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^{1}H NMR Study on Intramolecular Hydrogen Bonding in 2,3-*O*-Isopropylidene-D-ribofuranosides and Their 5(4)-Hydroxy Derivatives

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Abstract—^{1}H NMR study showed the possibility for intramolecular hydrogen bonding in 5(4)-hydroxy derivatives of 2,3-*O*-isopropylidene-β-D-ribofuranose in $CDCl_3$. The obtained data were used to interpret differences in the ^{1}H NMR spectra of structurally related 5-halo-2,3-*O*-isopropylidene-D-ribofuranosides and four newly synthesized diastereoisomeric 5-bromo-5-deoxy-4-hydroxy-2,3-*O*-isopropylidene-D-ribofuranosides.

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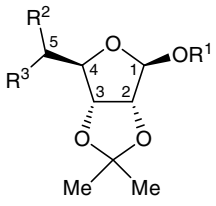
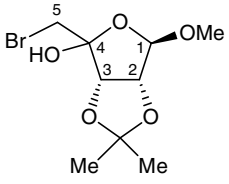
In the recent years, chiral blocks composed of sugars have found extensive application in target-oriented syntheses of natural compounds and their analogs [1–3]. This is explained by accessibility of a large number of sugars with known configuration of chiral centers and possibility for appropriate choice of required subunits for target molecules. Derivatives of D-ribose are successfully used in the synthesis of various biologically active cyclopentane-based compounds, such as prostaglandins, carbonucleosides, cyclopentane antibiotics, etc.

While studying the synthesis of cyclopentenone building blocks from D-ribose, we revealed that the assignment of NMR signals and values of spin–spin coupling constants for compounds **I**–**III** [4–6], **IV** [7], **V**, **VI** [8], and **VII**–**X** [9] are not always unambiguous and that interpretations of the spectral data are often superficial. In the present work we performed a thorough analysis of the ^{1}H NMR spectra of known D-ribofuranosides **I**–**III** which were synthesized according to known procedures [4–6] and newly synthesized bromide **XI** (Tables 1–4) and diastereoisomeric bromohydrins **XIIa**–**XIId** [10] (Table 5).



I–**XI**



XII

I, $R^1 = R^2 = H$, $R^3 = OH$; **II**, $R^1 = Me$, $R^2 = H$, $R^3 = OH$; **III**, $R^1 = Me$, $R^2 = H$, $R^3 = I$; **IV**, $R^1 = Me$, $R^2 = H$, $R^3 = TsO$; **V**, $R^1 = Me$, $R^2 = H$, $R^3 = AcO$; **VI**, $R^1 = Me$, $R^2 = H$, $R^3 = MeSCH_2O$; **VII**, $R^1 = Me$, $R^2 = R^3 = PhSC(NO_2)$; **VIII**; $R^1 = Me$, $R^2 = MeOCO$, $R^3 = TsO$; **IX**, $R^1 = Me$, $R^2 = MeOCO$, $R^3 = N_3$; **X**, $R^1 = Me$, $R^2 = PhSCO$, $R^3 = OH$; **XI**, $R^1 = Me$, $R^2 = H$, $R^3 = Br$.

The ^{1}H NMR spectra of all the examined compounds contained intense signals at δ 1.5 and 3.5 ppm due to protons in methyl and methoxy groups. No coupling was observed between 1-H and 2-H and between 3-H and 4-H, indicating that the dihedral angles between the corresponding C–H bonds are equal to 90° (an exception was compound **XIIc**, for which $J_{1,2}$ = 3.6 Hz). The coupling constant between 2-H and 3-H is 5.6–6.0 Hz. Methylene protons 5-H_a and 5-H_b are diastereotopic; their magnetic nonequivalence gives rise to different chemical shifts and a geminal coupling constant ^2J of 10–11 Hz.

Compounds **III** and **XI** (Table 1) showed in the spectra couplings between 4-H and each proton on C^5: $J_{5a,4}$ = 10.0, $J_{5b,4}$ = 6.0 Hz. The C^5H_2 protons in molecule **II** are coupled with both 4-H ($J_{5a,4}$ = 3.5, $J_{5b,4}$ = 2.8 Hz) and hydroxy proton; this interaction is characterized by *trans*-coupling along the C^5–O bond with a constant $J_{5a,OH}$ of 10.0 Hz) and *cis*-coupling with

Table 1. Proton chemical shifts (δ, ppm) in the ^{1}H NMR spectra of D-ribofuranosides **I–III** and **XI** ($CDCl_3$, 20°C)

Comp. no.	1-H	2-H	3-H	4-H	5-H$_a$	5-H$_b$	C^{1}OR[a]	C^{5}OH	Me	Me
I	5.36 d	4.76 d	4.52 d	4.33 br.s	[3.52] m	[3.70] m	5.60 d	4.30 br.s	1.25 s	1.45 s
II	4.90 s	4.82 d	4.60 d	4.45 d.d	3.62 d.d.d	3.70 d.d.d	3.36 s	3.25 d.d	1.32 s	1.50 s
III	5.05 s	4.74 d	4.62 d	4.42 d.d	3.18 t	3.27 d.d	3.36 s		1.32 s	1.47 s
XI	5.00 s	4.77 d	4.62 d	4.49 d.d	3.32 t	3.44 d.d	3.35 s		1.33 s	1.49 s

[a] **I**: R = H; **II**, **III**, **XI**: R = Me.

Table 2. Spin–spin coupling constants (J, Hz) in the ^{1}H NMR spectra of D-ribofuranosides **I–III** and **XI** ($CDCl_3$, 20°C)

Compound no.	$J_{1,OH}$	$J_{2,3}$	$J_{5a,5b}$	$J_{4,5a}$	$J_{4,5b}$	$J_{5a,OH}$	$J_{5b,OH}$
I	5.6	6.0	–	–	–	–	–
II	–	6.0	10.0	3.5	2.8	10.0	2.8
III	–	6.0	10.0	10.0	6.0	–	–
XI	–	6.0	10.0	10.0	5.9	–	–

Table 3. Proton chemical shifts (δ, ppm) in the ^{1}H NMR spectra of D-ribofuranosides **I**, **II**, and **XI** (DMSO-d_6, 20°C)

Comp. no.	1-H	2-H	3-H	4-H	5-H$_a$	5-H$_b$	1-OH (Me)	5-OH	Me	Me
I	5.15 d	4.69 d	4.45 d	3.99 d.d	3.40 d.d.d	3.44 d.d.d	6.50 d	4.95 t	1.24 s	1.36 s
II	4.86 s	4.65 d	4.52 d	4.00 d.d	3.30 d.d.d	3.40 d.d.d	3.20 s	4.82 t	1.26 s	1.35 s
XI	5.00 s	4.74 d	4.62 d	4.24 t	3.50 m	3.50 m	3.35 s	3.45 d.d	1.26 s	1.38 s

Table 4. Spin–spin coupling constants (J, Hz) in the ^{1}H NMR spectra of D-ribofuranosides **I**, **II**, and **XI** (DMSO-d_6, 20°C)

Compound no.	$J_{1,OH}$	$J_{2,3}$	$J_{5a,5b}$	$J_{4,5a}$	$J_{4,5b}$	$J_{5a,OH}$	$J_{5b,OH}$
I	4.9	6.0	10.0	5.1	7.4	5.6	5.6
II	–	6.0	10.0	5.8	10.0	5.8	5.8
XI	–	5.9	–	8.0	7.6	–	–

Table 5. ^{1}H NMR spectra (chemical shifts δ, ppm, and coupling constants J, Hz) of stereoisomers **XIIa–XIId** ($CDCl_3$, 20°C)

Comp. no.	1-H	2-H	3-H	5-H$_a$	5-H$_b$	OMe	4-OH	Me	Me
XIIa	5.03 s	4.80 d (J = 5.7)	4.69 d (J = 5.7)	3.43 d.d (J = 11.0, 1.5)	3.66 d (J = 11.0)	3.45 s	4.43 d (J = 1.5)	1.32 s	1.47 s
XIIb	4.95 s	4.63 d (J = 5.9)	4.77 d (J 5.9)	3.62 d (J = 10.8)	3.68 d (J = 10.8)	3.38 s	3.40 s	1.39 s	1.56 s
XIIc	5.26 d.d (J = 12.5, 3.6)	4.63 d.d (J = 5.9, 3.6)	4.58 d (J = 5.9)	3.61 d (J = 11.3)	3.60 d (J = 11.3)	3.31 s	4.03 d (J = 12.5)	1.41 s	1.55 s
XIId	5.35 d (J = 9.8)	4.77 d (J = 5.7)	4.62 d (J = 5.7)	3.62 d (J = 11.3)	3.60 d (J = 11.3)	3.40 s	2.99 d (J = 9.8)	1.35 s	1.48 s

a constant $J_{5a,OH}$ of 2.8 Hz. Correspondingly, the hydroxy proton resonates as a doublet of doublets. Raising the temperature to 50°C leads to upfield shift of the doublet of doublets located at δ 3.25 ppm by about 0.7 ppm, which confirms the above assignment. No changes in the spectral pattern were observed upon dilution; this means that intermolecular hydrogen bonds are not formed. Presumably, the hydroxy proton is involved in intramolecular hydrogen bond with the oxygen atom in the tetrahydrofuran ring; the five-membered H-chelate ring thus formed fixes the 4-H proton in pseudoequatorial position, and the coupling

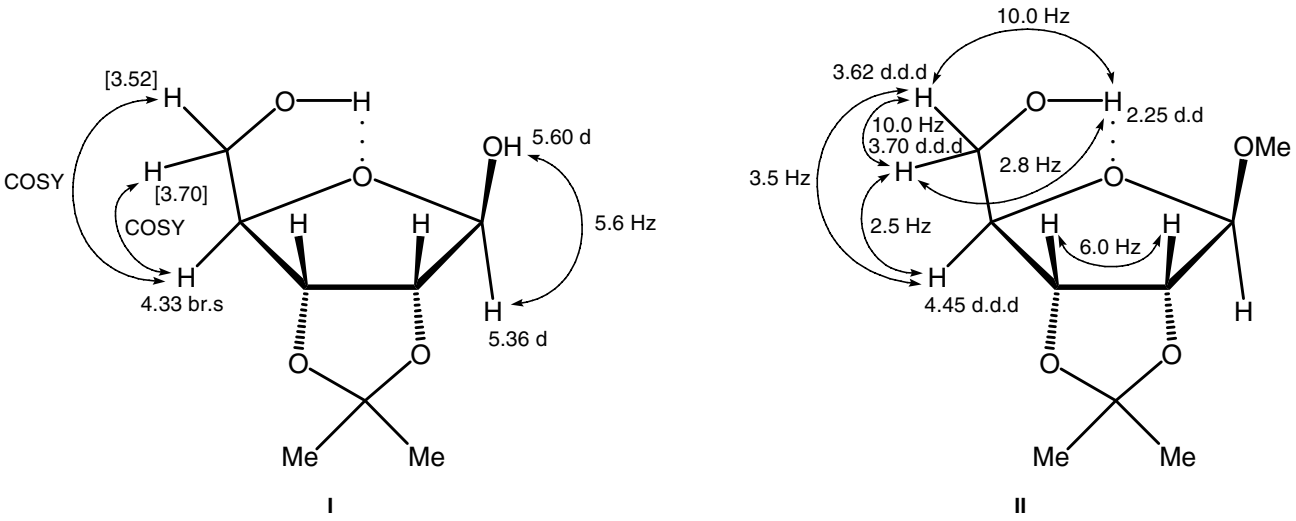


Fig. 1. Conformations of molecules **I** and **II** in a 5% solution in $CDCl_3$.

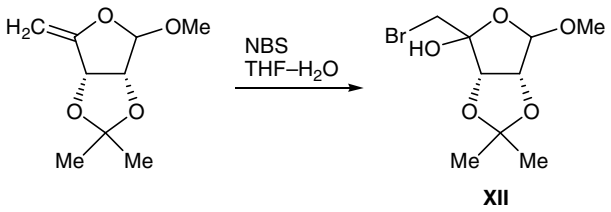
constants $J_{4,5a}$ and $J_{4,5b}$ are small. According to published data [5], the hydroxy proton appeared as a broadened singlet, and no coupling constants with 5-H were given.

The ^{1}H NMR spectrum of **II** changes in going to anhydrous DMSO-d_6, for the latter disrupts hydrogen bonds. As a result, the hydroxy group can freely rotate about the C–O bond, and the OH signal appears as a triplet, $J_{OH,5a} = J_{OH,5b} = 5.8$ Hz. The coupling constants for 4-H approach those found in halogen derivatives **III** and **XI**. Figure 1 shows the structures of molecules **I** and **II** in $CDCl_3$.

Most signals in the ^{1}H NMR spectrum of 2,3-*O*-isopropylidene-β-D-ribofuranose (**I**), recorded from a solution in $CDCl_3$, are either poorly resolved multiplets or broadened singlets. Therefore, the signals were assigned on the basis of two-dimensional COSY HH and CH CORR spectra. The COSY spectrum displayed cross peaks at δ 3.52–4.30 and 3.70–4.33 ppm, indicating that the hydroxy proton is coupled with diastereotopic protons of the C^5H_2 group and that intramolecular hydrogen bond is formed in molecule **I** in a way similar to **II**. The 1-OH proton is not involved in hydrogen bonding, and its signal is a doublet with $J_{OH,1} = 5.6$ Hz. In DMSO-d_6, the coupling constants are similar to the corresponding constants in **III** and **XI** (as with compound **II**).

The above data turned out to be useful for structure determination of bromohydrins **XII** which were synthesized by treatment of methyl 2,3-*O*-isopropylidene-4-methylidene-β-ribofuranoside with *N*-bromosuccinimide in aqueous THF [10] (Scheme 1). Isomer mixture **XIIa**–**XIId** was separated by column chromatography into diastereoisomer pairs **XIIa/XIIb** (55:45) and **XIIc/XIId** (65:35) (the diastereoisomer ratios were determined from the intensity ratios of the methoxy proton signals in the ^{1}H NMR spectra).

Scheme 1.



XII

Proton signals in the ^{1}H NMR spectra of diastereoisomers **XIIa**–**XIId** (Table 5, Fig. 2) were assigned taking into account the effect of electron-withdrawing substituent, which induces downfield shift of signals from vicinal *trans*-oriented protons. Signals of the β-oriented 1-H and 2-H protons in isomers **XIIa** and **XIId** having α-methoxy group are located in a weaker field (by 0.1–0.2 ppm) relative to the corresponding signals of isomers **XIIb** and **XIIc** due to *trans*-vicinal interaction with the oxygen atoms on C^2 and C^1, respectively. The 3-H proton in **XIIb** and **XIId** interacts in a similar way with the oxygen atom of the hydroxy group on C^4; therefore, its signal (δ 4.77 and 4.62 ppm for **XIIb** and **XIId**, respectively) is displaced downfield relative to the 3-H signal of **XIIa** (δ 4.69 ppm) and **XIIc** (δ 4.58 ppm).

trans-Effect of the oxygen atom in **XIIa**–**XIId** also extends to the OH proton. This proton in isomers **XIIa** and **XIIc** resonates about 1 ppm downfield (δ 4.43 and

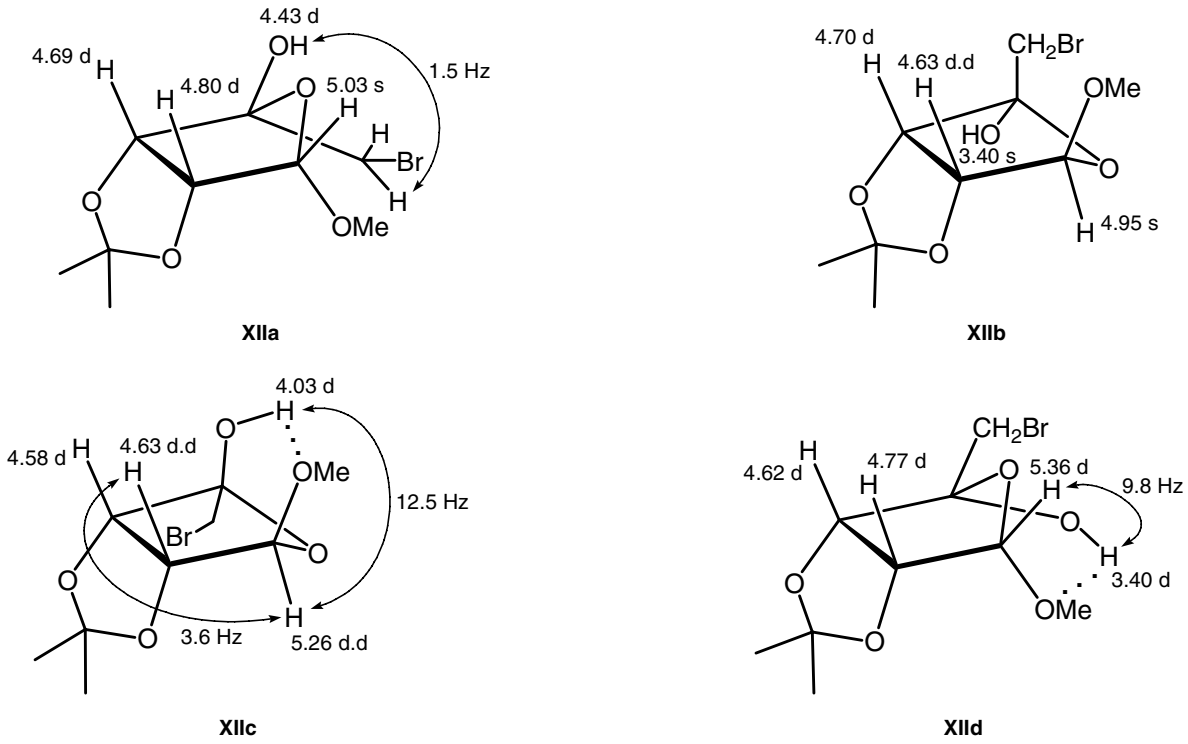


Fig. 2. Conformations of diastereoisomers **XIIa**–**XIId**.

4.03 ppm, respectively) as compared to **XIIb** and **XIId** (δ 3.40 and 2.99 ppm, respectively), for the β-oriented 4-OH group suffers from *trans*-effect of the oxygen atom in the isopropylidene fragment. Likewise, *syn*-interaction of the substituents on C^1 and C^2 in isomers **XIIa** and **XIId** leads to an upfield shift of the C^2 signal in the ^{13}C NMR spectra (δ_C 78.85 and 78.73 ppm, respectively) relative to the corresponding signals of **XIIb** and **XIIc** (δ_C 84.19 and 85.31 ppm, respectively).

We presumed that isomers **XIIc** and **XIId** with *syn* arrangement of the 1-methoxy and 4-hydroxy groups are characterized by intramolecular hydrogen bond (dilution of their solutions in $CDCl_3$ does not change the spectral pattern) between the hydroxy proton and oxygen atom of the methoxy group. The six-membered H-chelate ring and dioxolane ring are arranged *anti* (**XIIc**) or *syn* (**XIId**) with respect to the tetrahydrofuran ring. This assumption allowed us to rationalize the existence of coupling between the hydroxy proton at C^4 and 1-H, which are separated by five σ-bonds. The coupling constant $J_{1,OH}$ is 12.5 Hz in the *anti*-diastereoisomer and 9.8 Hz in the *syn*-diastereoisomer, and it may be regarded as pseudovicinal (through three bonds, two of which are σ-bonds, and the third is hydrogen bond). In both cases, the dihedral angle between the C^1–H and O···H bonds is close to 120°.

Intramolecular hydrogen bonds in 4- and 5-hydroxy derivatives of 2,3-*O*-isopropylidene-β-D-ribofuranosides are formed in different ways. The C^5H_2OH group in molecules **I** and **II** is β-configured; therefore, hydrogen bonding with oxygen atoms of the dioxolane ring is impossible. Among two possible versions of hydrogen bonding, with participation of oxygen atoms in the methoxy group and furan ring, the latter seems to be preferred. We believe that the formation of five-membered H-chelate ring is more favorable than the formation of seven-membered ring including oxygen atom of the methoxy group.

Hydrogen bonding with the furan ring oxygen atom in compounds **XII** (four-membered ring) is likely to be improbable. Intramolecular hydrogen bond is formed only in 1,4-*syn*-isomers **XIIc** and **XIId** with participation of the oxygen atom in the methoxy group, though formation of five- or six-membered H-ring involving one oxygen atom of the dioxolane ring is theoretically possible in stereoisomers **XIIb** and **XIId**. The validity of our assumptions on the location of hydrogen bonds in molecules **XII** is confirmed by readily interpretable chemical shifts and coupling constants for characteristic protons.

Thus, the results of our ^{1}H NMR study on compounds **I**–**III**, **XI**, and **XIIa**–**XIId** showed that intra-

molecular hydrogen bonds in hydroxy derivatives of 2,3-*O*-isopropylidene-β-D-ribofuranosides could involve different oxygen atoms. The main factors determining the mode of intramolecular hydrogen bonding are the position of the hydroxy group (on C^4 or C^5), its *syn* orientation with respect to the other oxygen atoms in the molecule (steric factor), and the size of the resulting H-ring.

The NMR spectra were recorded at room temperature on a Bruker AM-300 spectrometer (300.13 MHz for ^1H and 75.48 MHz for ^{13}C) from ~5% solutions in $CDCl_3$ or DMSO-d_6 using 5-mm thin-walled ampules. The chemical shifts were measured relative to the solvent signals ($CHCl_3$, δ 7.27; $CDCl_3$, δ_C 77.00 ppm; DMSO-d_6, δ 2.5 ppm). Multiplication by the Gauss function was applied to improve the signal shape. Signals were assigned using the double resonance technique. The two-dimensional NMR spectra of compound **II** were recorded using CH CORR and COSY HH-90 routines. The spectra of **I**, **II**, and **XIIa**–**XIId** were additionally recorded at 50°C and from threefold dilute solutions.

REFERENCES

1. Ferrier, R.J. and Middleton, S., *Chem. Rev*., 1993, vol. 93, p. 2779.
2. Chu, C.K., Jin, Y.H., Baker, R.O., and Huggins, J., *Bioorg. Med. Chem. Lett*., 2003, vol. 13, p. 9.
3. Berecibar, A., Grandjean, C., and Siriwardena, A., *Chem. Rev*., 1999, vol. 99, p. 779.
4. Jin, Y.H. and Chu, C.K., *Tetrahedron Lett*., 2002, vol. 43, p. 4141.
5. Ghosh, A.K. and Lui, W., *J. Org. Chem*., 1996, vol. 61, p. 6175.
6. Paquette, L.A. and Bailey, S., *J. Org. Chem*., 1995, vol. 60, p. 7849.
7. Sairam, P., Puranic, R., Rao, B.S., Swamy, P.V., and Chandra, S., *Carbohydr. Res*., 2003, vol. 338, p. 303.
8. Butterworth, R.F. and Hanessian, S., *Can. J. Chem*., 1971, vol. 49, p. 2755.
9. Barrett, A.G.M. and Lebold, S.A., *J. Org. Chem*., 1990, vol. 55, p. 3853.
10. Ivanova, N.A., Valiullina, Z.R., Shitikova, O.V., and Miftakhov, M.S., *Russ. J. Org. Chem*., 2006, vol. 42, p. 1701.