36. Conformation of Some Anomeric O-Benzylated D-Gluco-, L-Ido-, and Hex-4-enopyranoside Derivatives

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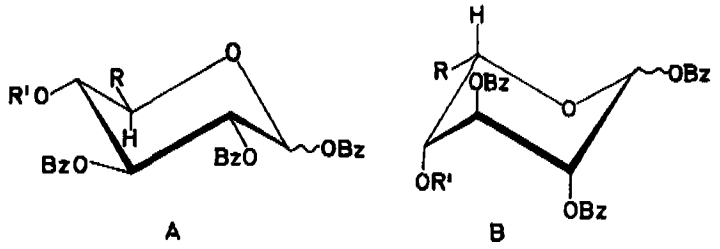
Summary. By use of ^{1}H-NMR. spectroscopy it is shown that in the anomeric tri-O-benzyl derivatives of D-gluco- and L-idopyranosides the C(5) (aliphatic) substituent has a strong tendency to assume an equatorial position. The conformer ($^4C_1$ or $^1C_4$) with C(6) in equatorial position is favoured, even if other bulky substituents are forced to occupy an axial position; the same effect is observed in some anomeric O-benzylated 6-deoxy-L-idopyranoside derivatives.

If, however, the tetragonal configuration of the saturated C(5) is changed into a trigonal (sp^2) configuration, *e.g.* in the anomers of 1,2,3-tri-O-benzylated L-*threo*-hex-4-enopyranosiduronates, the C(5)–C(6) bond no longer determines the equilibrium of (distorted) pyranoid conformations; the anomeric (*'Eduard-Lemieux'*) effect then becomes important in the stabilization of the corresponding half-chair ($^1H_2$ or $^2H_1$) conformations.

According to the 'conformational instability factors' rule of *Reeves & Kelly* [1], the stereochemical position of substituents on the pyranoside ring of sugars plays an important role in influencing conformational ($^4C_1 \rightleftarrows {}^1C_4$) equilibra [2]. It is also accepted that 'bulky substituents tend to assume equatorial or isoclinal rather than axial positions' [3]. Nevertheless, the basic principles of cyclohexane stereochemistry have only a restricted validity in the field of the pyranoside sugars [4].

In connection with the synthesis of heparin saccharides [5] we obtained some anomeric 1,2,3-tri-O-benzylated D-gluco-(A) and L-idopyranosides (B). With these two sets of hexopyranoside sugars (which only differ in the configuration of the C(5) atoms) the study of the influence of the stereochemical position of the C(6) on the stabilization of the $^4C_1$ or $^1C_4$ conformer seemed to be possible. Furthermore, the benzyl protecting groups proved to be more suitable for investigation of conformation than the acyl groups formerly used.



R = *vide infra*; R' = H, SO_2ClI_3

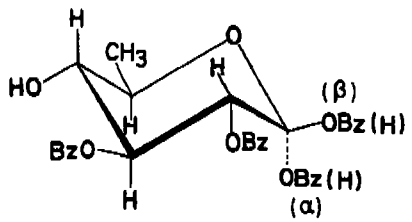
Using ^{1}H-NMR. spectroscopy (*vide infra*) we confirmed the earlier observations that the derivatives of A in solution exist in the $^4C_1$-conformation, whereas the derivatives of B prefer the $^1C_4$-conformation [6].

These observations provided more evidence that the favoured conformation is determined by the requirement that C(6) should be equatorial [7]. The axial effects of other substituents on the pyranoside ring [8], or the Δ_2-effect [1], seem to be less important in this respect.

Furthermore, we prepared some derivatives of the anomeric 1,2,3-tri-O-benzyl D-gluco- and L-idopyranosides described above, in which the size and oxidation level of the substituent on C(5) were varied, to see if these factors effected the stabilization of one or other of the possible pyranoside conformations.

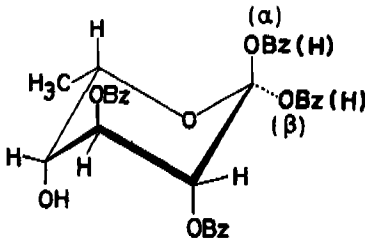
The groups with the following substituents were examined: 1) R = $-CH_2-OH$, 2) R = $-CH_2-OTs$, 3) R = $-CH_2-I$, 4) R = $-COOCH_3$, 5) R = $-CH_3$[1]).

Among these derivatives, group 5 (the anomeric 6-deoxy-D-gluco- and 6-deoxy-L-ido-derivatives) seemed to be particuliarly interesting:



I

$^4C_1$-conformer (D-gluco)
a: β-anomeric compound
b: α-anomeric compound



II

$^1C_4$-conformer (L-ido)
a: α-anomeric compound
b: β-anomeric compound

We found that the D-glucopyranoside derivatives (I) exist in the stable $^4C_1$-conformation, in which the large benzyl ether substituents, and the small C(5) methyl group occupy an *equatorial* position.

On the other hand, the anomeric 6-deoxy-L-idopyranoside derivatives (II) exist in the $^1C_4$-conformation; this fact is surprising; because *the small equatorially-linked C(5) methyl group pushes the large benzyloxy groups into the axial position.*

The conformations of compounds Ia, b, IIa, b, VI and X were assigned by use of ^{1}H-NMR. The Table presents the relevant ^{1}H-NMR. data of these substances.

The conformation of Ia and Ib and of IIa and IIb is derived from the coupling constants given in the Table. The value of 8–9 Hz for the coupling constants $J_{2,3}$, $J_{3,4}$ and $J_{4,5}$ in Ia and Ib is attributed to the *vicinal diaxial* position of the protons H–C(2), H–C(3), H–C(4) and H–C(5) relative to each other, thus proving the $^4C_1$-conformation. The difference in $J_{1,2}$ between Ia (~7.5 Hz) and Ib (3.5 Hz) reflects the usual effect of anomerization at the glycosidic carbon atom.

All coupling constants for vicinal interaction of protons in compounds IIa and IIb are smaller than 4 Hz. This, and the observation of additional *W*-type couplings between H–C(2) and H–C(4) (in IIa and IIb) and between H–C(1) and H–C(3) (in IIa only), prove the $^1C_4$-conformation of IIa and IIb. Furthermore, the *W*-type

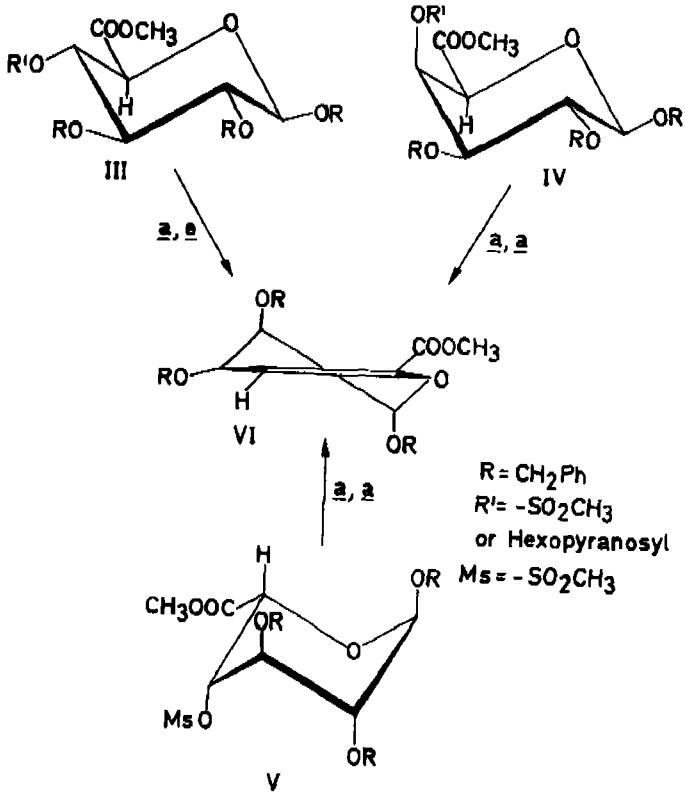
[1]) The preparation of these sugars will be described in a paper to be submitted to Helv. (1975), 'Synthesis of Heparin Saccharides.'

^{1}H-NMR.-Data

Compound	Ia		Ib	IIa	IIb	VI	X
frequency, MHz	220		100	100	100	100	100
solvent	$CDCl_3$	C_6D_6	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$
$\delta_{H-C(1)}$ (ppm)	4.49	4.40	4.79	4.93	4.83	5.11	5.13
$\delta_{H-C(2)}$	3.16 to 3.60	3.30	3.49	3.61	3.61	3.78	3.80
$\delta_{H-C(3)}$		3.58	3.80	3.79	3.83	4.41	4.14
$\delta_{H-C(4)}$		3.21	3.15	3.51	~3.4	6.13	6.17
$\delta_{H-C(5)}$		~3.15	~3.65	4.30	3.96	—	—
$J_{1,2}$ (Hz)	7.5	7.5	3.5	~1	~1	2.4	5.5
$J_{2,3}$	8–9	8–9	9.5	~3	3.5	7.5	4.5
$J_{3,4}$			9.0	~3	<1	2.7	3.5
$J_{4,5}$			9.0	~1.2	~0	–	–
additional coupling constants				$J_{1,3}$ ~1 $J_{2,4}$ ~1 J_{4-OH} = 11.0	$J_{2,4}$ ~1		

coupling $J_{1,2}$ allows differentiation of the α- and β-anomers (IIa and IIb, respectively) by ^{1}H-NMR.

These observations prove unambiguously the conformation-directing effect of the C(5) → C(6) bond of O-glycosides [9]; the latter bond *must assume an equatorial*

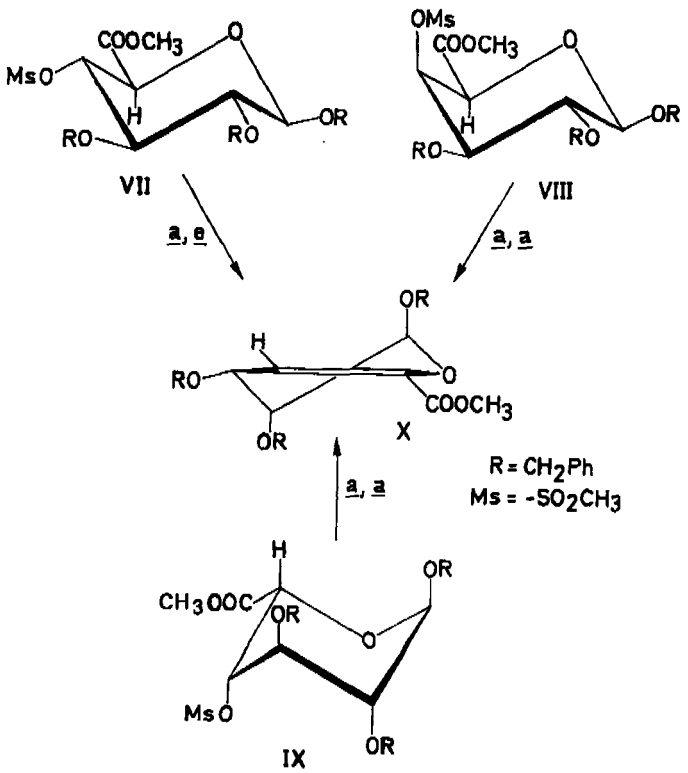


direction, and additionally, this conformation-directing effect seems to be largely independent of the size of the C(5) substituent.

If C(5) is trigonal (sp^2), however, C(6) does not influence the stabilization of the (distorted) pyranoid (half-chair, *H*) conformation. To prove the stereochemistry of the latter ring system, we synthesized the anomeric, benzyl-ether protected L-*threo*-hex-4-enopyranosiduronates VI and X.

Similar sugar uronates possessing an endocyclic enolacetal linkage are produced in nature from polyuronates (alginic acid, pectins, mucopolysaccharides) [10] by β-eliminative degradation in the presence of different lyase enzymes.

This group of enolacetal hexopyranoside sugar uronates can also be obtained in the laboratory by alkali- or diazoalkane-catalyzed β-elimination from the corresponding anomeric 4-O-substituted D-gluco-, D-galacto-, or L-idopyranosiduronates [11]:



Molecular models of the two possible half-chair conformations of VI and correlation of dihedral angles in these models with observed coupling constants support the $^2H_1$-conformation of VI. Particuliarly $J_{2,3} = 7.5$ Hz is in agreement with a dihedral angle between H–C(2) and H–C(3) of about 130–140°, as in the $^2H_1$-conformation, but not with the corresponding angle of about 90–100° for the $^1H_2$-conformation.

On the other hand, enolacetal anomer X, which was obtained from the corresponding β-D-gluco-, β-D-galacto-, or α-L-idopyranurono derivatives possesses the $^1H_2$-conformation. In this conformation the model shows a dihedral angle between H–C(1) and H–C(2) of about 60°, which is consistent with the observed coupling

constants, $J_{1,2} \approx 5.5$ Hz. The dihedral angle between H–C(1) and H–C(2) in the $^2H_1$-conformation would be about 180°, which would require a larger $J_{1,2}$.

Although the equilibrium between H-conformations ('sofa'-conformation was proposed fore some 2,3-unsaturated hexopyranoside derivatives by *Watanabe et al.* [12]) was investigated only with these two examples, it can be assumed that the stabilization of the corresponding conformers is to be explained by the stereochemical position of the glycosidic linkage and its dipolar interaction with the other groups of the molecule [13].

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37. Synthese einiger Glucuronid-Metaboliten von Phenacetin und Phenetidin, Teil II[1])

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Herrn Prof. Dr. *H. Bretschneider*, Institut für Organische und Pharmazeutische Chemie der Universität Innsbruck, zum 70. Geburtstag gewidmet.

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Summary. The anomeric configuration of the main metabolite of phenacetin, *p*-acetamidophenyl β-D-glucopyranosido-uronic acid, was established by configurative correlation with a cyclohexyl β-D-glucopyranosido-uronic acid derivative. Furthermore, some anomeric D-glucopyranoside conjugates of 2-ethoxy-5-acetamido-phenol were synthesized and characterized using NMR.-spectroscopy and ORD./CD.

[1]) Teil I, s. [1].