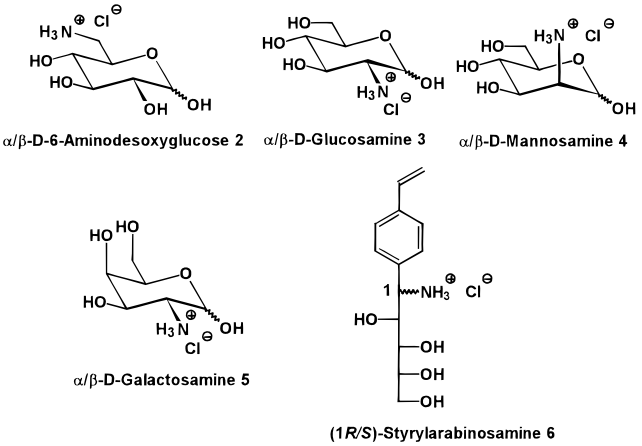

Figure 2. Amino sugars for the NMR titrations with bisphosphonate receptor molecule **1**.

Wilcox.[6] The results are given in Table 1; they were checked by using Whitlock's "sliding scales" technique[7], which produced similar relative ratios between the α- and *β*-association constants (see also Table 1). Curve fitting of the receptor signals to a 1:1-binding isotherm[8] gave apparent association constants for the respective anomeric mixture in the range of 10^4 to 10^5 M^{-1}, thus confirming the above calculations.

The binding constants of the 2-aminopyranosides are all in the same range. Sugar selectivity is found, however, when the ammonium functionality resides at the 6-position, leading to a 2−6-fold increase in K_a. The epimeric discrimination of receptor molecule **1** increases from **2**−**6** (i.e., from 13−90% de).[8b] Although the anomer selectivity for the different pyranosides does not exceed 51% de, it is remarkable, because it originates from the different strength of a single hydrogen bond between the bisphosphonate and the anomeric hydroxyl-OH in a competitive solvent. The high preference of the bisphosphonate for one epimer of the open chain aminosugar alcohol styrylarabinosamine **6**, however, is unprecedented.[9] It corresponds to a diastereomeric excess of 90%[8b] and must probably be explained by the different

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(3) Furthermore, the pK_a values of sugar hydroxyl groups are lower than those of the respective aliphatic alcohols. Hence, the more acidic sugar molecules should form stronger hydrogen bonds than aliphatic alcohols; Hamilton, A. D.; Das, G. *J. Am. Chem. Soc.* **1994**, *116*, 11139−11140.

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(5) Equilibration of both amino sugars in DMSO for one week resulted in no change; in water, only a slightly shifted anomer ratio was observed. The drastic change in the epimeric ratio reached in DMSO after receptor addition may in part be caused by the stabilization of the respective host−guest complex.

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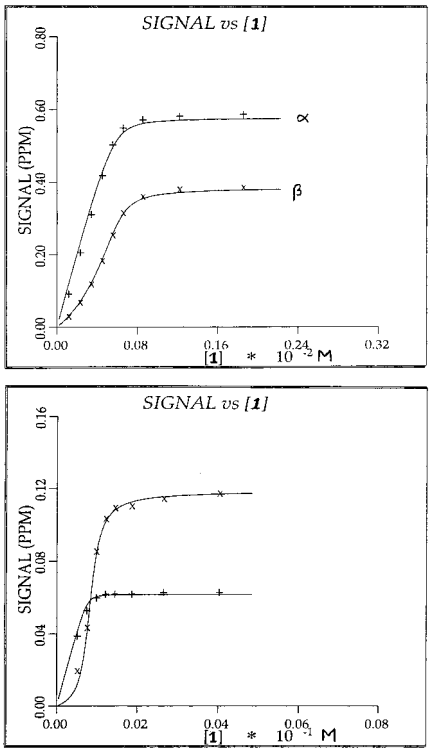

Figure 3. Top: Typical titration curve for **1**/mannosamine hydrochloride. Dependence of the change in chemical shift of the CH-1 protons of α- and *β*-anomer on addition of receptor molecule **1**. Bottom: Typical titration curve for the complex between **1** and styrylarabinosamine hydrochloride.

Table 1. Binding Constants for α- and *β*-anomers (C-1 epimers) between Amino Sugars [10^{-3} M] and the Receptor Molecule **1** in DMSO at 20 °C[a]

amino sugar	K_α [M^{-1}]	K_β [M^{-1}]	K_α/K_β[b]	K_α/K_β[c]	de [%][b]	de [%][c]
6-aminoglucose **2**	1.9×10^5	2.5×10^5	1:1.3	1:2.5	13	43
glucosamine **3**	5.7×10^4	9.2×10^4	1:1.6	1:2.0	24	33
mannosamine **4**	1.2×10^5	3.8×10^4	3.0:1	2.5:1	50	43
galactosamine **5**	3.3×10^4	1.0×10^5	1:3.1	1:2.7	51	44
styrylarabinosamine **6**	1.8×10^4	3.3×10^5	1:18.5[d]	1:9.1[d]	90	80

[a] Due to the strongly hygroscopic character of both titration partners, the d_6-DMSO solution contained ~0.1% of water. Each K_a value is the result of at least two independent titrations, which agreed in all cases within ±10% of the given value. Errors are standard deviations; they were estimated at 10−40% for $K_a \leq 10^5$ M^{-1} and at 30−50% for $K_a \geq 10^5$ M^{-1}. [b] According to the "competitive method".[6] [c] According to the "sliding scales method".[7] [d] Binding constants for the C-1 epimers.

sizes of the other three substituents at the stereogenic center (C-1).

Additional evidence for the strong binding of the *β*-anomer in 6-aminodesoxyglucose **2** comes from the NMR-experiments. In the 1:1-complex, the methylene protons of the C_{2v}-symmetrical receptor molecule become diastereotopic. Molecular dynamics calculations[10] offer a possible explanation, that is, only the *β*-anomer seems to be able to form an additional cooperative hydrogen bond between its OH-1 and the phosphonate. In this array which is also indicated by the high upfield-shift of the CH-1 proton (0.4 ppm), the OH-3 comes close to one of the receptor methylene protons and explains their magnetic nonequivalence (Figure 4).

Figure 4. Possible explanation for the diastereotopic character of the phosphonate methylene protons. Force-field optimized complex between the *β*-anomer of 6-aminodesoxyglucosamine and bisphosphonate receptor molecule **1**.[10] Several host and guest protons have been omitted for clarity.

Although several groups have been reporting on the enantioselective[11] and diastereoselective recognition[12] of sugar derivatives, they examined in most cases alkyl- or arylglycosides. In 1989, Aoyama[13] achieved selective extraction of free D-ribose α-pyranoside by a resorcinaldehyde cyclotetramer; two years later, Shinkai[14] introduced diphenylmethane diboronic acids which bind free D-glucose and their disaccharides in the α-form. To the best of our knowledge, we present the first example of an anomerselective molecular recognition of free aldohexoses by noncovalent interactions.

Experimental Section. 1-Amino-1-desoxy-1-(4-vinylphenyl)-D-gluco(D-manno)-pentitol 6. This amino sugar alcohol was prepared as a C-1 epimeric mixture from D-gluconolactone in 7 steps as a functional monomer for the polymerization to heparin-like compounds.[9] IR (KBr): $1/\lambda = 3320$(br), 2900, 1620, 1590, 1505. ^{1}H NMR (300 MHz, d_6-DMSO + D_2O): $\delta = 3.06-4.05$ (m, 6H), 5.22 (d, 1H, $J = 11.0$ Hz), 5.79 (d, 1H, $J = 17.6$ Hz), 6.72 (dd, $J = 11.0/17.6$ Hz), 7.33 (~dd, AA′BB′), 7.41 (~dd, AA′BB′). ^{13}C NMR (75 MHz, d_6-DMSO): $\delta = 57.5 + 58.1$, 63.4 + 63.5, 70.4 + 71.8, 71.1 + 72.44, 71.2 + 72.8, 113.4 + 113.5, 125.5, 125.6, 127.3, 127.5, 135.2, 135.4, 136.4, 136.5, 143.8, 144.0. MS (chem. ion. NH_3) *m*/*z* 254 [M^+ + H]. Elemental analysis: calcd. for $C_{13}H_{19}O_4N$ C 61.64, H 7.56, N 5.53; found C 61.53, H, 7.53, N 5.45.

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Supporting Information Available: Synthesis and characterization of **1**, Procedures for the NMR titrations and their evaluation, calculation of apparent binding constants, data sheets for the HOSTEST-program, calculation of relative ratios of binding constants, HOSTEST-printouts (4 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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