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CARBON-13 AND PROTON MAGNETIC RESONANCE SPECTRA OF D-GLUCOSE-^{13}C

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Relatively few compounds enriched with carbon-13 (^{13}C) have been examined by nuclear magnetic resonance spectroscopy (n.m.r.), and of these most have been labelled at one or two positions (1-3). We now report some ^{13}C and proton magnetic resonance (p.m.r.) data for D-glucose in which each of the six carbon atoms is isotopically enriched, approximately uniformly, to the extent of about 50%[1].

In water, the α:β anomeric composition of D-glucose is close to 2:3. Hence the p.m.r. spectrum of D-glucose-^{13}C in deuterium oxide (Fig. 1A) - in reflecting this mixture and the high isotope enrichment - shows two strong low-field satellite signals ($S_1\alpha$ and $S_1\beta$) associated with coupling of the two anomeric protons (H_1) with $^{13}C_1$. The observed splittings are 169 Hz (α anomer) and 160 Hz (β anomer). The upfield, satellite, signals of H_2 to H_6 show ^{13}C couplings of 140-145 Hz, close to the value for simpler alcohols (4). Hence the presence of the extra oxygen atom at C_1 increases splitting by 20-30 Hz, analogous to the effect of successively adding halogen atoms to an alkyl group (4).

Particularly noteworthy, as seen from a comparison of Figs. 1A and 1B, is the fact that ^{13}C enrichment of D-glucose gives rise to two discernable extra splittings[2] of 5-6 Hz when H_1 is equatorial (α anomer), whereas the $H_1\beta$ (axial) signal remains a sharp doublet. If such a difference proves to be characteristic of orientation, it should constitute a useful stereochemical parameter. In this context, $H_1\alpha$ is oriented <u>trans</u> with respect to $^{13}C_3$ (across

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1 Sample supplied by Merck, Sharp and Dohme, Montreal, Que., with the kind helpfulness of Miss A. Williams.

2 This multiplet and other signals arise from the superposition of simpler signals produced independently by the various species present (e.g., $-^{12}C_2-^{13}C_1-H_1$, $-^{13}C_2-^{12}C_1-H_1$, etc.; see (2,3)).

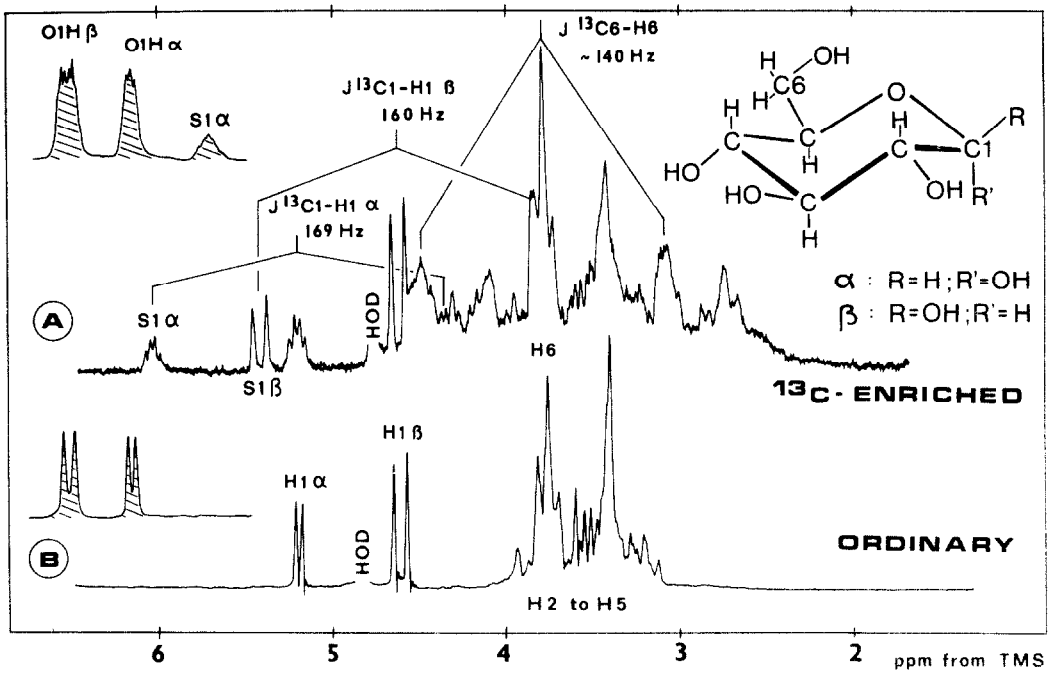

FIG. 1 - PMR SPECTRA OF D-GLUCOSE in D_2O (100 MHz)

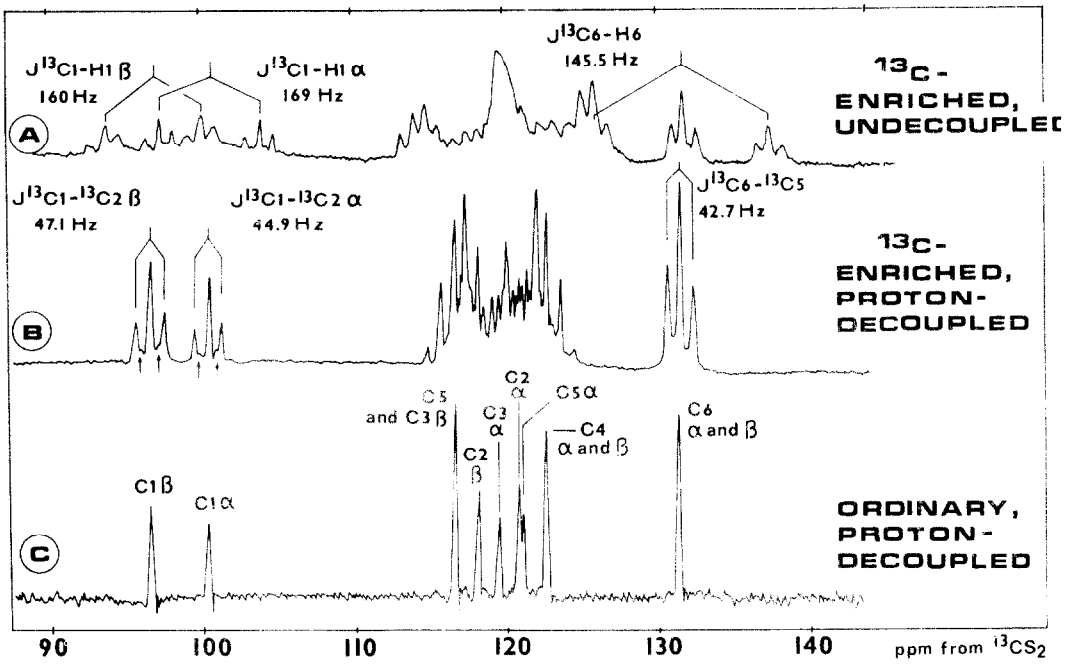

FIG. 2 - ^{13}C NMR SPECTRA OF D-GLUCOSE in H_2O (25.1 MHz)

the C_1-C_2 bond) and to $^{13}C_5$ (across the C_1-O_5 bond), whereas $H_1\beta$ is gauche relative to both of them, which at least qualitatively agrees with calculated values of 7.8 and 0.7 Hz, respectively, for trans and gauche ^{13}C couplings in ^{13}C-C-C-H systems (1). Similarly, spin-spin splitting of about 4Hz is to be expected for coupling between H_1 and $^{13}C_2$ (5) and, presumably, accounts for part of the multiplicity of the $H_1\alpha$ signal. However, $H_1\beta$ clearly does not interact appreciably with $^{13}C_2$, implying that ^{13}C-C-H coupling also is subject to steric influence.

Hydroxyl proton resonance signals for α- and β-D-glucose in dimethyl sulphoxide also are affected by the ^{13}C enrichment (shaded inset Fig. 1A and 1B). For example, the OH_1 signals are multiplets arising probably from two to four spin systems because of additional coupling with $^{13}C_1$ and/or $^{13}C_2$ (Fig. 1A). All spacings are of the order of a few Hz, which suggests that in each isomer the orientation of the O-H bond relative to neighboring atoms is similar.

The ^{13}C n.m.r. spectrum of the enriched D-glucose (Fig. 2A; 0.3g/0.5ml H_2O, 30 (50 sec.) scans) confirms the magnitude of ^{13}C-H couplings associated with C_1 and C_6. Complete decoupling of ^{13}C-H interactions[3] permits a clearer observation of ^{13}C resonance signals and ^{13}C-^{13}C spin-spin splittings, particularly for the $C_1\alpha$, $C_1\beta$ and $C_6\alpha+\beta$ signals (Fig. 2B; 10 (50 sec.) scans). Each appears to be a composite of a singlet[4] (due to the absence of $^{13}C_2$ and $^{13}C_5$) and a doublet of 40-45 Hz[5] (due to the presence of an adjacent ^{13}C atom); these two signal components are of about the same intensity, in accord with the approximately equal probability that isolated ^{13}C and adjacent ^{13}C-^{13}C arrangements occur at positions 1 and 2, or 5 and 6.

Surprisingly, when considered relative to proton resonance characteristics, there is no indication that spin-spin coupling (> 0.5-1.0 Hz) occurs across more than one bond, aside from very weak signals designated by (↑). That is, there appears to be little or no "geminal" coupling between $^{13}C_1$ and $^{13}C_3$, $^{13}C_1$ and $^{13}C_5$, or $^{13}C_6$ and $^{13}C_4$. Similarly, no interaction is evident in the trans structures $^{13}C_1$-O_5-C_5-$^{13}C_6$, $^{13}C_3$-C_4-C_5-$^{13}C_6$, nor in the gauche structure

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[3] By means of a Varian 25.1/100 MHz doubly-tuned probe and Heteronuclear Decoupler.

[4] Note that these central components have the same chemical shift and approximate line width as the corresponding singlets of the natural abundance ^{13}C spectra (Fig. 2C).

[5] These much larger spacings than found for adjacent sp^3 carbons of enriched hydrocarbons (34 Hz (2,3)) are attributed to the associated oxygen atoms.

comprising $^{13}C_1$-C_2-C_3-$^{13}C_4$. We associate the multiplicity of the signals of carbons 2-5 with the fact that each can couple with two adjacent nuclei, although some of the splittings could arise from longer range interactions.

Fig. 2 serves also to illustrate the range of ^{13}C chemical shifts that are encountered with some sugar molecules. This range is typical of the simple sugars, as determined from proton-decoupled natural-abundance ^{13}C n.m.r. spectra such as shown for ordinary D-glucose (Fig. 2C; 0.5g/0.5ml H_2O, 800 (50 sec.) scans). Assignments in Fig. 2C were obtained by a combination of procedures, including selective deuteration to eliminate various ^{13}C resonance signals (6) and reference to chemical shifts in the spectra of derivatives[6]. The large difference between chemical shifts for $C_1\alpha$ and $C_1\beta$ - which is opposite in sign to that of the two H_1 signals - shows the impact of orientation on ^{13}C chemical shifts, and is in accord with observations on cyclohexanols (7). Moreover, since C_2, C_3 and C_5 (each of which has an equatorial OH group) show similar α β differences in chemical shift (Fig. 2C), this impact of orientation is felt across one and two bonds (but not three; i.e., C_4 and C_6 are unaffected).

A fuller treatment of these data, and related findings with other carbohydrates, is to be presented elsewhere.

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[6] As would be expected, the chemical shift of a given carbon atom is affected strongly by introduction of such groups as O-methyl or O-acetyl, or by oxidation, etc.