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CONFORMATIONAL STUDIES ON ALDONOLACTONES BY N.M.R. SPECTROSCOPY. CONFORMATIONS OF D-GLUCONO-1,5-LACTONE AND D-MANNONO-1,5-LACTONE IN SOLUTION*†

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ABSTRACT

The conformations of D-glucono-1,5-lactone (**1**) and D-mannono-1,5-lactone (**2**) in solution were investigated by ^{1}H- and ^{13}C-n.m.r. spectroscopy. Conformational equilibria for **1** and **2** were found to lie strongly in favor of the $^4H_3$(D),*gg* and $B_{2,5}$(D),*gg* conformations, respectively.

INTRODUCTION

Earlier papers in this series described the conformational properties of some biologically important aldaro- and aldono-1,4-lactones in solution[2-4]. The conformational behavior of aldono-1,5-lactones remains to be discussed.

X-Ray crystallographic studies of various 1,5-lactones have demonstrated both half-chair and boat conformations[5]. Calculations by molecular mechanics indicate two minimum-energy conformations of 5-hydroxypentanoic 1,5-lactone (δ-valerolactone), a half-chair and a boat form (a classical boat, not a skew form), with the half-chair form being, by ~2.5 kJ/mol (~0.6 kcal/mol), the more stable[6]. Conformational equilibria between the boat and half-chair conformations have been studied for various 1,5-lactones in solution by such techniques as optical rotatory dispersion[7], and circular dichroism[7-9], ^{1}H-n.m.r.[9,10], microwave[6], and Raman spectroscopy[6].

Aldono-1,5-lactones of various configurations have conventionally been depicted in the literature either as chair conformations (as, for example, in refs. 11–15), or as half-chair conformations (as in refs. 16–18). In one example, that of D-glucono-1,5-lactone, the crystal structure was studied by X-ray diffraction, and the lactone-ring conformation was described[19,20] as a "distorted half-chair". From the results of

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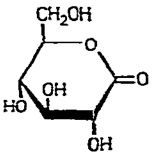
^{1}H-n.m.r. spectroscopy, half-chair[9] or boat[9,21,22] conformations, or both, have been assigned for several deoxy- and dideoxy-1,5-lactones and their derivatives in solution.

The objective of the present work was the conformational analysis, by ^{1}H- and ^{13}C-n.m.r. spectroscopy, of two key aldono-1,5-lactones, namely, D-glucono-1,5-lactone (**1**) and D-mannono-1,5-lactone (**2**) in solution.



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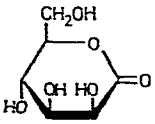

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RESULTS AND DISCUSSION

D-*Glucono-1,5-lactone* (**1**). — Comparison of ^{1}H-n.m.r. coupling-constants observed experimentally for **1** in Me_2SO-d_6 with those calculated from crystallo-

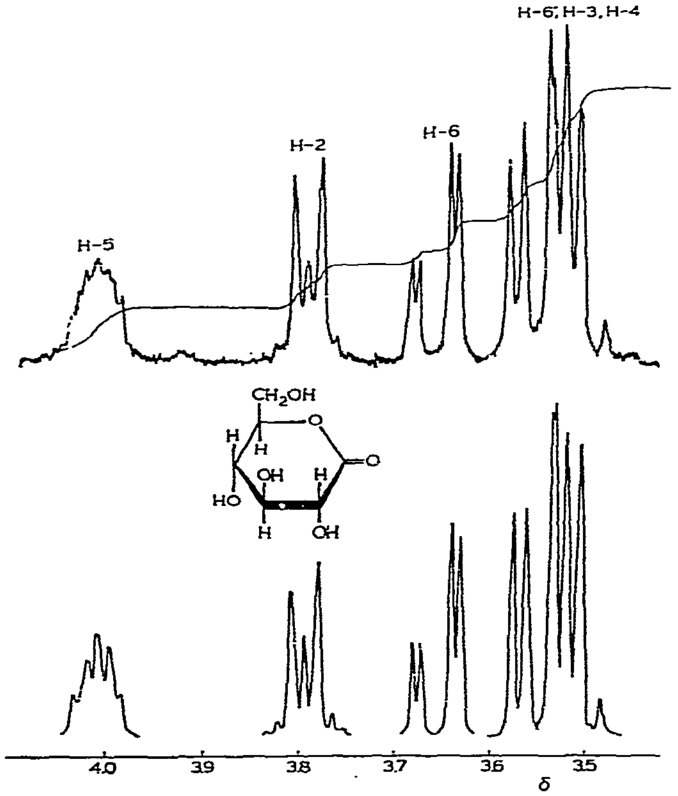


Fig. 1. The 300-MHz, ^{1}H-n.m.r. spectrum of D-glucono-1,5-lactone (**1**) in dimethyl sulfoxide-d_6 (upper trace), and the simulated spectrum (lower trace).

TABLE I

300-MHz, ^{1}H-N.M.R.-SPECTRAL DATA FOR D-GLUCONO-1,5-LACTONE (**1**) IN DIMETHYL SULFOXIDE-d_6[a]

Chemical shifts (δ)[b]						*Coupling constants (Hz)*						
H-2	*H-3*	*H-4*	*H-5*	*H-6*	*H-6′*	$^3J_{2,3}$	$^3J_{3,4}$	$^3J_{4,5}$	$^3J_{5,6}$	$^3J_{5,6'}$	$^2J_{6,6'}$	$^4J_{2,5}$
3.79m	3.53m	3.51m	4.01o	3.65q	3.55m	8.5	7.5	8.1	2.5	4.4	−12.2	0.5

[a]In the presence of CF_3CO_2H. [b]Signal multiplicities: m, complex multiplet; o, octet; q, quartet.

TABLE II

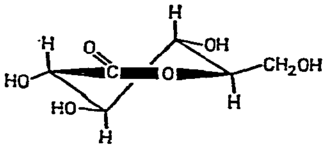
COMPARISON OF DIHEDRAL ANGLES AND ^{1}H-N.M.R. COUPLING-DATA FOR RING PROTONS OF D-GLUCONO-1,5-LACTONE (**1**)

Vicinal protons	*Crystallographic dihedral angle*[a] *(degrees)*	*N.m.r. proton–proton coupling-constants (Hz)*				
		Calc.[b]	*Calc.*[c]	*Calc.*[d]	*Calc.*[e]	*Obs.*[f]
2,3	167.3	8.8	9.2	9.0	9.0	8.5
3,4	178.3	9.2	9.5	9.4	9.7	7.5
4,5	170.9	9.0	9.3	9.2	9.0	8.1

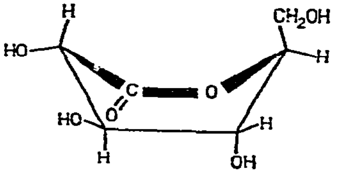
[a]Observed[20]. [b]By using the Karplus equation[23]. [c]By using a modified equation, as in ref. 24. [d]By using a modified equation, as in ref. 25. [e]By using a modified equation, as in ref. 26. [f]In dimethyl sulfoxide-d_6 (present work). The rotamer contributions of the exocyclic CH_2OH group were calculated as for nucleosides[27]: 60% *gg*, 30% *gt*, and 10% *tg*.

graphic, dihedral angles[20] by using various Karplus-type equations (see Fig. 1 and Tables I and II) leads to the conclusion that a conformational equilibrium between various conformers in solution is shifted far toward the ${}^{4}H_{3}$(D),*gg* conformation*. Interestingly, almost the same conformation was found for **1** in the crystal[19,20].

The observed coupling-constants, especially $J_{3,4}$, are somewhat smaller than those predicted theoretically (see Table II), indicating a detectable, although not substantial, proportion of the ${}^{2,5}B$(D) conformation. The contribution of the ${}^{2,5}B$(D) form, estimated on the basis of n.m.r. coupling-data found for related 1,5-lactones[9,28], is less than 20%. It is noteworthy that the coupling constants reported in ref. 28 do, in fact, indicate the ${}^{2,5}B$(D) conformation to be favored for 2,3,4-tri-*O*-acetyl-D-xylono-1,5-lactone.



1-${}^{4}H_{3}$(D)



1-${}^{2,5}B$(D)

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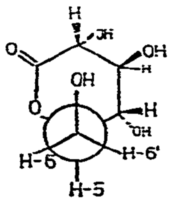
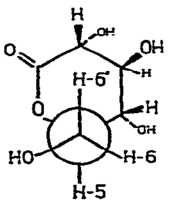
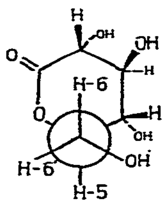
*Note added in proof. Since the time of submission of this article, a report has appeared [C. R. Nelson, *Carbohydr. Res.*, 106 (1982) 155–159] on the conformation of 2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone in solution. Our interpretation of the ^{1}H-n.m.r.-spectral data for this compound, the tetraacetate of **1**, is that it exists in the ${}^{4}H_{3}$,*gg* conformation.



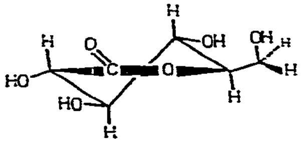
1-*gg*



1-*gt*



1-*tg*



1-$^4H_3$(D),*gg*

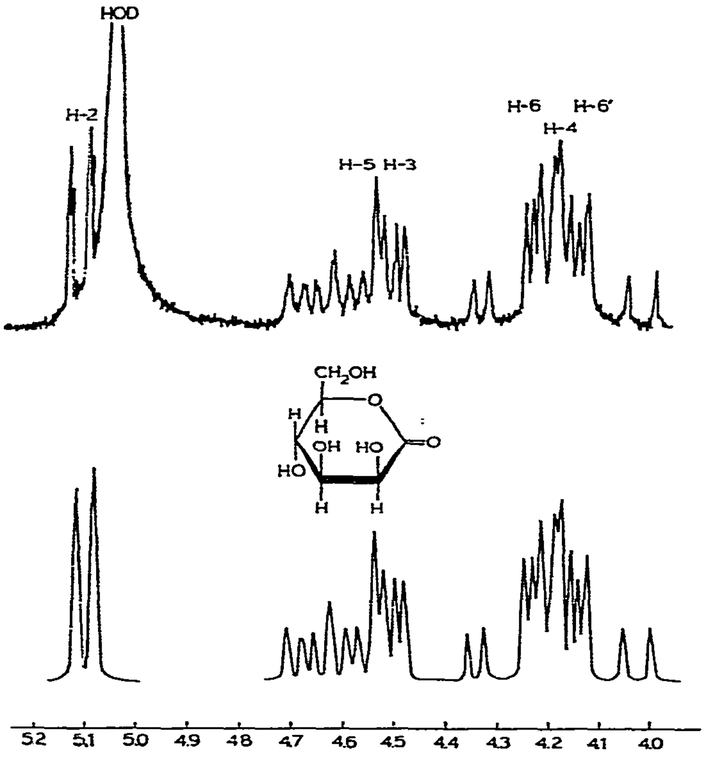


Fig. 2. The 100-MHz, ^{1}H-n.m.r. spectrum of D-mannono-1,5-lactone (**2**) in deuterium oxide (upper trace), and the simulated spectrum (lower trace).

TABLE III

100-MHz, ^{1}H-N.M.R.-SPECTRAL DATA FOR D-MANNONO-1,5-LACTONE (2)

Solvent	*Chemical shifts (δ)*[a]						*Coupling constants (Hz)*						
	H-2	*H-3*	*H-4*	*H-5*	*H-6*	*H-6′*	$^3J_{2,3}$	$^3J_{3,4}$	$^3J_{4,5}$	$^3J_{5,6}$	$^3J_{5,6'}$	$^2J_{6,6'}$	$^4J_{2,5}$
Deuterium oxide	5.10dd	4.51dd	4.20dd	4.62o	4.25q	4.12q	3.6	1.6	8.5	2.8	5.4	−12.8	0.5
Dimethyl sulfoxide-d_6[b]	4.93dd	4.31dd	4.03dd	4.49o	4.12q	3.98q	3.4	1.2	8.3	2.6	5.4	−12.6	

[a]Signal multiplicities: dd, doublet of doublets; o, octet; q, quartet. [b]In the presence of CF_3CO_2H.

TABLE IV

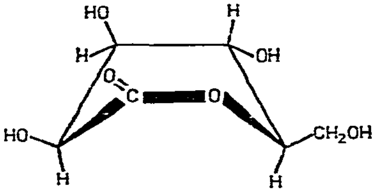
COMPARISON OF DIHEDRAL ANGLES AND ^{1}H-N.M.R. COUPLING-DATA FOR RING PROTONS IN D-MANNONO-1,5-LACTONE (2)

Vicinal protons	*N.m.r. proton–proton coupling constants (Hz)*		*Dihedral angle (degrees)*			
	Obs.[a]	*Obs.*[b]	*Calc.*[a,c]	*Calc.*[b,c]	*Calc.*[a,d]	*Calc.*[b,d]
2,3	3.6	3.4	45	50	55	55
3,4	1.6	1.2	115	110	100	[e]
4,5	8.5	8.3	165	160	160	160

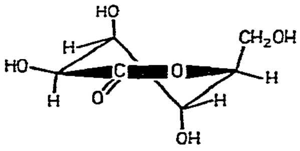
[a] In deuterium oxide (present work). [b] In dimethyl sulfoxide-d_6 (present work). [c] By using the Karplus equation[23]. [d] By using a modified, Karplus equation, as in ref. 24. Conformer contributions of the exocyclic CH_2OH group were calculated as for nucleosides[27]: 50% of *gg*, 40% of *gt*, and 10% of *tg* both in deuterium oxide and dimethyl sulfoxide-d_6. [e] Not obtainable from the modified equation.

Aqueous solutions of **1** show[29] i.r. carbonyl absorption at 1740 cm^{-1}, consistent with the $^4H_3$ conformation as the preponderant form[5,30,31].

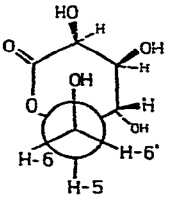
D-*Mannono-1,5-lactone* (**2**). — The coupling constants found for **2** (see Fig. 2 and Table III) demonstrate that the equilibrium population among the different conformers in solution is strongly weighted in favor of the $B_{2,5}$(D),*gg* conformation. Comparison of the ^{1}H-n.m.r. coupling-data for ring protons in **2** with the dihedral angles calculated by using various Karplus-type equations (see Table IV) indicates only slight distortion from the ideal, $B_{2,5}$(D) conformation. The frequency of the carbonyl absorption (1754 cm^{-1}) in the infrared spectrum observed for **2** in aqueous solution[29] supports the $B_{2,5}$(D) conformation as the favored form of **2** in solution[5,30,31].



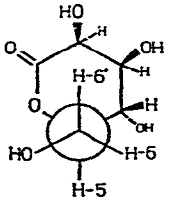
2-$B_{2,5}$(D)



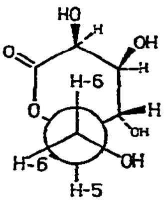
2-$^3H_4$(D)



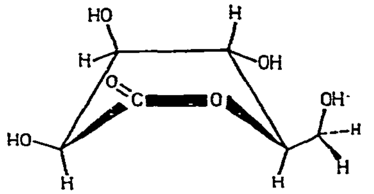
2-*gg*



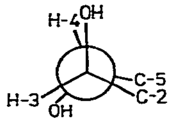
2-*gt*



2-*tg*



2-B_{25}(D).gg



2- C-3 —C-4

General correlations. — The ^{1}H-n.m.r. coupling-data reported here for **1** and **2** are similar to those found for deoxy- and dideoxy-hexono-1,5 lactones and their derivatives[9,21,22].

In the ^{13}C-n.m.r. spectra of **1** and **2** (see Tables V and VI), the C-1 and C-6 resonances appear at slightly higher fields than in those of the corresponding 1,4-lactones[4] and acids[33]. The C-5 atoms in **1** and **2** are deshielded by comparison with the C-4 atoms in the corresponding 1,4-lactones[4]. The shielding of C-3 in **2** might be explained in terms of the γ-effect and its dependence on the dihedral angle between

TABLE V

CARBON-13, CHEMICAL SHIFTS FOR D-GLUCONO-1,5 LACTONE (**1**) AND D-MANNONO-1,5-LACTONE (**2**) IN D_2O AT 30°

Compound	*Chemical shifts in p.p.m. downfield from Me_4Si^a*					
	C-1	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*
D-Glucono-1,5-lactone (**1**)	174.6	71.8^b	73.6^b	68.0^b	82.45	61.0
D-Mannono-1,5-lactone (**2**)	175.8	70.4^b	75.2^b	69.1^b	81.2	61.6

[a]Original data, referenced to the highest-field resonance of sodium 4,4-dimethyl-4-silapentane-1-sulfonate (DSS) were converted according to the equation[32]: δ Me_4Si = δ DSS − 1.6. [b]Assignments may have to be interchanged.

TABLE VI

CARBON-13, CHEMICAL SHIFTS OF D-GLUCONO-1,5-LACTONE AND D-MANNONO-1,5-LACTONE IN Me_2SO-d_6

Compound	*Chemical shifts in p.p.m. downfield from internal Me_4Si and solvent-induced shifts, $\Delta\delta$ (in parentheses)^a*					
	C-1	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*
D-Glucono-1,5-lactone (**1**)	172.2	71.4^b	73.6^b	67.8^b	81.4	60.3
	(2.4)	(0.4)	(0.0)	(0.2)	(1.15)	(0.7)
D-Mannono-1,5-lactone (**2**)	172.4	69.7^b	74.9^b	68.1^b	80.7	60.8
	(3.4)	(0.7)	(0.3)	(1.0)	(0.5)	(0.8)

[a]$\Delta\delta$ = δ in D_2O − δ in Me_2SO-d_6. [b]Assignments may have to be interchanged.

the C-1–O-5 and C-2–C-3 bonds[34]. All resonances are shifted to higher field in dimethyl sulfoxide-d_6 compared to solutions in D_2O, but not to the same extent. Regularities similar to those found for aldono-1,4-lactones[2,4] are observed.

The ^{1}H-n.m.r. and the ^{13}C-n.m.r. data both accord with a half-chair for **1**, and a boat for **2**, as the favored conformations of the lactone ring. As with pentono-1,4-lactones when compared with furanoid sugars[3], the contribution of the *gauche-gauche* orientation of the exocyclic CH_2OH group is slightly higher in the lactones **1** and **2** when compared with corresponding aldohexopyranose structures[35]. Interestingly, this contribution is also slightly higher for aldopentono-1,4-lactones in comparison with aldopentofuranoses[3].

Some general conclusions may be drawn from consideration of the conformational properties of **1** and **2** in comparison with those of some deoxy- and dideoxy-hexono-1,5-lactones[9,21,22]. The lactone ring of the hexono-1,5-lactones may adopt either a half-chair or a boat conformation, or both. The relative configuration of the bulky groups at C-2 and C-5 is the main factor determining the conformation. A half-chair conformation prevails when bulky substituents on C-2 and C-5 are *trans*-disposed, as in **1**, whereas a boat conformation is the preponderant form when the relationship is *cis* (as in **2**). The bulky groups at C-2 and C-5 adopt either the quasiequatorial or the bowsprit orientations in the favored half-chair and boat conformations, respectively.

In the light of these conformational findings, some earlier interpretations of the chemical and biochemical properties of hexono-1,5-lactones must be revised. In particular, in elucidating the mechanism of the hydrolysis of glycopyranosides by glycosidases (which show high affinity for 1,5-lactones of appropriate configuration), not only the half-chair conformations[16,17] but also the boat forms should be taken into consideration when conformational similarities between the lactone and the transition state of the enzyme-catalyzed hydrolysis of pyranoside substrate are discussed.

EXPERIMENTAL

Materials. — D-Glucono-1,5-lactone (**1**) and D-mannono-1,5-lactone (**2**) were prepared according to the methods described by Isbell and Frush[36]. Both lactones were chromatographically homogeneous, and their physical constants were in good agreement with published values. T.l.c. was performed as described earlier[2].

^{1}H-N.m.r. spectra. — Spectra were recorded as described earlier[2]. The 300-MHz spectrum of **1** was recorded with a Varian HA 300 instrument at the University of Akron (Akron, Ohio). Spectra were computer-simulated with the aid of the program LAOCOON III.

^{13}C-N.m.r. spectra. — Proton-decoupled, natural-abundance-^{13}C, pulse Fourier-transform, n.m.r. spectra were recorded as described earlier[2,32].

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