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IONIZATION AND MUTAROTATION OF HEXOSES IN AQUEOUS ALKALINE SOLUTION AS STUDIED BY ^{13}C-NMR SPECTROSCOPY

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Ionization and mutarotation phenomena of hexoses have been studied extensively in the literature[1,2]. However, neither the precise nature of the ionized species nor the rate-determining step of the mutarotation in aqueous alkaline solution has been established as such. Moreover, the differences in the acid strength between the anomeric forms of the hexoses never have been measured.

We have performed a ^{13}C-NMR spectroscopic investigation of glucose, mannose and fructose in aqueous alkaline solution, from which further conclusions may be drawn with respect to the above-mentioned phenomena. The spectra have been measured at 3-4 ^{o}C in order to prevent degradation reactions in the alkaline medium[3]. The ^{13}C-chemical shift data for glucose and mannose were correlated with a mixture of α - and β -pyranose forms in neutral medium, which is in accordance with the literature[4,5]. For fructose only the concentration of the β-pyranose form allowed accurate measurements. The assignments of this fructose form reported in the literature[6,7] are contradictory. The present data point to the assignment as given in Table 1 (δ_o-values).

The ^{13}C-resonances of the hexoses were found to shift substantially upon ionization. As an example, the dependence of the ^{13}C-chemical shifts of α-glucopyranose(1) in deuterium oxide as a function of the amount of KOH added is given in Fig. 1. (The numbering of the carbon atoms of the hexoses is given in Fig. 2). For convenience, the differences in chemical shift of the completely ionized and the neutral hexoses ($\Delta\delta$) are defined as the variation of chemical shift (ppm) going from 0 to 1.45 equiv. KOH. Positive $\Delta\delta$ values denote a downfield shift, negative $\Delta\delta$ values an upfield shift. The chemical shifts (δ_o, without KOH) and the $\Delta\delta$ values for α- (1) and β-glucopyranose (2), α- (3) and β-mannopyranose (4), and β-fructopyranose (5) are summarized in Table 1.

The chemical shifts of the anomeric carbon atoms were influenced rather strongly upon addition of KOH ($\Delta\delta$ is 3.1-5.8 ppm to lower field). A similar effect was observed for the neighbouring carbon atoms (C-2 for 1-4, C-1 and C-3 for 5; 1.5-3.7 ppm to lower field). On the other hand the resonance of carbon atom C-5 (i.e. C-6 for 5) was found to shift to higher field (0.4 ppm for 2 and 0.6 ppm for 4, 1.4 ppm for 1 and 1.5 ppm for 3, 1.8 ppm for 5).

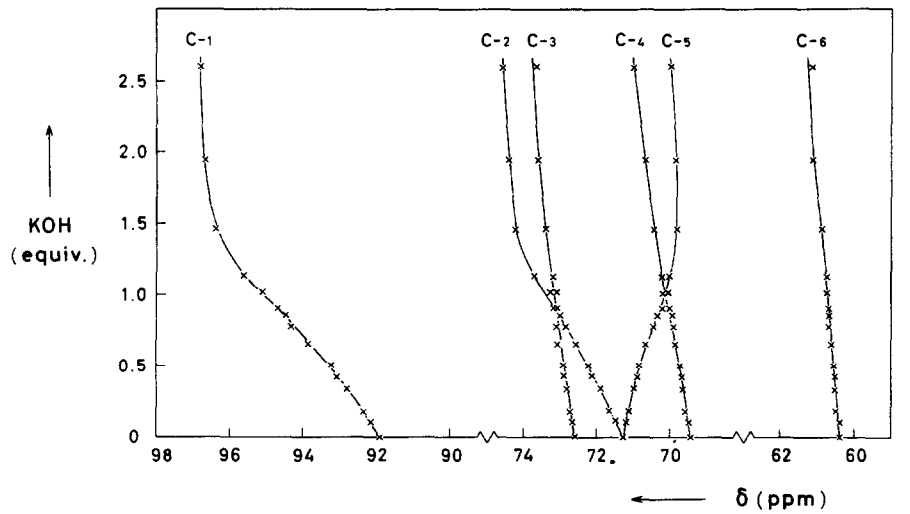
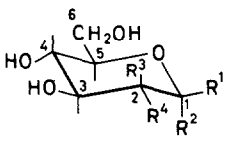


Fig. 1 ^{13}C-NMR chemical shifts of α-glucopyranose (1, 5.67 mmole) in deuterium oxide (5.0 ml) at 3-4 °C as a function of KOH added.

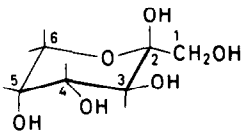


1 α - glucopyranose R^1=H, R^2=OH, R^3=H, R^4=OH

2 β - glucopyranose R^1=OH, R^2=H, R^3=H, R^4=OH

3 α - mannopyranose R^1=H, R^2=OH, R^3=OH, R^4=H

4 β - mannopyranose R^1=OH, R^2=H, R^3=OH, R^4=H



5 β-fructopyranose

Fig. 2

Table 1. δ_o (ppm,TMS) and Δδ (ppm) values of 1-5 in D_2O at 3-4 °C

hexose:	1		2		3		4		5	
carbon atom	δ_o	Δδ	δ_o	Δδ	δ_o	Δδ	δ_o	Δδ	δ_o	Δδ
1	94.9	4.8	95.7	5.5	93.9	5.8	93.5	5.5	63.7	1.5
2	71.2	3.0	74.0	3.0	70.6	3.7	71.1	3.1	98.0	3.1
3	72.6	1.0	75.6	0.7	70.1	1.0	72.9	1.2	67.3	1.6
4	69.4	1.0	69.4	1.2	66.7	0.7	66.4	0.9	69.6	1.2
5	71.2	-1.4	75.6	-0.4	72.2	-1.5	76.1	-0.6	69.1	0.7
6	60.4	0.4	60.6	0.6	60.9	0.2	60.9	0.2	63.3	-1.8

The shifts observed cannot be explained by a simple ionization according to

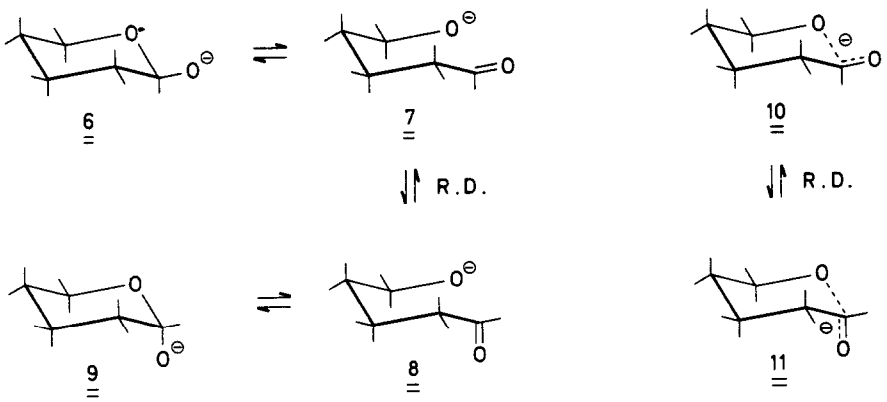
since then a slight upfield shift would be expected for the anomeric carbon atom. For this reason, the ionized species has to be considered either as rapid equilibrium between cyclic and acyclic ionized species (6 ⇄ 7 or 8 ⇄ 9) or as a non-classical anion (10 or 11). It may be noted that the occurrence of 1,2-enediol anions is less probable since no mannose-glucose interconversion could be detected under these conditions. The induced shift of the anomeric carbon atom upon ionization points to the presence of about 5 per cent open-chain ion i.e. C=O bond character[8,9]. The occurrence of such ionized species is further in accordance with the variation in chemical shift for the 5- and 6- carbon atoms of 1-4 and 5, respectively. The upfield shift mainly will be brought about by the diamagnetic anisotropy of the carbonyl group[11]. Molecular models show (assuming a chair-like conformation of 7 and 8 with a minimum of geometric change upon ionization) that for 8 C-5 is situated (i) more closer to the C=O bond (about 0.4 Å) and (ii) more in the middle of the shielding cone of the carbonyl group as compared to C-5 of 7. Consequently, the C-5 atoms of 1 and 3 (and the C-6 atom of 5) will be more shielded as compared to 2 and 4, which is in agreement with the experimental data. A similar explanation may be given assuming 10 and 11 as the anionic species.

In conclusion the rapid C-O bond -breaking and -making process (or the non-classical anion) in combination with the observed rather slow α-β isomerization reaction (both with respect to the ^{13}C-NMR time scale) clearly shows that the rate-determining step of the mutarotation reaction in aqueos alkaline medium is the rotation around the -CHOH—C(=O)R bond (7 ⇄ 8 or 10 ⇄ 11, respectively).

With this mechanism of mutarotation it is to be expected that the rate of mutarotation of glucose and mannose (R=H) will be greater than that of fructose (R=CH_2OH, α- to β-pyranose), which is in agreement with preliminary results from the degradation of glucose, mannose and fructose in aqueous alkaline medium[12]. Furthermore, the energy barrier of rotation will be dependent on the position of the 2-OH group, which explains the difference in rate of mutarotation between mannose and glucose[3].

Finally, the ^{13}C-NMR titration curves[13], as given in Fig. 1, allow an estimation of the difference in pKa between the various anomers. Compounds 1, 4 and 5 were found to be less acidic (ΔpKa ≈ 0.6) than 2 and 3, showing that an eq-ax sequence of the anomeric hydroxyl and its neighbour results in a less favourable ionization as compared to an ax-ax or eq-eq sequence.

Further work regarding the accurate determination of the pKa values and the mechanism of mutarotation in aqueous and other media is in progress.



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8. The percentage of the open-chain ion is calculated from $\Delta\delta / (\delta_{C=O} - \delta_{O}) \cdot 100$ per cent, with $\delta_{C=O}$ = 200 ppm.
9. In neutral aqueous solution the percentages of the open form for glucose and mannose[3], and for fructose[10] are 0.024, 0.064 and 0.5-0.6, respectively.
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