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Note

Factors influencing conformational preference and equilibria in solutions of aldono-1,5-lactones

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An important phenomenon in solutions of aldono-1,5-lactones is the equilibrium between half-chair and boat conformations[1–8]. In this report, results are presented concerning the conformational equilibrium, in solution, of 2,4,6-tri-*O*-benzoyl-3-deoxy-D-*arabino*-hexono-1,5-lactone (**1**) as determined from the high-resolution, ^{1}H-n.m.r.-spectral data given in Table I.

Assuming a Karplus-type dependence of coupling constants[9,10] for protons of the lactone ring, the small values (see Table I) for the vicinal couplings $J_{3,4}$ and $J_{3',4}$ are characteristic of ring-hydrogen atoms having approximately *gauche* orientations. The magnitude of the geminal coupling ($J_{3,3'}$) indicates that BzO-4 has an *anti*-periplanar relationship with one of the C-3 hydrogen atoms. Only the $^3H_4$(D) and $B_{2,5}$(D) conformations are consistent with these n.m.r. data.

The expected[11–15] $J_{4,5}$ vicinal-coupling would be ~2.5 Hz for the $^3H_4$(D) conformer and ~9.2 Hz for the $B_{2,5}$(D) conformer. The experimentally observed value of $J_{4,5}$ 5.8 Hz suggests either an equilibrium containing populations of both the $^3H_4$(D) and $B_{2,5}$(D) conformers or a single, stable conformation in which the torsional angles deviate substantially from those of ideal conformers. Although it is often possible to test for conformational nonhomogeneity by low-temperature n.m.r. spectroscopy, the available literature data[7,11,16], although limited, indicate that the effect of temperature on the $^3H_4(\text{D}) \rightleftharpoons B_{2,5}(\text{D})$ equilibrium should be negligible.

From the experimentally observed value, $J_{4,5}$ 5.8 Hz, the equilibrium for **1** is estimated, by application of the weighted-average, coupling-constant method[16,17], to contain ~51% of the $^3H_4$(D) conformer and ~49% of the $B_{2,5}$(D) conformer. Qualitatively, these results are predictable, based on interaction energies[16] and the

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TABLE I

270-MHz, ^{1}H-N.M.R.-SPECTRAL DATA FOR 2,4,6-TRI-*O*-BENZOYL-3-DEOXY-D-*arabino*-HEXONO-1,5-LACTONE (**1**) IN CHLOROFORM-*d*

Chemical shifts (δ)[a]

H-2	*H-3*	*H-3'*	*H-4*	*H-5*	*H-6*	*H-6'*	*OBz*
6.00 dd	2.77 o	2.65 o	5.61 s	5.05 q	4.73 dd	4.65 dd	7.39–8.09

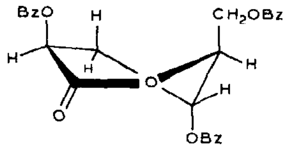
Coupling constants (Hz)[b]

$J_{2,3}$	$J_{2,3'}$	$J_{3,4}$	$J_{3',4}$	$J_{3,3'}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6}$	$J_{6,6}$
12.3	7.3	5.8	3.5	−14.2	5.8	4.2	4.5	−12.4

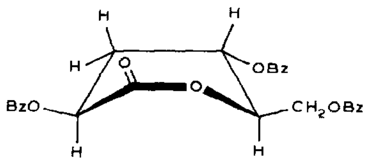
[a]Signal multiplicities: dd, doublet of doublets; o, octet; q, quartet; s, sextet. [b]First-order coupling-constants.

experimentally observed conformational behavior of 3-deoxyaldopyranose ring-systems[18].

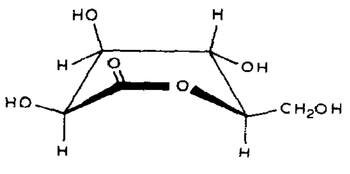
The configurational relationships of the ring substituents in **1** are identical to those in D-mannono-1,5-lactone (**2**) and 2,3,4-tri-*O*-benzoyl-L-rhamnono-1,5-lactone (**3**). The vicinal-coupling data for **2** ($J_{4,5}$ 8.3–8.5 Hz)[15] and **3** ($J_{4,5}$ 8.5 Hz)[13] are similar, and indicate that the conformational equilibria are strongly weighted in favor of boat conformations (~86–90%). These data[13,15], as well as literature data[5,7,11,14] for a wide variety of 1,5-lactones, reveal that solvent polarity does not have a very significant effect upon the positions of the observed conformational equilibria.



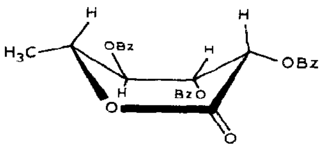
1 - $^{3}H_4$ (D)



1-$B_{2,5}$ (D)



2-$B_{2,5}$ (D)



3 - $^{2,5}B$ (L)

It is a striking fact that removal of the oxygen substituent on C-3 of **2**, which contains ~86–90% of the $B_{2,5}$(D) conformer at equilibrium[15], to give **1**, shifts the equilibrium in favor of the $^{3}H_{4}$(D) conformer (~51%). Because the position of equilibrium is determined by the differences between the free energies of the conformational isomers, it is obvious that a major interaction has been removed. In both **1** and **2**, the group on C-5 is the bulkiest substituent and, in the half-chair conformation, its interaction with other ring substituents is expected to be the largest of the nonbonding interactions in these molecules. For **2** in the $^{3}H_{4}$(D) conformation, there is a nonbonding, 1,3-*syn* (O:C) interaction between the axial 3-hydroxyl group and the bulky, quasiaxial 5-(hydroxymethyl) group. Evidently, in the $^{3}H_{4}$(D) $\rightleftharpoons$ $B_{2,5}$(D) equilibrium for **2**, this nonbonding 1,3-*syn* (O:C) interaction makes the $^{3}H_{4}$(D) conformation energetically unfavorable, such that the equilibrium is shifted predominantly toward the $B_{2,5}$(D) conformation. The absence of this type of unfavorable steric interaction accounts for the significant proportion (~51%) of the half-chair conformer observed in the equilibrium for **1**.

The free-energy (ΔG^{0}) values calculated[16] from the n.m.r. data, although probably of only semiquantitative significance, reveal that the overall, interaction-energy difference for **1** and **2** has a value of ~5.55 kJ/mol. This value is in good agreement with a previously reported value of ~5.63 kJ/mol for the nonbonding, 1,3-axial–quasiaxial (C:O) interaction for the C-1 and C-5 substituents of the glyc-3-enopyranose ring-system[16]. This result provides additional supporting evidence that the vicinal-coupling values observed for **1** are, to a first approximation, the weighted time-averages of those for the conformers of the $^{3}H_{4}$(D) $\rightleftharpoons$ $B_{2,5}$(D) equilibrium.

The observations reported here should be of predictive value for interpretation of steric and configurational effects of ring substituents with respect to their influence upon the conformational preference and equilibria exhibited by aldono-1,5-lactones.

EXPERIMENTAL

General methods. — The high-resolution, ^{1}H-n.m.r. spectrum was recorded at the Francis Bitter National Magnet Laboratory, Massachusetts Institute of Technology, with a Bruker 270-MHz spectrometer. The spectrum was recorded in chloroform-*d* (10% solution), and the data are reported in parts per million (δ) relative to Me_4Si. Mass-spectral data were obtained with an AEI MS-1201 spectrometer with direct sample-introduction; data are reported in the form *m/z* (percent base-peak intensity).

*2,4,6-Tri-O-benzoyl-3-deoxy-*D-arabino-*hexono-1,5-lactone* (**1**). — 2,4,6-Tri-*O*-benzoyl-3-deoxy-D-*erythro*-hex-2-enono-1,5-lactone[19] (1.74 g) was dissolved in ethyl acetate (100 mL), and hydrogenated over 5% palladium–charcoal (300 mg) at atmospheric pressure and ambient temperature for 2 h. The suspension was filtered through Celite, and the filtrate evaporated (<60°, bath), to give **1** as a syrupy residue that crystallized spontaneously on standing. After recrystallization from acetone, **1** (1.7 g, 98%) had m.p. 154–156° (lit.[19] m.p. 158–160°); for ^{1}H-n.m.r. data, see Table I; *m/z* 474 (M$^+$, 3%), 369 (2), 352 (4), 339 (2), 296 (2), 230 (55), and 105 (100).

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