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Selective Sugar Binding with a Synthetic Polyhydroxy Macrocycle. A Remarkable Selectivity for Fructose over Glucose[1)]

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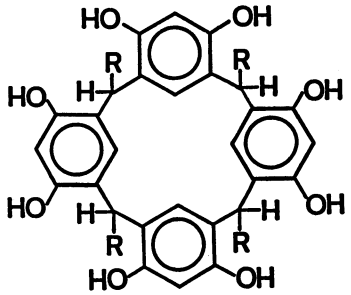
D-Fructore, a ketohexose, is readily solubilized in CCl_4 via complex formation with resorcinol-dodecanal cyclotetramer (1), in marked contrast to D-glucose, a closely related aldohexose, which shows almost no affinity to 1. The affinity of fructose can be further enhanced by oligomeric modification of 1.

Resorcinol-dodecanal cyclotetramer 1 has recently been shown to form hydrogen bonded complexes with sugars such as ribose in apolar organic media, where ribose is bound highly selectively in the α-pyranose form.[2)] The two factors governing the affinities of various aldoses (polyhydroxy aldehydes) to 1 have also been suggested; the stereochemistry of the 3-OH and 4-OH groups (cis >> trans) and the lipophilicity of the sugar molecule as a whole. Aldohexoses (R = CH_2OH where R is the substituent on 5-C of an α-pyranose ring) have lower affinities than aldopentoses (R = H) and 6-deoxyaldohexoses (R = CH_3) on this ground. Glucose, an aldohexose having trans 3-OH and 4-OH groups, thus shows almost no affinity to 1. Now, we wish to report that fructose, a ketohexose closely related to glucose, is readily bound with 1 and the affinity can be further enhanced by oligomeric modification of host 1.



1 ; R = $(CH_2)_{10}CH_3$

Vigorous stirring of a CCl_4 solution of 1 (7.2×10^{-3} M, 4.0 mL) with an aqueous solution (3.5 M, 0.8 mL) of D-fructose (2, in a Fischer projection formula)[3)] at 20 °C for 12 h resulted in extraction of 2 into the organic phase, in marked contrast to D-glucose (3) which could not be extracted under otherwise

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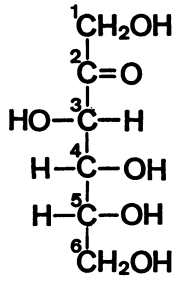
identical conditions. The sugar (2) extracted was completely reextracted with D_2O and was analyzed by means of ^1H NMR with CH_3CO_2Na as internal standard to give the molar ratio of 2 extracted to 1 used; (2/1) x 100 = 13% (Table 1). Varia-



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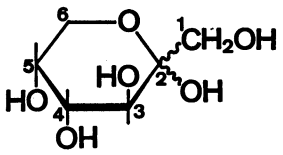

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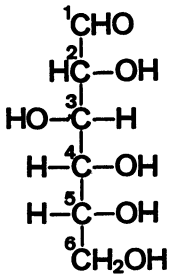

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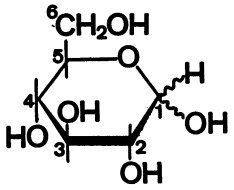


3′

Table 1. Extraction of Sugars with Hosts 1 and 5[a)]

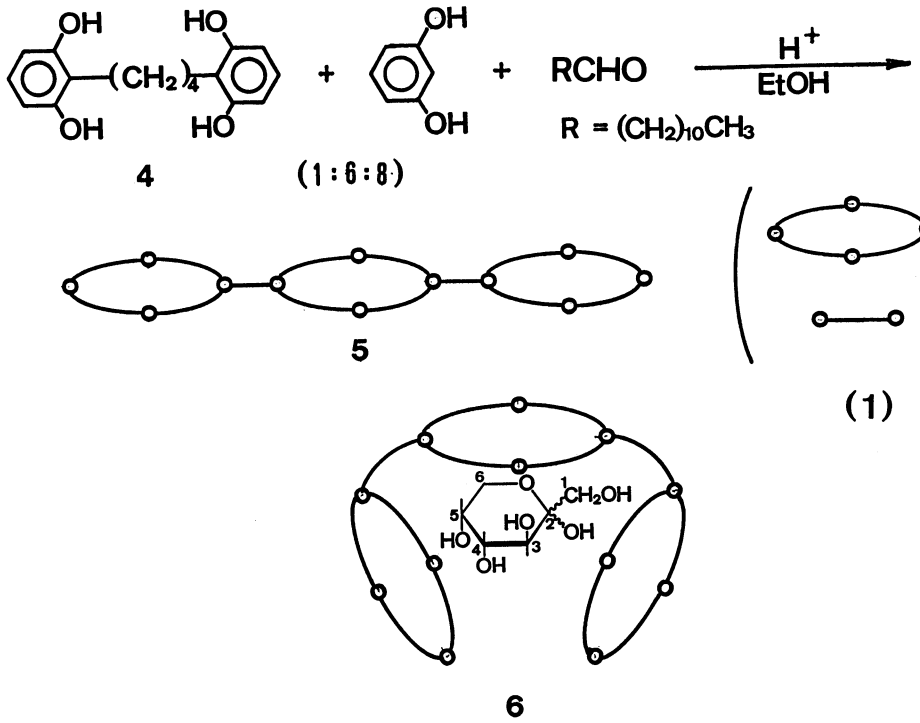
Host	Sugar/Host (%) Fructose (2)	Glucose (3)	Ribose
1	13	≈ 0	100
5	84	< 2	300

a) A CCl_4 solution of 1 (7.2×10^{-3} M) or 5 (7.0×10^{-3} M) was vigorously stirred with an aqueous solution of sugar (3.5 M) at 20 °C for 12 h. The amount of sugar extracted was determined by ^1H NMR after reextraction into D_2O.

tion in [1] in the organic phase had little effect on the ratio 2/1, and no solubilization of 2 was observed in the absence of 1. These results, as obtained for the extraction of ribose,[2)] are consistent with an apparent complexation equilibrium; $1_{org} + 2_{aq}$ (large excess) $\rightleftharpoons (1 \cdot 2)_{org}$. The remarkable selectivity for 2 over 3 was also confirmed by competitive extraction runs. Thus, from an equimolar mixture of 2 and 3 (2.3 M) was extracted 2 almost exclusively, as shown by the ^1H NMR spectum after reextraction into D_2O.[4)] Sugars exist predominantly as six-membered pyranoses in water. Glucopyranose (3') as an aldose shows a characteristic signal for the hemiacetalic 1-H in a lower field (δ 5.2), while fructopyranose (2') is a ketose and has no corresponding absorption. Distinction between 2 and 3 by means of ^1H NMR can be readily made on this ground. Apparently, 2 is closely related to 3; they have trans OH groups on 3-C and 4-C in the projection formulae. In fructopyranose (2'), however, 2-C becomes the anomeric center and, as a consequence, 4-C and 5-C with cis OH groups occupy the positions of 3-C and 4-C of glucopyranose (3'). A significant affinity of 2 to 1 in marked contrast to 3 is thus consistent with the selectivity observed for the binding of

aldoses; high-to-moderate affinities of ribo- and arabinopyranose having cis 3-OH and 4-OH vs. almost no affinities of xylo- and lyxopyranose having trans 3-OH and 4-OH.[2)]

The exocyclic CH_2OH group of a hexopyranose is not involved in the hydrogen bonding interaction with 1 and is only exposed to bulk solvent. This is why hexoses have significantly lower affinities to 1 than pentoses.[2)] The affinities of hexoses might be enhanced by suitable oligomeric modification of host 1 so as to allow sandwich-like encapsulation of bound sugars. An initial attempt along this line was to prepare a dimeric species of 1 having a covalently linked bis-resorcinol moiety as a bridging unit. Thus, acid catalyzed reaction of tetramethylene-bisresorcinol 4,[5)] resorcinol, and dodecanal in a molar ratio of 1:6:8 was carried out under similar conditions as for the preparation of 1. The product was purified by means of gel filtration (Sephadex LH-20 with $CHCl_3$-CH_3OH (1:1) as eluant) after exhaustive acetylation of the OH groups, and was found to be not a dimer but a trimer 5 (in a schematic representation, Eq. 1) possibly as a mixture of linkage isomers, the identification being based on the ^1H NMR spectrum and the molecular weight as determined by vapor pressure osmometry.[6)]



The sugar-binding ability of 5 was examined in a similar manner as above. The results are also shown in Table 1. A 300% binding (on a molar basis) of D-ribose, a high-affinity sugar, clearly indicates that each macrocycle in 5 binds a ribose molecule. On the other hand, the binding of 2 with 5 takes place with an 84% efficiency, which may roughly be approximated to 100% and is significantly larger than an expected value (13 x 3 = 39%) if the three macrocycles in 5 bind 2

independently. A cooperative binding of 2 with 5 is suggested, as schematically shown in 6. In marked contrast, glucose (3) still resists to be bound even with 5, indicating again that the stereochemistry of 3-OH and 4-OH groups is a decisive factor.

This work demonstrates a novel discrimination of closely related fructose and glucose in the host-guest type complexation via hydrogen bonding. Fructose is the sweetest natural sugar.[7] Isolation of fructose from an invert sugar, a mixture of fructose and glucose, is of industrial significance. The work also suggests that a better binding of sugars can be achieved by suitable modification of a host system so as to increase the area of host-guest interaction surface.[8] Further work now under way in this laboratory includes the preparation of polyhydroxy cavities as three-dimensional sugar receptors.

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3) C. P. Barry and J. Honeyman, Adv. Carbohydr. Chem., 7, 53 (1952); L. M. Verstraeten, ibid., 22, 229 (1967); M. Chen and R. L. Whistler, Adv. Carbohydr. Chem. Biochem., 34, 286 (1977).

4) The amount of sugar reextracted was evaluated by the ratio of ^{1}H NMR integration of the total sugar CH proton resonances to that of CH_3CO_2Na after calibration by authentic samples.

5) Prepared by the coupling of 1,4-diiodobutane and the 2-lithio derivative of resorcinol dimethyl ether, followed by demethylation of the resulting bis-resorcinol tetramethyl ether with pyridinium chloride. Cf; a) G. Wittig, Angew. Chem., 53, 241 (1940); b) L. H. Sommer and W. D. Korte, J. Org. Chem., 27, 4660 (1962); c) R. Filler, B. T. Khan, C. W. McMullen, ibid., 27, 4660 (1962).

6) The characteristic ^{1}H NMR absorptions of 5 for a $CDCl_3$ solution are δ 6.04 (s, 8H, 2-H on the aromatic ring), 7.13 (s, 12H, 5-H on the aromatic ring), and 9.20 and 9.51 (br s, each 24H, OH). Acetylation of 5 with acetic anhydride and pyridine gave the peracetylated derivative of 5 in a total yield of 32% after purification by means of gel filtration: δ 6.02 (br, 8H, 2-H on the aromatic ring), 6.90 (s, 12H, 5-H on the aromatic ring), and ca. 2.2 (br, ca. 70H, CH_3CO); ν_{CO} 1765 cm^{-1}. Molecular weight by means of vapor pressure osmometry for a C_6H_6 solution is 4490 (calcd for 5, 4434).

7) E.g., A. L. Lehninger, "Principles of Biochemistry," Worth Publishers, Inc., New York (1982).

8) For the enhancement of hydrophobic binding ability of cyclodextrin by capping, see: I. Tabushi, K. Shimokawa, N. Shimizu, H. Shirakata, and K. Fujita, J. Am. Chem. Soc., 98, 7855 (1976).

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