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^{1}H-NMR STUDIES OF (6R)- AND (6S)-DEUTERATED D-HEXOSES: ASSIGNMENT OF THE PREFERRED ROTAMERS ABOUT C5-C6 BOND OF D-GLUCOSE AND D-GALACTOSE DERIVATIVES IN SOLUTIONS

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Summary: The conformational analysis of the hydroxymethyl groups of free, acetylated and benzoylated D-glucopyranoses and D-galactopyranoses was described based on the ^{1}H-NMR spectra of sugars chirally deuterated at C6.

The conformational analysis of the rotamers arising from the C5-C6 bond of D-hexopyranoses or 1,6-bonded saccharides is one of the important, however unsettled problems in the stereochemical studies of sugars. The two physical methods, optical rotation[1,2,4)] and NMR[3-6,8-11)] have been used to solve the problem. Hall et al.[3)] reported the preferred rotamer of acetylated D-glucose to be GL (Fig. 1) based on the ^{1}H-NMR data. On the other hand, Lemieux and Martin[4)] suggested that of free and acetylated D-glucoses to be GR by their NMR and optical rotational study. The discrepancy between the two chemists was attributed to the difficulty to differenciate the two protons at C6, H6R and H6S, which were the key informations for the study. Recently, Lew and Nakanishi calculated the preferred rotamers of benzoylated D-glucose and D-galactose to be GL and T, respectively based on their 'dibenzoate rule'.[7)] However, it is still uncertain whether the result can be extended to their free or acetylated sugars.

In our previous reports,[12,13)] we showed a stereospecific synthesis of (6R)- and (6S)-(6-$^{2}H_{1}$)-D-glucose[12)] and D-galactose.[13)] In these compounds, the stereoselective replacement of one of the methylene protons at C6 by deuterium ($^{2}H_{1}$) enables us to differenciate the H6R and the H6S signals in the ^{1}H-NMR spectra together with their coupling constants, δH6R and δH6S and coupling constants $J_{H5,H6R}$ and $J_{H5,H6S}$. In this report, we discuss the conformational analysis of hydroxymethyl groups in methyl α-D-glucopyranoside and D-galactopyranoside (II and V, Table), their acetylated derivatives (III and VI) and benzoylated derivatives (IV and VII). To examine the solvent effect ^{1}H-NMR spectra of II and V were measured in three different solvents, i.e., D_2O, 5% D_2O/dimethylsulfoxide-d_6 (DMSO-d_6) and DMSO-d_6.

The results, shown in Fig. 2 and Table are summarized as follows.

1) The H6R and the H6S peaks were clearly differenciated and showed their coupling constants and chemical shifts.
2) The coupling constants showed the rotamer distributions in D-glucose deri-

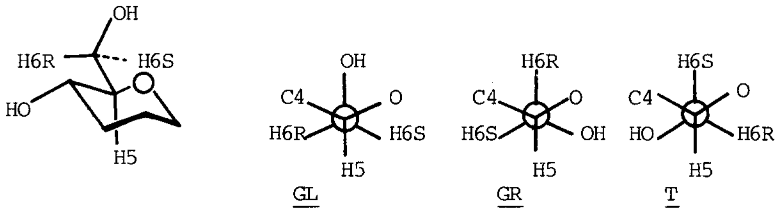

Fig. 1 The Possible Rotamers about C5-C6 Bond, GL, GR and T.

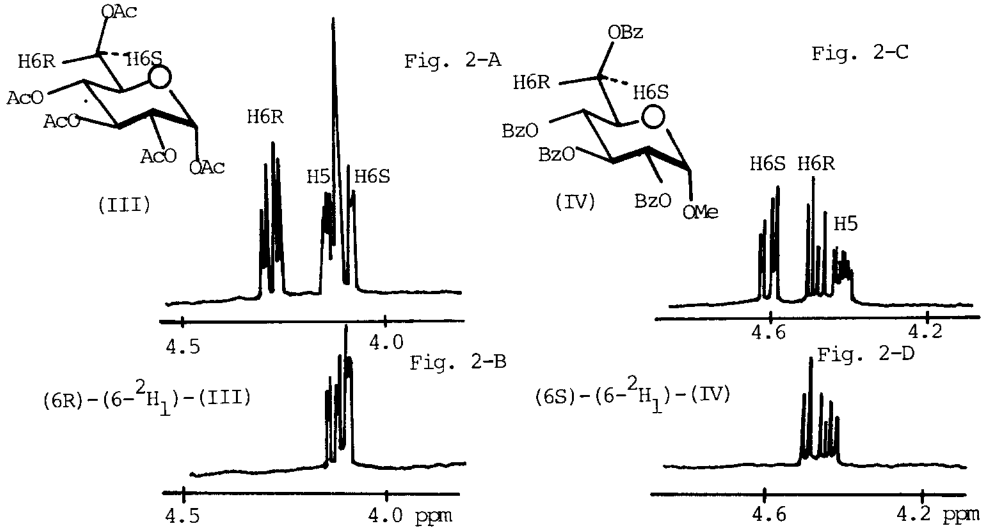

Fig. 2 400 MHz ^{1}H-NMR Spectra of Penta-O-Acetyl-α-D-Glucopyranose (III) and its (6R)-Deuterated Derivative, (Fig. 2-A and B) and Methyl Tetra-O-Benzoyl-α-D-Glucopyranoside (IV) and its (6S)-Deuterated Derivative, (Fig. 2-C and D). NMR spectra were measured on a JEOL JNM FX 400 Spectrometer with an Internal TMS Standard in $CDCl_3$.

vatives (I-IV) as GL $>$ GR $\gg$ T and in D-galactose derivatives (V-VII) as GR, T $>$ GL.

3) D-Glucose derivatives gave almost the same distributions independent of the solvent and the derivatization, while D-galactose derivatives showed significant changes in the distributions due to the solvent and the derivatization.

The above rotamer distributions could be explained by the interaction between C6-OR and -OR' in the vicinity. Thus, in D-glucose derivatives the population of T was very low due to the unfavored interaction between C6-OR and C4-OR in syn-diaxial relation.[3,4] GL is more popular among them than GR because of the favored exo conformation over the pyranose ring as well as of the stabilizing gauche effect.[3,11] In D-galactose derivatives, the lower population of GL could be understood by the similar syn-diaxial interaction. The change of ratio of GR and T due to the solvnet and the derivatization might be determined by the balance of the two destabilizing effects, exoanomeric effect between C6-OR and C5-O- and steric effect between C6-OR and C4-OR (or C4-H) in syn relation. The former destabilizes GR and the latter does T, respectively. Since the latter is expected to increase as the increment of the bulkiness of the substituents at C6 or C4, the solvent and the derivatization effects of D-galactoses can be rationalized. The higher population of GR in IV than V may be attributed to the strong solvation effect to increase the bulkiness of C6-OH (or C4-H). Here, the exceptional T preference of benzoylated D-galactose (VII) in

Table The Rotamer Populations about C5-C6 Bond of Hexopyranoses.

	Compounds	Solvents	δ (ppm) H6R	δ (ppm) H6S	$J_{H5,H6}$ (Hz)[a] H5,H6R	$J_{H5,H6}$ (Hz)[a] H5,H6S	Rotamers (%)[b] GL	Rotamers (%)[b] GR	Rotamers (%)[b] T
(I)	D-Glucopyranose								
	α anomer	D_2O	3.76	3.85	5.8	1.0	56	44	0
	β anomer	D_2O	3.72	3.90	6.0	2.1	53	45	2
(II)	Methyl-α-D-glucopyranoside	D_2O	3.76	3.89	5.4	2.3	57	38	5
		5% D_2O/DMSO-d_6	3.50	3.70	5.9	1.5	55	45	0
		DMSO-d_6	3.49	3.65	6.1	1.0	53	47	0
(III)	Penta-O-acetyl-α-D-glucopyranose	$CDCl_3$	4.28	4.08	4.3	2.1	68	28	4
(IV)	Methyl tetra-O-benzoyl-α-D-glucopyranoside	$CDCl_3$	4.50	4.62	5.1	2.9	57	32	11
		50% C_6D_6/$CDCl_3$	4.43	4.56	5.0	2.9	57	31	12
(V)	Methyl-α-D-galactopyranoside	D_2O	3.70	3.70	7.8	6.0	14	47	39
		5% D_2O/DMSO-d_6	-[c]	-	6.6	-	-	-	-
		DMSO-d_6	-	-	6.3	-	-	-	-
(VI)	Penta-O-acetyl-α-D-galactopyranose	$CDCl_3$	4.07	4.12	6.4	6.4	25	30	45
(VII)	Methyl tetra-O-benzoyl-α-D-galactopyranoside	$CDCl_3$	4.61	4.41	-	8.8	-	-	80
		50% C_6D_6/$CDCl_3$	4.57	4.30	7.1	5.7	22	41	37

a) $J_{H5,H6} \pm 0.2$Hz. c) The value could not be obtained because of the overlap of the signals.

b) The ratio of GL, GR and T was calculated with following equations,[11,14)]

$$1.3\,GL + 2.7\,GR + 11.7\,T = J_{H5,H6S} \quad \text{--- 1}$$

$$1.3\,GL + 11.5\,GR + 5.8\,T = J_{H5,H6R} \quad \text{--- 2}$$

$$GL + GR + T = 1 \quad \text{--- 3}$$

$CDCl_3$ is worth to discuss. This might be due to the specific intramolecular attractive effect between the two aromatic groups at C4 and C6.[16] The destruction of the effect by adding benzene to the solution means the formation of the competitive intermolecular attraction with benzene.

Although it was reported that the H5S proton shifted at a lower field than the H5R in D-pentofuranoside in aqueous solution,[11] the rule was not kept in D-hexopyranoside derivatives or possibly in D-pentofuranoside derivatives. This means that the chemical shift has less diagnostic value to differenciate the two protons at $-CH_2OR$. In benzoylated derivatives in $CDCl_3$, our results accorded with those obtained from dibenzoate rule.[7] Here, it should be noted that care should be taken to extend the result to other derivatives. In D-glucose derivatives, free and acetylated sugars had almost the same rotamer distributions as benzoylated sugar, while in D-galactose derivatives, free and acetylated sugars gave the different distributions from those of benzoylated sugar. Some discrepancies between Lemieux and Hall's results in acetylated or free glucoses could be settled by our results that GL and GR is about 7:3 to 5:5.

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