

^1H and ^{13}C N.M.R. Observation of ^2H Isotope Effects transmitted through Hydrogen Bonds

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Observation of novel isotope effects by ^1H and ^{13}C n.m.r. spectroscopy of cyclodextrins in which exchangeable hydroxy-protons are partially deuteriated is reported.

We report on novel isotope effects observed by ^1H and ^{13}C n.m.r. spectroscopy of cyclodextrins in which exchangeable hydroxy-protons are partially deuteriated. In addition to positive isotope effects on the residual water signal (2 bonds, HOD vs. HOH)[†] and on the sugar ring methine protons (3 bonds, HCOH vs. HCOH), a new isotope effect is observed that is transmitted through hydrogen bonds ($\text{O}-\text{D} \cdots \text{O}-\text{H}$ vs. $\text{O}-\text{H} \cdots \text{O}-\text{H}$). The latter effect has important practical applications in observing and understanding hydrogen-bonded systems and important theoretical implications because both positive and negative isotope shifts are observed in the same molecule.

α -, β -, and γ -cyclodextrins are cyclic oligosaccharides consisting of six, seven, or eight 1 \rightarrow 4 linked α -D-glucose units. They form inclusion compounds with smaller molecules which fit into their 5–8 Å cavity and the complexes have a wide range of uses in research and industry.¹ In the solid state, X-ray crystallographic studies have shown that the 'round' but slightly conical form of cyclodextrins is stabilised by intramolecular hydrogen bonds between OH-2 and OH-3

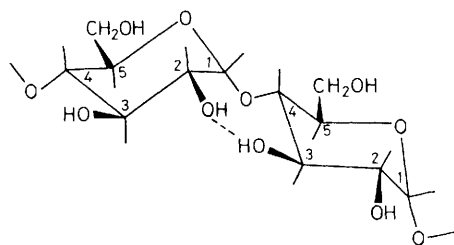


Figure 1

groups of adjacent glucose units. Both $\text{O}-3-\text{H} \cdots \text{O}-2$ and $\text{O}-3 \cdots \text{H}-\text{O}-2$ hydrogen bonds exist¹ as indicated in the partial structure shown in Figure 1. ^1H N.m.r. studies of cyclodextrins show that such hydrogen bonds are stable even in dimethyl sulphoxide solution and analysis of $^3J(\text{HCOH})$ magnitudes together with the temperature dependence of OH-2 and OH-3 signals is consistent with predominance of the $\text{O}-3-\text{H} \cdots \text{O}-2$ hydrogen bond.² After partial deuteration of the hydroxy-groups, the 400 MHz ^1H n.m.r. spectra of cyclodextrins in dry $(\text{CD}_3)_2\text{SO}$ solution (Figure 2) exhibit two resonances for both the OH-3 and OH-2 signals (labelled OH

[†] For clarity ^2H is designated D to distinguish the isotope from ^1H for exchangeable protons.

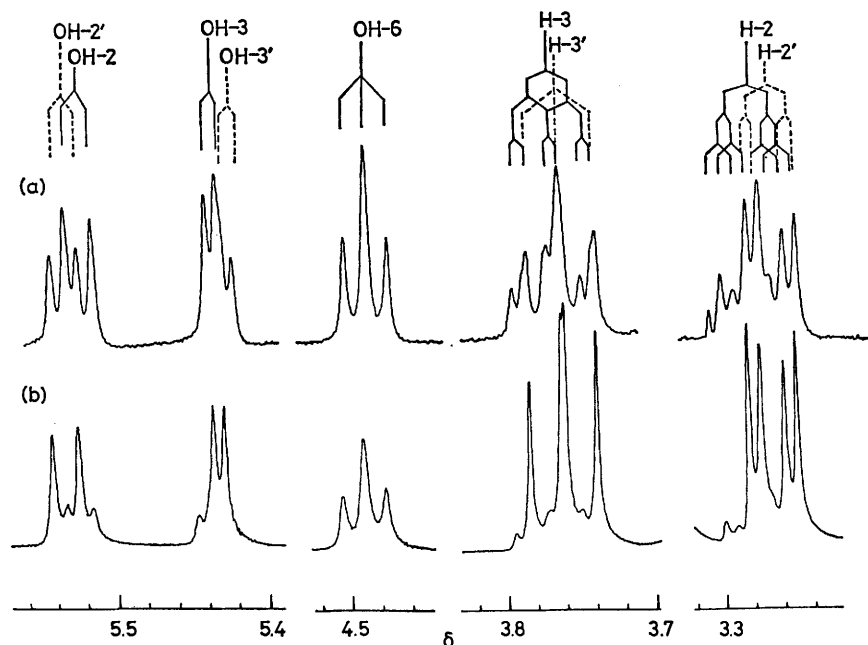
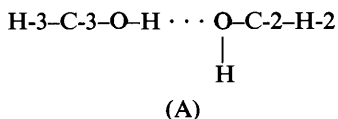


Figure 2. Part of the 400 MHz ^1H n.m.r. spectrum of α -cyclodextrin in $(\text{CD}_3)_2\text{SO}$ solution at different levels of deuteration: (a) 40%, (b) 80%.

and OH') and each resonance exhibits the same coupling constant to the corresponding methine proton *i.e.* OH-2 , 7.1 Hz; OH-3 , 2.3 Hz. The spectra of α -cyclodextrin at two different deuteration levels (40 and 80%, Figure 2) show that isotope effects are exhibited not only by the OH-2 and OH-3 signals but also by the corresponding methine signals H-2 and H-3 and the residual water signal. The intensities of the OH and OH' signals vary with the ratio of the two water signals and the two signals for both the C-2 and C-3 methine protons (H-2 and $\text{H-2}'$, H-3 and $\text{H-3}'$). The two-bond isotope effect has been observed previously for water (HOD vs. HOH) in a number of solvents⁹ and the present observations of the C-2 and C-3 methine and hydroxy-protons can be rationalised⁴ quantitatively in terms of the statistical distribution of hydrogen and deuterium atoms between the hydroxy-groups and water, assuming the hydrogen-bonding scheme (A) of Marchessault and co-workers.²



The three-bond isotope effects on H-2 and H-3 signals are exhibited by those species where OD replaces OH-2 and OH-3 , respectively; the isotope shifted signals ($\text{H-2}'$ and $\text{H-3}'$) move to low frequency (positive effect) and exhibit a simplified coupling pattern because the vicinal coupling to the hydroxy-proton cannot be observed for the deuteriated species. The isotope effects observed on the hydroxy-protons are manifested by those species in which D replaces H in the adjacent hydroxy-group. $\text{C-3-O-H} \cdots \text{OD-C-2}$ vs. $\text{C-3-O-H} \cdots \text{OH-C-2}$ for OH-3 and $\text{C-3-O-D} \cdots \text{OH-C-2}$ vs. $\text{C-3-O-H} \cdots \text{OH-C-2}$ for OH-2 . The magnitudes of these 'two-bond' isotope effects (*ca.* 0.01 p.p.m.) are about half that observed for water (0.023 p.p.m.) in the same solvent and, whereas OH-3 exhibits a positive effect (similar to HOH , H-2 , and H-3) the OH-2 signal exhibits an unusual negative isotope effect.

Introduction of a heavier isotope is known to cause increased shielding in nuclei up to two bonds away by shortening of the bonds involved;⁵ similar positive effects are observed on the H-2 and H-3 signals of cyclodextrin over three bonds though the effect of deuteration on the H-C-O-D bond lengths is not known. Up to the present time only a few negative isotope shifts have been observed⁶ during measurements of a number of primary isotope shifts, $\sigma(\text{H})-\sigma(\text{D})$.[†] Negative effects are exhibited by the hydrogen maleate anion, hydrogen phthalate anion, and benzyl alcohol and have been qualitatively explained in terms of the effects of ^1H , ^2H , and ^3H on the vibrational amplitudes of corresponding bonds.⁶ The isotope shifts exhibited by the hydroxy-groups of cyclodextrin represent secondary isotope effects, $\sigma(\text{HH})-\sigma(\text{HD})$, and both factors may need to be taken into account to explain the positive and negative effects because deuterium substitution of hydrogen bonds can either weaken or strengthen the bond.⁷

Although there is no direct evidence of the effect of deuteration on the hydrogen bond strength, present studies show that there is a small variation in the magnitude of the isotope effect on OH-2 and OH-3 ($\Delta\delta$, α 0.01 > β 0.009 > γ 0.006 p.p.m.) which mirrors the variation in $\text{O} \cdots \text{O}$ distance observed in *X*-ray crystallographic studies of cyclodextrin complexes (α 3.00, β 2.86, and γ 2.81 Å). It is expected that ^1H n.m.r. isotope shift studies of partially deuteriated species can be extended to other hydrogen bonding systems of the type $\text{H} \cdots \text{X-H}$ ($\text{X} = \text{O}, \text{N}, \text{S}$ etc.), and to the general type $\text{X-H} \cdots \text{Y}$ by observation of other nuclei (^{13}C , ^{15}N , ^{17}O etc.). Indeed the latter prediction is confirmed by observation of the isotope effect in the ^{13}C n.m.r. spectra of the cyclodextrins.⁴ Not only is the expected two-bond effect observed on the C-2 , C-3 , and C-6 signals (D-O-C vs. H-O-C)⁸ but also, in our work, the isotope effect transmitted through a hydrogen bond is observed on the C-2 signal ($\text{D} \cdots \text{O-C}$ vs. $\text{H} \cdots \text{O-C}$).⁴ This confirms the hydrogen bond conformational model for cyclo-

[†] The primary isotope effect on n.m.r. chemical shifts of hydrogen isotopes may be expressed as $\Delta\delta(^1\text{H}, ^2\text{H}) = \delta(^1\text{H}) - \delta(^2\text{H})$.

dextrin in solution, and the explanation of signals observed in the ^1H n.m.r. spectra in terms of a novel isotope effect being transmitted through hydrogen bonds.

Added in proof. A similar isotope effect observed by partial deuteration of hydroxy-groups of sucrose has recently been reported by K. Bock and R. U. Lemieux (*Carbohydr. Res.*, 1982, **100**, 63).

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