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Note

The conformation of 2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone

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In a previous report[1], an unusual type of conformational preference was described for the ring system of 2,3,4-tri-*O*-acetyl-D-xylono-1,5-lactone (**1**). From ^{1}H-n.m.r. spectral data, it was evident that the 3- and 4-acetoxyl groups in **1** were antiperiplanar. On this basis and in agreement with other spectral data, it was deduced that, for **1**, conformation **2** having the 3- and 4-acetoxyl groups *endo* was favored. The unexpected *endo* conformational preference of these 3- and 4-acetoxyl groups was attributed to conformationally stabilizing, attractive electrostatic interactions between the two *endo*, electronegative acetoxyl groups in **2** and the electropositive lactone-ring oxygen atom.

It was recognized[1], however, that attractive electrostatic interactions apparently make an important contribution to the ground-state conformational energy of **1** because of a fortuitous absence of unfavorable steric interactions in the pentono-1,5-lactone ring-system of **1**, which permits the ring to have considerable conformational flexibility. Understandably, these conformationally stabilizing and conformationally directive electronic effects might be energetically less favorable in the presence of unfavorable steric interactions. Hence, steric rather than electronic factors might be expected to contribute more of a conformationally stabilizing influence in hexono-1,5-lactones where the bulky C-5 substituent would make the ring less conformationally mobile and hence might make the *endo* ring-substituent-directing influence of the electropositive, lactone-ring oxygen atom energetically unfavorable[1]. In an attempt to evaluate further the various steric, electronic, and configurational effects of ring substituents of D-aldono-1,5-lactones with respect to their conformation-stabilizing influences, we now report a study by ^{1}H-n.m.r. spectroscopy of the conformation of 2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone (**3**).

X-Ray analysis[2-4] has shown that the lactone group of D-glucono-1,5-lactone (**4**) deviates slightly from exact planarity. In the solid state, **4** has a distorted half-chair conformation (**5**). There has been considerable speculation that the con-

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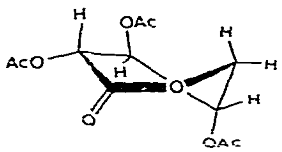

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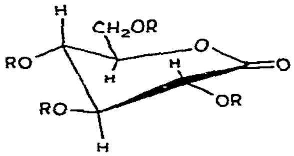

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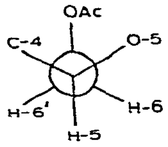
8 R = Ac



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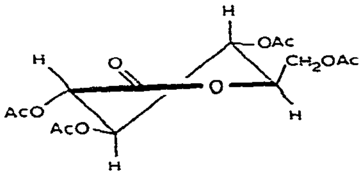

7 ($^4H_3$)

formational characteristics of **4** account, at least in part, for the biological properties[5-9] of this molecule, and it has been widely assumed that the conformation of **4** and its derivatives in solution is similar to that found for **4** in the solid state[2-9]. It is of considerable interest, nevertheless, to obtain a more detailed conformational picture of **4** to aid in the interpretation of both the chemical[10-12] and biological[5-9] properties of this molecule.

Examination of the 100-MHz, ^{1}H-n.m.r.-spectral data (Table I) of **3** reveals information about the conformation of the lactone ring and the rotational orientation

TABLE I

^{1}H-N.M.R. SPECTRAL DATA FOR 2,3,4,6-TETRA-*O*-ACETYL-D-GLUCONO-1,5-LACTONE (**3**)

Solvent	*Chemical shifts (τ)*[a]						
	H-2	*H-3*	*H-4*	*H-5*	*H-6*	*H-6′*	*OAc*
$CDCl_3$	4.84 d	4.42 t	4.63 t	5.40 m	5.61 dd	5.74 dd	7.75–8.00
CCl_4	4.90 d	4.53 t	4.71 t	5.45 m	5.62 dd	5.83 dd	7.80–8.05
C_6D_6	4.95 d	4.29 t	4.58 t	5.56	—	6.04	8.10–8.30
$(CD_3)_2CO$	4.53 d	4.35 t	4.52 t	5.27 m	5.61 dd	5.73 dd	7.80–8.05
Solvent	*Coupling constants (Hz)*[b]						
	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	
$CDCl_3$	8.7	9.1	8.8	3.7	2.9	12.7	
CCl_4	8.7	9.2	8.8	4.0	2.5	12.0	
C_6D_6	8.8	9.2	8.9	[c]	[c]	[c]	
$(CD_3)_2CO$	8.6	9.2	9.2	3.9	2.8	12.7	

[a] Signal multiplicities are indicated by: d, doublet; t, triplet; m, complex multiplet; dd, double doublet. [b] First-order coupling constants. [c] Complex multiplet not analyzed on a first-order basis.

of the exocyclic, 5-acetoxymethyl substituent. As 3 has the D-*gluco* stereochemistry and assuming the Karplus-type dependence of coupling constants[13,14] for protons of the lactone ring, the magnitudes of the vicinal couplings ($J_{2,3}$ = 8.6–8.8, $J_{3,4}$ = 9.1–9.2, and $J_{4,5}$ = 8.8–9.2 Hz) clearly indicate that H-2,3,4, and 5 must all be *endo* and hence that the 2-, 3- and 4-acetoxyl, and the 5-acetoxymethyl substituents have approximately *exo* orientations. From these n.m.r. data it is evident that, in 3, steric factors (presumably arising from the presence of the bulky 5-acetoxymethyl ring-substituent) restrict the conformational flexibility of the lactone ring and prevent the substituent-directing influence of the electropositive lactone-ring oxygen atom from playing a significant role in determining the conformational preference of the electronegative ring substituents of 3. Hence, the conformationally stabilizing, attractive, electrostatic interactions that would be expected to favor *endo* 3- and 4-acetoxyl substituents in 3 must be small energetically in comparison with steric factors that favor *exo* orientations for these substituents.

Another conformational feature of 3 concerns the stereochemistry about the C-5–C-6 bond. In the solid state, the exocyclic 5-hydroxymethyl substituent of D-glucono-1,5-lactone (**4**) exhibits the *gauche–gauche* rotamer stereochemistry about the C-5–C-6 bond[2,3]. For 3, both of the vicinal couplings ($J_{5,6}$ = 3.7–4.0 and $J_{5,6'}$ = 2.5–2.9 Hz) are small, and from the rotamer conformational populations calculated[15] from these spin-coupling data, the *gauche–gauche* rotamer **6** is preponderant (~70%) in solution over the other two rotamers fully staggered about the C-5–C-6 bond. Previous studies of the rotamer conformational populations about the C-5–C-6 bond of glucopyranose derivatives indicate that, in solution, the *gauche–gauche* rotamer is favored (~53%)[16–18]. However, for 3 there exists the possibility that the *gauche–gauche* rotamer **6** may be stabilized, and hence favored, through the operation of an intramolecular, attractive electrostatic interaction between the exocyclic 6-acetoxyl group and the electropositive lactone-ring oxygen atom.

Of the possible half-chair and boat conformations required for 3 by the approximately planar lactone group[19–24], only the $^4H_3$ conformation (**7**) is consistent with the ^{1}H-n.m.r. spectral data (Table I). Although these spectral data for 3 may be accommodated by this kind of half-chair conformation, the arguments are not unequivocal. In fact, the stereochemistry and dihedral angles indicated by the n.m.r. data suggest that 3 may actually have the distorted half-chair conformation **8**. There follow several arguments which pertain to this latter possibility.

First, for 3, the $^4H_3$ conformation 7 requires that the lactone group be planar. However, the slight distortion from planarity expected[1–3] for the lactone group in D-aldono-1,5-lactones probably prevents 3 from adopting an ideal, half-chair conformation such as 7. Second, in the half-chair conformation 7, the expected[25–27] vicinal coupling constants $J_{2,3}$ and $J_{4,5}$ would be ~7–8 Hz. The experimentally observed values of $J_{2,3}$ = 8.6–8.8 and $J_{4,5}$ = 8.8–9.2 Hz suggest that the dihedral angles H-2–C-2–C-3–H-3 and H-4–C-4–C-5–H-5 may be somewhat larger than indicated by conformation 7. This evidence supports the conclusion that the overall conformation of 3 may be best represented by the distorted half-chair conformation **8**.

It is noteworthy that the conformational features of **3** indicated by the distorted half-chair conformation **8** are essentially identical to those observed[2,3] in the solid state for D-glucono-1,5-lactone (**4**).

The foregoing observations, together with the previously reported data[1] regarding the conformational characteristics of the ring system of D-aldono-1,5-lactones **1** and **3**, may prove useful in providing insights into the chemical[10-12] and biological[5-9] properties of these molecules. For instance, it is now evident that the ground-state conformational energy of the ring system of D-aldono-1,5-lactones is sensitive to steric requirements of the substituents for minimum conformational energy, and the *endo* ring-substituent-directing influence of the electropositive, lactone-ring oxygen atom is small energetically in comparison with steric factors arising from the presence of large, bulky substituents.

EXPERIMENTAL

General methods. — ^{1}H-N.m.r. spectra were recorded for 10% solutions (internal Me_4Si) with a Varian HA-100 spectrometer; chemical shifts are reported on the τ scale, and coupling constants (J) in Hz. Assignments were substantiated by double-irradiation experiments. Mass spectra were obtained with an AEI MS-1201 spectrometer with direct sample introduction; data are reported in the form m/z (percent of base-peak intensity).

2,3,4,6-Tetra-O-acetyl-D-glucono-1,5-lactone (**3**). — D-Glucono-1,5-lactone (2.0 g) was slowly added to a magnetically stirred solution of acetic anhydride (10 mL) and zinc chloride (1.0 g). After 40 min at room temperature, the solution was poured onto crushed ice (200 mL). The solution was extracted with chloroform (2 × 50 mL), and the extract was washed with ice-cold water (2 × 50 mL), dried (magnesium sulfate), and evaporated (<60°, bath) to give a colorless syrup (3.69 g, 95%), $[\alpha]_D$ +79.7° (*c* 2, chloroform); lit.[28] $[\alpha]_D$ +64.35° (6 min) (*c* 4, 80% acetone–water); ^{1}H-n.m.r. see Table I; m/z 346 (M^+, 2%), 304 (12), 273 (12), 231 (14), 226 (26), 184 (55), 158 (22), 157 (27), 145 (43), 142 (25), 125 (2), 115 (60), 112 (100), 103 (64), 97 (34), 73 (26), 43 (55), and 42 (100).

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