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THE HYDROXYL GROUP PROTONATION RATES OF α, β and γ-CYCLODEXTRINS IN DIMETHYL SULPHOXIDE

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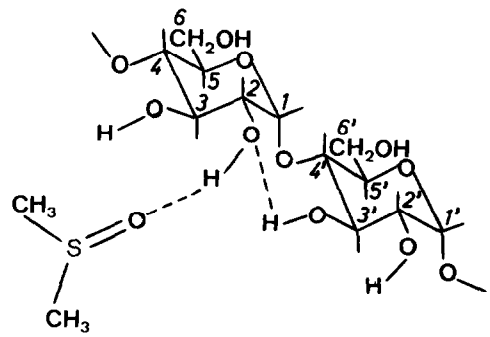
Abstract : The mobility k of the hydroxylic protons of α, β and γ-cyclodextrins are in the order $k_{OH(6)} > k_{OH(2)} > k_{OH(3')}$, thus revealing an intramolecular HO(2)...HO(3') hydrogen-bond in which the OH(2) hydroxyl group is the donor.

Three types of NMR experiments are currently used to study hydrogen-bonded species in solution (1) Solvent effects, (2) Dilution shifts (3) The temperature coefficient $p = d\delta/dT$ of the chemical shifts δ of the acidic hydrogens[1]. For solutions of carbohydrates in dimethyl sulphoxide (DMSO-d_6), the chemical shifts of the various hydroxyl groups are found to be independent from the concentration up to *ca.* 0.7 mol.dm^{-3}, thus showing the absence of dimer solute-solute associations[2,3]. Only method 3 is therefore meaningful in this case. The purpose of this method is to distinguish between hydroxyl groups of the solute molecules which are hydrogen-bonded to the solvent and those which can establish an intramolecular hydrogen-bond with a donor site - a neighbouring hydroxyl group in the case of carbohydrates - born by the same solute molecule. Temperature coefficients have been widely used by peptide chemists to delineate between NH protons which are solvent shielded ($p \approx 0$) and those which are accessible to the solvent ($p \neq 0$)[4]. The method has been recently extended to the case of oligo- and polysaccharides, such as maltose, α and β- cyclodextrins (CD), or amylose[5,6]. The crystal structure[7,8] of these compounds has revealed an intramolecular hydrogen-bond between the OH(2) and



OH(3') hydroxyles born by two adjacent glucopyranose units, the OH(2) hydroxyl group being the donor in this interaction. In dimethyl sulphoxide solutions, St-Jacques and his coworkers[5] proposed, on the basis of the temperature dependence of the hydroxyl groups chemical shifts, the existence of an intramolecular hydrogen-bond between the OH(2) and OH(3') hydroxyl groups of maltose and cyclodextrins, but with the OH(2) group being the acceptor. Another independent method would therefore be most useful to put these conclusions on a firmer basis. In fact, peptide chemists are currently using a second criterion to distinguish between intra and intermolecular hydrogen bonding in cyclic oligopeptides, namely the deuterium-proton exchange rate k_{HD} in a DMSO/D_2O mixture[4]. The exchange is assumed to be faster for acidic protons which are the more accessible to D_2O molecules, i.e.,in the above example, for the N-H protons which are not hydrogen-bonded to the carbonyl group of a neighbouring peptide residue.

Deuterium exchange rates however cannot be easily measured for hydroxyl protons of carbohydrates in DMSO as they exchange much more rapidly with D_2O than amide protons. This drawback can be easily circumvented by studying the protonation rates of the various hydroxyl groups contained in a given carbohydrate molecule, measured by proton DNMR[11]. We have recently described experimental procedures for this purpose, using aliphatic alcohols[12], cyclohexanols[13] and monosaccharides[11]. In slightly acidic DMSO, proton exchanges are shown to arise exclusively from the protonation of the hydroxyl groups (denoted ROH) by solvated protons followed by the fast reverse reaction[12] :

$$ROH + DMSO...H^+ \overset{k}{\underset{}{\rightleftharpoons}} ROH_2^+ + DMSO$$

$$ROH_2^+ + DMSO \overset{fast}{\rightleftharpoons} ROH + DMSO...H^+$$

Chemical exchange (k) is consequently twice as fast as the NMR site exchange $k = 2k_{NMR}$. Using a series of 26 monosaccharides, we have shown that the exchange rate k might constitute a reliable non-destructive reactivity index of carbohydrates[11].

This paper reports preliminary results obtained by this method with the α, β and γ- CD. These three molecules are torus-shaped cyclic oligosaccharides consisting of six, seven or eight α-(1→4)-linked glucopyranose residues, respectively[9-10]. The OH(6) hydroxyl groups of each glucose unit are attached to the top, and the OH(2) and OH(3') hydroxyl groups to the bottom of the torus[14]. Operating at high frequencies - 250 MHz for the α- and β-CD, and at 400 MHz for the γ-CD - was necessary to prevent line overlapping. The improved resolution thus achieved allowed us to complete the data from the literature[5-6] obtained at lower frequencies for the hydroxyl groups chemical shifts and temperature coefficients. Our results are summarized in Table 1.

Looking first at α-cyclodextrin, the OH(6) hydroxyl group has parameters δ and p very similar to those obtained for the hydroxyl groups of an individual D-glucose molecule.The OH(2) and OH(3') hydroxyl groups are both deshielded by about 1 ppm, as observed by Casu and coworkers[2]. The temperature coefficient

Table 1. Chemical shifts δ (in ppm from TMS at 25°C), rate constants k ($10^6 M^{-1}s^{-1}$ at 25°C) and temperature coefficients p = dδ/dT (in Hz/°C at 250 MHz) of the OH(2), OH(3') and OH(6) protons of α, β and γ-cyclodextrins in 0.05M-DMSO-d_6 solutions

		α-CD	β-CD	γ-CD
OH(2)	δ	5.52	5.72	5.74
	p	1.15	1.35	1.36
	k	2.55	2.32	2.06
OH(3')	δ	5.43	5.66	5.77
	p	0.72	1.02	1.15
	k	1.38	1.08	0.94
OH(6)	δ	4.50	4.47	4.53
	p	1.33	1.40	1.46
	k	3.57	3.90	3.57

of OH(2) is relatively close to the one of OH(6), while the temperature coefficient of OH(3') is clearly smaller, as observed by St-Jacques and coworkers[5]. The existence of an intramolecular hydrogen-bond is nicely confirmed by the hydroxyl groups protonation rates which follow the expected order : OH(6) and OH(2)>OH(3'). However a closer examination of all these data makes the situation less straightforward than it looks at first sight. The OH(6) parameters δ and p are indeed quite similar to those of α-D-glucose[5], while the proton exchange is approximately slower by half[11] (3.57 against $7.31\times10^6 M^{-1}s^{-1}$). This is presumably due to the attachment of the OH(6) hydroxyl group to the torus which considerably decreases the number of incoming DMSO...H^+ ions (by half if the basis of the torus could be assimilated to an indefinite plane). Parameters δ and k of OH(2) are substantially different from those of OH(6), while they are expected to be very similar if we assume that the acidic hydrogen of OH(2) is not engaged in the intramolecular hydrogen-bond. We must then admit that the formation of the intramolecular hydrogen-bond $_{H}$-O(2)...H-O(3') is closely paralleled by an increase of the acidity of OH(2). Such a consideration is reminiscent of a classical observation in coordination chemistry for quite similar situations in which a donor atom bearing a hydrogen atom is joined to a Lewis acid in a coordination compound[15]. The resultant displacement of electronic charge toward the Lewis acid is expected to facilitate the ionization of a proton from the ligand and this has been demonstrated in numerous examples, e.g. in the aquo-complexes of metal ions in which the acidity of the water molecules may be drastically increased.

Finally, if we compare the results obtained for the α, β and γ-CD, we observe no alteration of the OH(6) parameters, within experimental uncertainties. On the contrary, a slight increase of δ and a parallel clear decrease of

k is observed for OH(2) and OH(3') by going from the α to the β and γ-CD. This behaviour reveals a reinforcement of the intramolecular hydrogen bond (from the α to γ-CD), itself resulting into a parallel increase of the acidity of the OH(2) hydroxyl group,as mentioned above. The strengthening of the intramolecular hydrogen bond can be traced to slight conformational changes in the structure of α, β, γ-CD, themselves resulting into a shortening of the O(2)-O(3') distance (from the α to γ-CD). The only discrepancy in this picture is the temperature coefficient of OH(3') which unexpectedly increases from the α to γ-CD. It must be observed that the temperature coefficients of OH(2), and even of OH(6) to a lesser extent are also increasing from the α to γ-CD. Temperature effects are presumably rather complex because of the great variety of hydrogen-bonded species present in the solution and of the unknown effects of diamagnetic anisotropies[1] in each of them.

In conclusion, protonation rates of the hydroxyl groups of cyclodextrins may bring important information upon intramolecular hydrogen-bonding. Further investigations are in progress to extend these results to linear oligo and polysaccharides.

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