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SYNTHESIS AND ^{13}C N.M.R. SPECTRUM OF D-GLUCOSE-*3-d*. BOND-POLARIZATION DIFFERENCES BETWEEN THE ANOMERS OF D-GLUCOSE*

H. J. KOCH** AND A. S. PERLIN
Department of Chemistry, McGill University, Montreal (Canada)

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ABSTRACT

D-Glucose-*3-d* (**1**) has been synthesized by reactions involving, as the key step, conversion of 1,2:5,6-di-*O*-isopropylidene-3-*O*-tosyl-α-D-allofuranose-*3-d* into 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose-*3-d*. Compound **1**, together with D-glucose-*5-d* and D-glucose *5,6,6-d*$_3$, have facilitated the assignment of signals in the ^{13}C and ^{1}H n.m.r. spectra of α,β-D-glucose; the 220-MHz p.m.r. spectrum of the latter is described. A comparison of ^{13}C and ^{1}H chemical shifts for α- and β-D-glucose, and of the corresponding hydroxyl-proton resonances, shows that there is a widespread difference between the anomers in the polarization of their various bonds. That is, inversion of the anomeric hydroxyl group from an equatorial to an axial orientation is associated with a uniform increase in shielding of ^{13}C, decrease in shielding of the appended proton, and increase in shielding of the hydroxyl proton, at all positions except 4 and 6, which remain virtually unaffected.

RESULTS AND DISCUSSION

N.m.r. spectra and bond polarization. — The proton-decoupled ^{13}C n.m.r. spectra of α- and β-D-glucose have been examined in this laboratory[1,2] and by Dorman and Roberts[3]. Signal assignments for these spectra are in agreement in the two studies, except for the C-2 and C-3 resonances. This difference has now been resolved by examining the spectrum of D-glucose-*3-d* (**1**) (a synthesis of which is described below), with the result that our initial assignments have been confirmed.

The presence of a deuterium atom has the effect of altering the resonance signal due to the appended ^{13}C atom, sometimes causing disappearance of the signal[4] and sometimes giving rise to a triplet ^{13}C resonance[5]. Under the conditions of our n.m.r. experiment, two signals, produced by an equilibrated, aqueous solution of D-glucose and ascribed previously to ^{13}C-3 of the α- and β-anomers[1,2], were now found to be absent from the spectrum of **1** (Table I.) Similarly, the use of D-glucose-*5,6,6'-d*$_3$ (**2**)[6] has served to confirm assignments for the ^{13}C-5 and ^{13}C-6 resonances (Table I). Because chemical shifts from ^{13}C-1 to ^{13}C-4 of α-D-xylose are virtually the same as

*Dedicated to Professor F. Micheel in celebration of his 70th birthday.
**Postdoctoral Fellow with Professor Dr. F. Micheel, 1967–69.

for α-D-glucose, it is highly probable that the same assignments apply for the pentose[2] which, again, requires a reversal of the ^{13}C-2 and ^{13}C-3 shifts reported in other studies[3,7].

TABLE I

^{13}C AND ^{1}H CHEMICAL SHIFTS FOR α- AND β-D-GLUCOSE

Nucleus	$^{13}C^{c}$		$^{1}H^{d}$	
	α	β	α	β
1	100.4	96.5	5.27	4.67
2	120.9	118.2	3.56	3.29
3	119.5[a]	116.6[a]	3.75	3.59
4	122.8	122.8	3.44	3.45
5	121.2[b]	116.6[b]	3.81	3.52
6	131.4[b]	131.4[b]	4.05/4.12	3.91/4.22

[a]Signal not observed with compound **1**. [b]Signal not observed with compound **2**. [c]Chemical shift (p.p.m.) relative to downfield carbon disulfide. [d]Chemical shift (δ, p.p.m.) relative to upfield tetramethylsilane.

As noted previously[2,3], a change in orientation at the anomeric centre of D-glucose has an impact on ^{13}C electron densities over a large portion of the molecule, carbon atoms 1, 2, 3, and 5 all being affected substantially. Parallel effects are observed for cyclohexane derivatives[8-10]. In the latter series, moreover, there appears[11] to be an intimate steric relationship between chemical shifts for protons and ^{13}C nuclei, *i.e.*, an increase in the shielding of carbon associated with a steric interaction generally is accompanied by a decrease in shielding of the appended proton. Analysis of the proton spectra of α and β-D-glucose (Table I and below) now shows that the same kind of relationship applies. Thus, a change in anomeric configuration produces chemical-shift differences for protons 1, 2, 3, and 5, in a direction opposite to those of the corresponding carbon atoms. As illustrated in Fig. 1, the transformation β- → α-D-glucose is characterized by increased shielding (−) at all carbons, except 4 and 6, whereas the appended protons, except 4 and 6, become less shielded (+). It is noteworthy that the corresponding hydroxyl-proton resonances[12,13] (measured with methyl sulfoxide as solvent) are affected in parallel with those of the ^{13}C nuclei, *i.e.*, the difference between β- and α-D-glucose in the chemical shift of all hydroxyl protons, except 4 and 6, amounts to a general increase in shielding (Fig. 1). Hence, inversion of the anomeric hydroxyl group from an equatorial orientation to an axial one is accompanied by a widespread change in polarization within most H–C–O–H groups of the molecules. The effects are distributed rather uniformly over positions 1, 2, 3, and 5, and fall off abruptly with positions 4 and 6 for each of the nuclei. This overall distribution is thus closely similar to the bond-polarization pattern exhibited by the isomeric 1,3,5-trimethylcyclohexanes[11]. It may be noted that the signs in Fig. 1 (+ and −) are reversed relative to the corresponding data on cyclohexanes[11]. In the

latter instances, they were used to express a numerical increase (+) or decrease (−) in shielding, whereas here they are intended to denote relative differences in electron density.

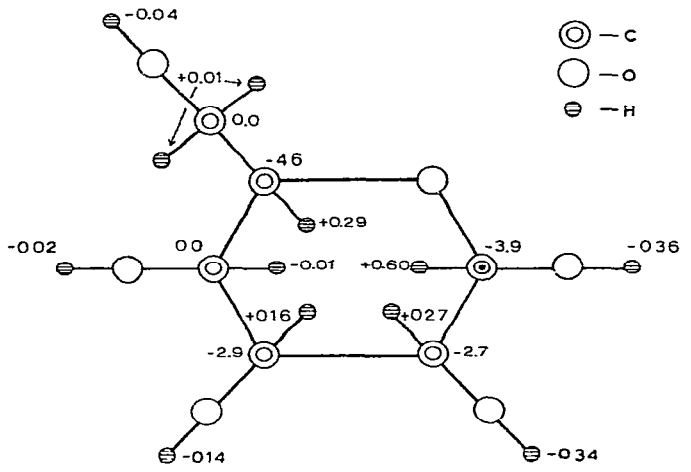


Fig. 1. ^{13}C and ^{1}H chemical-shift differences ($\Delta\delta$) between α- and β-D-glucose, corresponding to the changes observed when the orientation of the anomeric hydroxy group (at C*) is altered from *eq* to *ax* (β to α); −, increased shielding; +, decreased shielding.

A change in the polarization of a C–H bond may be ascribed to steric compression, or crowding[2,11,14–16]. Thus, the enhanced electron density of carbon and decreased shielding of its appended proton has been depicted as a preferential displacement towards carbon of the electron clouds of the interacting bonds[14]. In accord with this view are the several recognized instances in which sterically crowded hydrogens give rise to signals at lower field than those in a chemically similar, but less crowded, environment (see Ref. 15). Differences in the shielding of methyl protons of diastereoisomeric orthoacetates[17] or of isopropylidene groups[18] possibly arise in the same way. In these terms, increased polarization of the 3 and 5 C–H bonds of α-D-glucose may then be attributed to compression caused by the axial, anomeric hydroxyl-group. However, it is difficult to visualize how the same mechanism leads to increased polarization of the 1 and 2 C–H bonds, since the latter do not appear to be directly involved in the steric interaction. Although bond-anisotropy differences may account[19] for the lower-field resonance signal of equatorial H-1 than of axial H-1, it is not clear that they should account also for the observed change in polarization of the 1 C–H bond, nor that of the 2 C–H bond, and, presumably, of O–H bonds. Alternatively, as we have suggested in connection with cyclohexane derivatives[11], it is possible that the numerous readjustments of electron densities (represented by Fig. 1) originate in steric compression due to the anomeric inversion, and proliferate as part of a strain delocalization process whereby the molecule attains a minimum, overall energy-level.

P.m.r. spectra of α- and β-D-glucose. — Chemical shifts for the signals produced by α- and β-D-glucose in deuterium oxide solution (Table I) have been measured from

the spectrum recorded at 220 MHz (Fig. 2). Spacings are listed in Table II, and are described as J values because they differ little (not more than +0.5 Hz) from the corresponding spacings measured at 100 MHz (Fig. 3). In interpreting this 220-MHz spectrum, the following observations on spectra recorded at 100 MHz were utilized: H-2α, quartet in spectrum of α-D-glucose-*5,6,6'-d_3* in methyl sulfoxide-d_6–deuterium oxide (10:1) (Fig. 3A), and of α,β-D-glucose-*5,6,6'-d_3* in deuterium oxide (Fig. 3B), confirmed by spin-decoupling from H-lα. Chemical shifts differ slightly in these two solvents; H-2β, triplet in Fig. 3B, not present in 3A, confirmed by spin-decoupling from H-1β; H-3α, triplet in Fig. 3A, absent from spectrum of **1**; H-3β, triplet in Fig. 3B (in addition to that due to H-2β), absent from spectrum of **1**; H-4α, doublet in Fig. 3A; H-4β, second doublet in Fig. 3B; H-5,6 of each anomer, from comparisons of peak intensities and patterns in the spectra of D-glucose, D-glucose-*5-d* (Ref. 6), and D-glucose-*5,6,6'-d_3* (Ref. 6); *i.e.*, of pure anomers in methyl sulfoxide-d_6–deuterium oxide (10:1) and of α,β anomeric mixtures in deuterium oxide (*e.g.*, Fig. 3C).

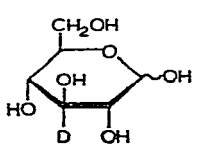
TABLE II

COUPLING CONSTANTS (Hz) FOR α- AND β-D-GLUCOSE[a]

	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
α	3.8	10.0	9.5	9.0	2.5[b]	4.0[b]	−12.0
β	8.1	8.5	8.8	9.0	2.0	5.0[b]	−12.2

[a] ±0.1 Hz. [b] ±0.5 Hz.

The H-5 resonance assignments listed in Table I are approximate, although probably good to within 0.1 p.p.m., and values for the 6-protons in Fig. 1 are averaged. The H-5,H-6 spacings (Table II) are close to those recorded for some acetates possessing the D-*gluco* configuration[20,21], which is pertinent to a recent discussion[21] of the preferred orientation of the primary carbinol group (free *vs.* acetylated) in such compounds.



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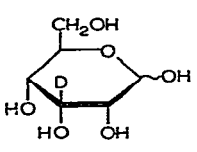

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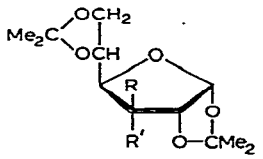
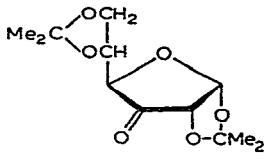


4 R = OH; R' = H
6 R = D; R' = OH
7 R = D; R' = OTs
8 R = OBz; R' = D
9 R = OH; R' = D



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Synthesis of D-*glucose*-3-d. — D-Glucose-*3-d* (**1**) and also D-allose-*3-d* (**3**) were synthesized* from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**4**). The latter was

*The authors gratefully acknowledge helpful discussion on this subject with Dr. W. A. Szarek.

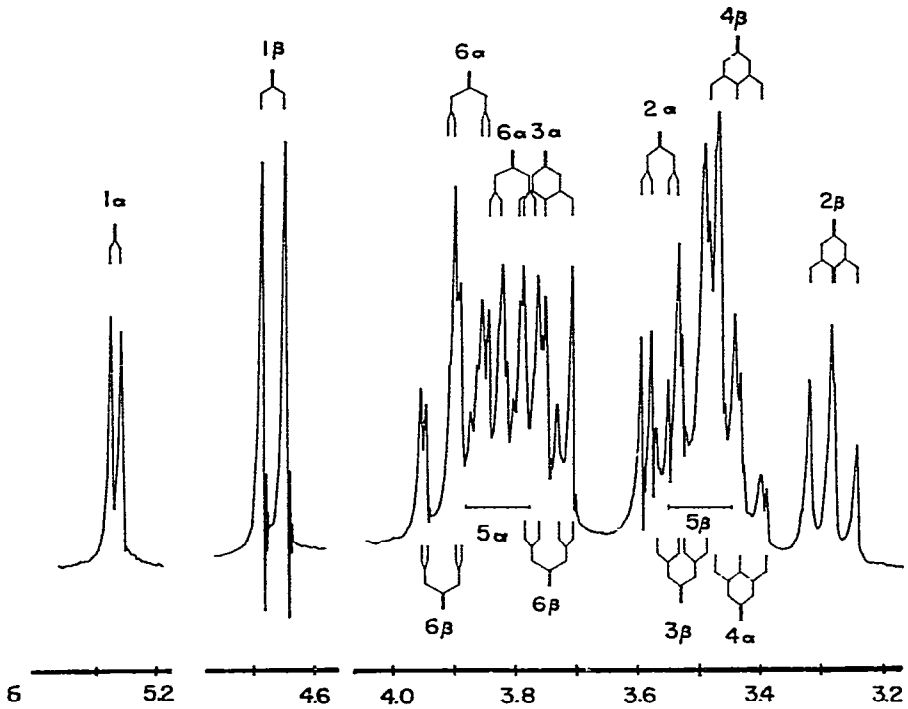

Fig. 2. 220-MHz p.m.r. spectrum of α,β-D-glucose in deuterium oxide at 60°.

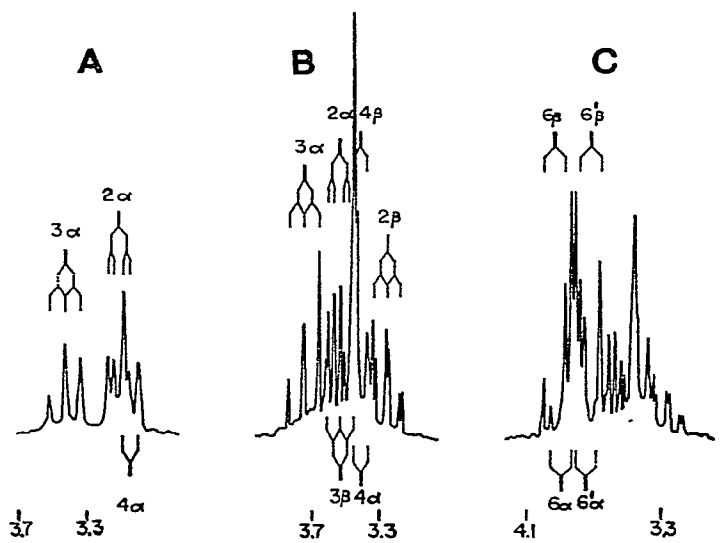

Fig. 3. Partial p.m.r. spectrum of A, α-D-glucose-5,6,6'-d_3 in methyl sulfoxide-d_6–deuterium oxide (10:1); B, α,β-D glucose-5,6,6'-d_3 in deuterium oxide; C, α,β-D-glucose-5-d in deuterium oxide (mainly α-D anomer, *i.e.*, a partially mutarotated solution of the α-D anomer).

oxidized with methyl sulfoxide and acetic anhydride[22], yielding 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose[23] (**5**). Hydride reduction of **5** is highly stereospecific and leads to the D-*allo*-hexose configuration[24]. Hence, reduction of the ketose with sodium borodeuteride afforded 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose-*3-d* (**6**). Compound **6** was converted into the toluene-*p*-sulfonate (**7**), and inversion at C-3 to the product having the D-*gluco* configuration (**8**) was effected readily by treatment of **7** with sodium benzoate in hot *N,N*-dimethylformamide[25]. On deacylation, **9** was obtained, which on acid hydrolysis yielded D-glucose-*3-d* (**1**). Similarly, **3** was obtained by acid hydrolysis of **6** and has been utilized in assigning ^{13}C resonance signals produced by D-allose[2].

EXPERIMENTAL

^{13}C-N.m.r. spectra were measured at 55° and with water as solvent, as described previously[2] with a Varian HA-100 spectrometer, modified for 25.15-MHz operation and using a Varian time-averaging computer (C-1024) and a doubly tuned probe (25 and 100 MHz). The sample was continuously proton-decoupled with a Varian heteronuclear decoupler. Methyl-^{13}C iodide (~90% enriched; Merck, Sharpe and Dohme, Montreal), contained in a coaxial capillary, furnished the internal reference "lock" signal. Chemical shifts are reported relative to carbon disulfide, which produces its resonance signal 213.1 p.p.m. (5370 Hz) downfield from the methyl iodide reference signal. Resolution was 0.1 p.p.m. or better.

1,2:5,6-Di-O-*isopropylidene*-α-D-*allofuranose*-3-d (**6**). — 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (**4**) (26.0 g) was oxidised[22] by methyl sulfoxide (300 ml) and acetic anhydride (200 ml) to give impure 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**5**, 31.1 g). Product **5** was not purified further, but a portion (3.0 g) was dissolved in 50% aqueous methanol (40 ml) and treated with sodium borodeuteride (0.5 g) during 20 min. Since small amounts of methyl sulfoxide, which is also reduced, may have been present, sufficient sodium borodeuteride was added to maintain an effervescence of hydrogen throughout the reaction period. The solution was diluted with water (20 ml) and extracted with chloroform (3 × 30 ml), and the extract was dried and evaporated to a colourless syrup (3.0 g). The product was crystallised from petroleum ether (b.p. 65–100°), giving a crude product (2.1 g) which was recrystallized once from petroleum ether and once from benzene–petroleum ether, to give 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose-*3-d* (**6**), m.p. 76–78°, $[\alpha]_D^{21}$ +34° (*c* 0.7, water); lit.[24], m.p. 77–78°, $[\alpha]_D^{22}$ +36° (*c* 0.5, water).

1,2:5,6-Di-O-*isopropylidene*-α-D-*glucofuranose*-3-d (**9**). — 1,2:5,6-Di-*O*-isopropylidene-α-D-allofuranose-*3-d* (**6**) (2.0 g), when treated with dry pyridine (20 ml) and toluene-*p*-sulfonyl chloride (1.8 g) in the usual manner, gave the 3-toluene-*p*-sulfonate (**7**) (2.9 g) which, when recrystallised twice from methanol–water, had m.p. 148.5–150°*, $[\alpha]_D^{22}$ +68.3° (*c* 0.8, ethanol).

*A lower-melting form (undeuterated) has been described by Foster *et al.*[26] and we also have obtained this form (m.p. 122°) by recrystallizing **9** from ethanol–hexane.

Compound **7** (0.8 g) was dissolved in dry *N*,*N*-dimethylformamide (40 ml), and sodium benzoate (3.0 g) was added. The suspension was heated under reflux for 24 h, water (50 ml) was then added to dissolve sodium benzoate, and the solution was extracted with chloroform (60 ml). The chloroform extract in turn was washed ten times with its own volume of water to remove *N*,*N*-dimethylformamide. After drying and filtering, concentration of the solution gave a colourless syrup of 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose-*3-d* (**8**) which was not purified further. Saponification was effected with dry methanol (40 ml) containing sodium methoxide (0.2 g), at room temperature for 2 h. The solution was neutralised with carbon dioxide and evaporated to dryness, and the residual solid was extracted thoroughly with chloroform. Evaporation of the extracts afforded a light-yellow, semi-crystalline mass, which was recrystallised twice from petroleum ether (b.p. 65–110°) to give 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose-*3-d* (**9**, 0.3 g), m.p. and m.m.p. 109–110°, $[\alpha]_D^{21} -12.0°$ (*c* 1.1, chloroform)*.

D-*Glucose*-3-d. — 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose-*3-d* (0.3 g) was dissolved in water (20 ml) containing Amberlite IR-120 (H^+) resin (5 ml), and the suspension was heated on the steam bath for 5 h. The resin was then filtered off and the filtrate evaporated to a syrup (0.18 g) which, dissolved in 1 ml of water, afforded the spectrum described in Table I.

β-D-*Allose*-3-d. — 1,2:5,6-Di-*O*-isopropylidene-α-D-allofuranose-*3-d* (**6**) (1.0 g) was hydrolysed, as described above, for the corresponding glucose isomer. The resulting syrup (0.6 g) was crystallised from ethanol to give material having m.p. 126–127°, $[\alpha]_D^{22} +12°$ (*c* 1, water, equil.).

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*Comparison of the p.m.r. spectrum of **9** with that of **4** ($CDCl_3$) showed, as required for **9**, the absence of a signal attributable to H-3 and collapse of signal H-4 to a doublet.

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