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HIGHLY STEREOSELECTIVE GLYCOSIDATION OF RIBOSE SOLUBILIZED IN APOLAR ORGANIC MEDIA VIA HOST-GUEST COMPLEXATION[1]

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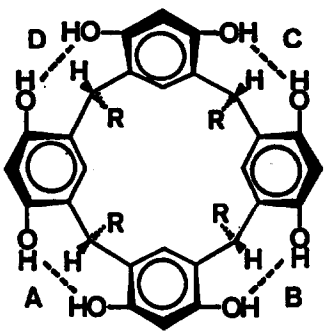
Summary: Ribose complexed with resorcinol-dodecanal cyclotetramer via hydrogen bonding in CCl_4 undergoes highly stereoselective glycosidation with methanol to give methyl β-ribofuranoside under mild and neutral conditions.

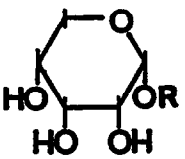
Ribose can be solubilized in CCl_4 upon formation of a hydrogen-bonded 1:1 complex with resorcinol-dodecanal cyclotetramer 1.[3] An interesting and important application of this complexation is development of a new synthetic chemistry of unprotected sugars in apolar organic media. We wish to report here that bound ribose undergoes glycosidation with methanol in a highly stereoselective manner.

Ribose actually exists as a cyclic hemeacetal, either six-membered pyranose (2p) or five-membered furanose (2f), each of which has a pair of α- and β-anomers. ^{13}C NMR spectroscopy of 1-ribose complex indicates that ribose is bound highly selectively in the α-pyranose form (2p-α), the ratio of anomers 2p-α /2p-β being approximately 10:1.[3b] Stirring for 24 h at room temperature of a CCl_4 solution (16 mL) of 1-ribose complex (1.0×10^{-2} M) and a 10-fold molar excess of methanol (1.0×10^{-1} M) resulted in a 100% conversion of ribose into methyl β-ribofuranoside (3f-β) as the almost exclusive glycosidation product; this was confirmed by ^{13}C NMR spectroscopy of the H_2O extract of the reaction mixture.[4] Riboside 3f-β was independently shown to form complex with 1.[5] Prolonged reaction times (≥ 48 h) promoted isomerization of the initial product (3f-β), leading to a mixture of all possible glycosides (3p-α, 3p-β, 3f-α, and 3f-β). The amount of mathanol was important; use of a 50- (5.0×10^{-1} M) or 100-fold molar excess of methanol (1.0 M) resulted only in recovery of unreacted ribose.

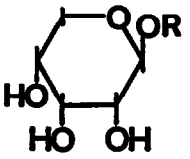
Methanol, like other alcohols,[6] was independently found to form complex with 1. The ^1H NMR spectrum of a $CDCl_3$ solution of 1-ribose complex (1.0×10^{-2} M) and CD_3OD (2.2×10^{-1} M) showed characteristic C-H proton resonances (especially, readily detectable one at 0.19 ppm)[3b] for bound ribose (2p-α). These signals, however, completely disappeared upon



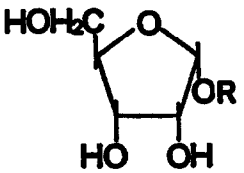
1 ; R = $(CH_2)_{10}CH_3$



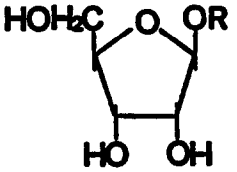
2p-α ; R = H
3p-α ; R = CH_3



2p-β ; R = H
3p-β ; R = CH_3



2f-α ; R = H
3f-α ; R = CH_3

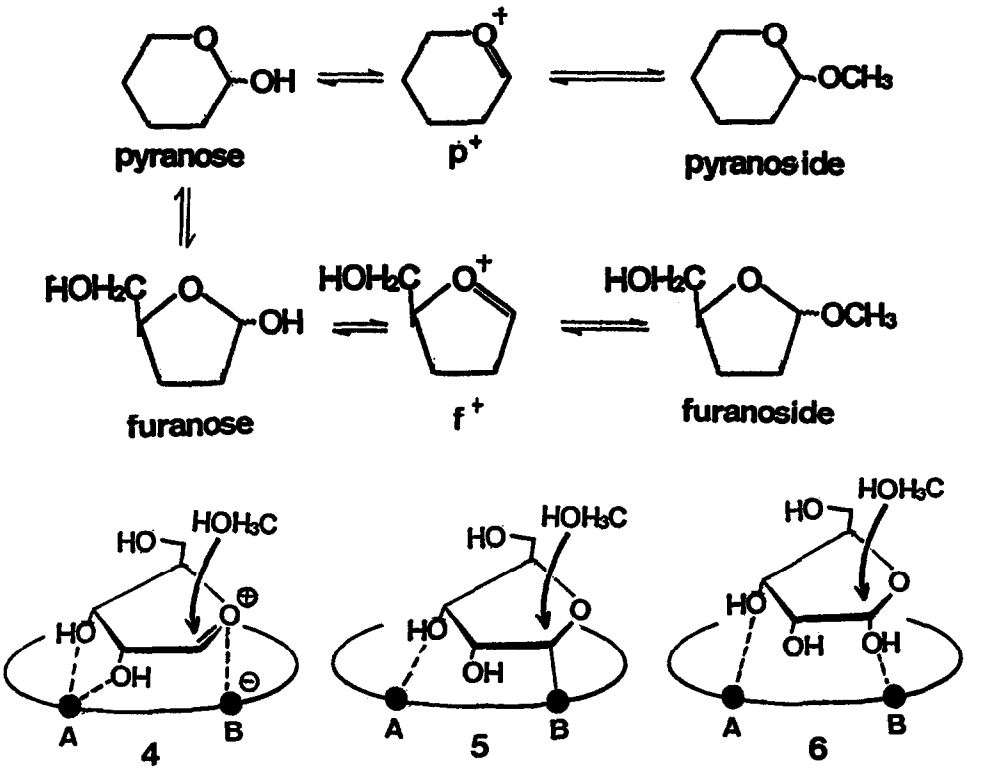


2f-β ; R = H
3f-β ; R = CH_3

addition of more CD_3OD (4.4×10^{-1} M), indicating that methanol molecules at that concentration range expel bound ribose and occupy the binding sites (A, B, C, and D) of 1. This is presumably why glycosidation at higher methanol concentration (5.0×10^{-1} or 1.0 M) does'nt work.

Methyl glycosides can be conveniently obtained by treating a mixture of sugar and methanol with acid such as HCl and H_2SO_4;[7,8] the initial formation of furanoside as the kinetic product is followed by its gradual conversion to pyranoside which is thermodynamically more stable. The mechanism involves protonation of the anomeric OH group of furanose or pyranose and subsequent loss of H_2O to give five-membered or six-membered oxonium ion ($\underline{f}^+$ or $\underline{p}^+$, respectively), followed by its capture by methanol to afford methyl furanoside or pyranoside (Scheme I, where substituents other than 1-OH are omitted).[9] All the steps are reversible, and a key point is that $\underline{f}^+$ is more readily formed than $\underline{p}^+$ so that initial formation of furanoside is favored under kinetic conditions, but pyranoside which is *less* labile accumulates later. This is also what was observed in the present glycosidation of ribose as promoted by 1 in CCl_4, although such a high selectivity for β-furanoside as observed here can not be realized in the conventional CH_3OH-HCl procedure. The similarity in the overall features suggests that the mechanisms involved are also similar. The implication of this is two fold. First, a pair of OH groups (A, B, C, and D) of 1 as the site of hydrogen-bonding interaction with 1-OH of bound ribose act as an acid catalyst. Second, the precursors of 3f and 3p are interconvertible. The precursor of 3f may be a five-membered oxonium ion

Scheme I



($\underline{f}^+$) complexed with deprotonated anion of $\underline{1}$ ($\underline{4}$),[10] a $\underline{1}$-sugar glycoside intermediate ($\underline{5}$),[10] or simply a hydrogen-bonded complex ($\underline{6}$).[10] The identification must await further elucidation; a fundamental question is whether or not the intimate ion-pair ($\underline{4}$) can be formed in such an apolar solvent as CCl_4. The highly selective formation of the β-anomer ($\underline{3f}$-β), on the other hand, suggest that the sugar moiety in the precursor is bound with $\underline{1}$ so as to allow attach of methanol only from the β-direction for steric reasons, as schematically shown in $\underline{4}$-$\underline{6}$.

Sugars are not soluble in most organic solvents. They have many OH groups which are not distinguished readily. They constitute a family of closely related stereoisomers. These are major difficulties encoutered in the synthetic chemistry of sugars. Under these circumstances, one of the most important guiding principles in the current synthetic chemistry of sugars is selective protection-deprotection of OH groups. The host-guest complexation via hydrogen bonding, on the other hand, seems to provide a new strategy to overcome these difficulties. Sugars are solubilized in apolar organic media,[3] in which various reactions may be

carried out. The OH groups of solubilized sugars are distinguished at least to some extent on the basis of whether or not they are involved in the hydrogen bonding with host.[3b] The complexation is highly stereoselective with respect to both the anomeric and other centers.[3,11] Furthermore, the hydrogen bonding which is essential for the complexation is a potential source of acid catalysis. The present reaction takes advantage of solubilization, acid catalysis, and stereoselectivity. The glycosidation itself is a simple reaction, but the present one is presumably the first example of synthetic reactions of unprotected sugars in apolar organic media under mild and neutral conditions.

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4. ^{13}C NMR data for 3f-β in D_2O; δ 55.0 (CH_3), 62.6 (5-C), 70.7 (2-C), 74.1 (3-C), 82.7 (4-C), and 107.8 (1-C).

5. ^{13}C NMR data for 3f-β bound with 1 in $CDCl_3$; δ 52.9 (CH_3), 62.5 (5-C), 70.0 (2-C), 74.3 (3-C), 82.5 (4-C), and 107.0 (1-C).

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10. A filled circle and that with negative charge represent an OH pair (Ar-O-H---OH-Ar) and a deprotonated OH pair (Ar-O-H-----$\bar{O}$-Ar).

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