

Disposition of Copper(II) in β -Cyclodextrin

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Abstract. Distances of glucose protons in β -cyclodextrin (BCD) from copper(II) in copper(II)- β -cyclodextrin have been determined from ^1H NMR spin-lattice relaxation time (T_1) measurements for the first time. Very low T_{1p}/T_{2p} values indicated the dipolar mechanism to be the most dominant one in determining the paramagnetic contribution to relaxation. The distances of copper(II) from BCD glucose protons indicated copper(II) to be present almost in the centre, inside the cavity in the same plane as H-1 and H-4. An average distance of about 5.0–5.9 Å was obtained for copper(II) from the H-2, H-3, H-1, H-4 and H-6 a and b protons in BCD.

Key words: Cu(II)- β -cyclodextrin, T_1 , proton distances, copper disposition.

1. Introduction

Copper(II) forms a 1 : 1 as well as a 2 : 1 complex with cyclodextrins in alkaline solutions [1]. The exact structure of the complexes is still not known with certainty. However, molecular models have suggested that two pairs of C-2 and C-3 hydroxyl groups of contiguous glucose units are cross-linked by a $\text{Cu}(\text{OH}^-)(\text{O}_2^-)\text{Cu}$ ion bridge in the β -cyclodextrin complex with a probable distortion in the cyclodextrin ring due to complex formation [1].

In order to arrive at the disposition of copper(II) in cyclodextrin, ^1H NMR T_1 measurements were carried out and distances of sugar protons from copper(II) within BCD were determined for the first time.

2. Materials and Methods

β -Cyclodextrin was a gift from Amaizo Inc. (USA). Copper sulphate pentahydrate and zinc sulphate heptahydrate were purified by recrystallization. The complexes were prepared as follows. Typically, 5 mL of 0.08M BCD was added to a 5 mL alkaline solution of CuSO_4 (0.005 M, pH 13.0), when the precipitated $\text{Cu}(\text{OH})_2$ dissolved to give a clear blue solution of Cu(II)-BCD complex. The complex was precipitated with ethanol and washed with ethanol repeatedly before drying in air. The complexes were used within one or two days of preparation to avoid decomposition reactions, which were apparent from color changes observed in the complex after a time. The concentration of the complexed Cu(II) was determined

titrimetrically against EDTA [2]. A Zn(II) complex of BCD was also prepared similarly.

About 20 mg of the freshly prepared complexes and BCD were dissolved in 0.5 mL D₂O for T_1 measurements. Bruker AM-300 and AC-200 NMR instruments operating at 300 MHz and 200 MHz for protons, respectively, fitted with a Spectrospin magnet and an Aspect 3000 computer were used. The probe temperature was maintained at $20 \pm 1^\circ\text{C}$. The inversion recovery method involving a 180° - τ - 90° -Acq- $5T_1$ pulse sequence was employed for determining T_1 . The other details regarding the measurements of T_1 values were as described before [3].

T_{1p}^{-1} was determined by detecting the contribution of the diamagnetic term T_{1d}^{-1} from T_{1M}^{-1} as shown below

$$T_{1M}^{-1} = T_{1d}^{-1} + T_{1p}^{-1}$$

T_{1M}^{-1} was obtained from the relation

$$T_{1\text{obs}}^{-1} = X_f T_{1,0}^{-1} + X_b T_{1M}^{-1}$$

where T_{1M}^{-1} = measured relaxation rate; $T_{1\text{obs}}$ = observed relaxation time for the complex; T_1 = relaxation time of the free sugar; and X_f and X_b are free and bound fractions of BCD, respectively.

T_{2p}^{-1} values were obtained from the relation

$$T_{2p}^{-1} = \pi(W_{\text{Cu}} - W_0).$$

W_{Cu} and W_0 are the line-widths at half-height in Hz, with and without BCD, respectively.

T_{1p}^{-1} can be related to the distance by a simplified Solomon [4]–Bloembergen [5] equation

$$T_{1p}^{-1} = 6a \tau_c r^{-6}$$

where $a = \gamma_I^2 g^2 \beta^2 I(I+1)/15$ which is equal to $3.689 \times 10^{-42} \text{ cm}^{-6} \text{ s}^{-2}$. Since $\omega^2 \tau_c^2 \ll 1$ (ω = Larmor precession frequency of protons), even the usual Solomon–Bloembergen equation without the scalar term, but containing the frequency term (ω) reduces to this form, which shows a frequency independence.

The dipole-dipole interaction between the electron S and the nuclear spin I is modulated by the correlation time τ_c , which is composed of several components.

$$\tau_c^{-1} = \tau_r^{-1} + \tau_S^{-1} + \tau_m^{-1}$$

where τ_r is the correlation time characteristic of the rotational motion of the internuclear ion-nucleus radius vector and τ_S is the electron-spin relaxation time. In the aquo-complexes of paramagnetic ions of the first transition series elements, τ_r is of the order 10^{-11} s, τ_m is several orders of magnitude larger and τ_S is longer than τ_r for Cu(II) (3.3×10^{-10} s, [6]). Since the correlation time is determined by the fastest rate process τ_r^{-1} contributes to τ_c^{-1} more than τ_S^{-1} or τ_m^{-1} [8].

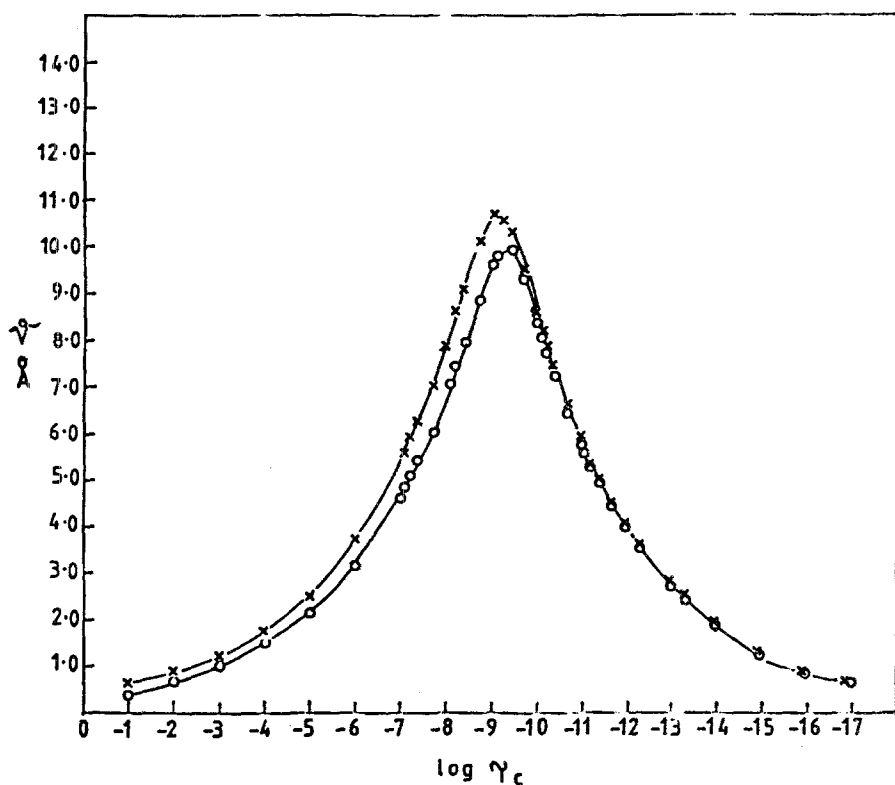


Fig. 1. Determination of electron-nuclear dipolar correlation time. The T_1 values were determined for the H-2 signal at 3.51 ppm measured at 200 MHz (X) and 300 MHz (O). Distances calculated using different values of τ_c by employing the equation above were plotted against $\log \tau_c$. The other data used in the calculation are given in Table I.

If τ_m does not dominate the relaxation rate T_{1p}^{-1} , then the latter will exhibit frequency dependence only for certain values of τ_c [7]. This was found to be so, when distances for the H-2 signal of BCD glucose units, calculated from the equation given below, were plotted against $\log \tau_c$ at two frequencies, namely 200 and 300 MHz (Fig. 1). Hence τ_m was found to be a non-dominant factor for the relaxation rate. Frequency dependence was observed for τ_c values greater than 1×10^{-11} s. Due to overlap of signals T_1 measurements were not possible for the other protons.

$$T_{1p}^{-1} = 6a r^{-6} \left(\tau_c / (1 + \omega^2 \tau_c^2) \right).$$

3. Results and Discussion

The alkaline solution employed results in deprotonation of secondary hydroxyl groups of BCD at C-2 and C-3 ($pK = 12.1$, [8]) to facilitate complex formation

TABLE I. Determination of distances of glucose protons from copper(II) in β -cyclodextrin.

Signal	Chemical shift (ppm)	$T_{1,0}$ (s)	$T_{1,obs}$		T_{1p}^{-1}	r (Å)
			Cu(II)	Zn(II)		
200 MHz ^a						
H-4	3.43	0.678	0.0357	0.498	231.7	5.02
H-2	3.51	0.641	0.0769	0.279	96.3	5.81
H-5	3.72	1.076	–	–	–	–
H-6 a&b	3.76	0.556	0.0474	0.204	163.1	5.32
H-3	3.87	1.035	–	0.298	–	–
H-1	5.14	0.699	0.0952	–	80.3	5.98
300 MHz ^b						
H-4	3.43	0.528	0.123	0.499	102.7	5.74
H-2	3.51	0.633	0.122	0.501	107.5	5.70
H-5	3.72	0.73	–	–	–	–
H-6 a&b	3.76	0.327	0.103	0.282	108.6	5.69
H-3	3.87	0.742	0.138	0.396	94.8	5.82
H-1	5.14	0.585	–	0.221	–	–

^a Cu(II)-BCD: $X_b = 0.114$; Zn(II)-BCD: $X_b = 0.499$

^b Cu(II)-BCD: $X_b = 0.061$; Zn(II)-BCD: $X_b = 0.499$.

with $\text{Cu}(\text{OH})_2$. At such low ratios the 1 : 1 complex is formed predominantly [1]. The measured T_1 and T_2 values and the determined distances are shown in Tables I and II as the average values for the signals from seven glucose units. The values for sugar protons were found to be considerably reduced in the presence of low ratios of Cu(II). The values of all the sugar protons could not be measured for the Cu(II) complex due to broadening of some signals (Tables I and II). The chemical shift values of BCD and its metal complex protons were not found to be different.

The broadening of proton signals in Cu(II) complexes is largely determined by scalar interactions which increase in importance as the ligand donor groups vary from carboxylate oxygen to π bonding amines and nitrogens in aliphatic amines [9]. However, under the fast exchange conditions a value around unity for the ratio of paramagnetic contributions to spin-lattice (T_{1p}) and transverse (T_{2p}) relaxation times indicate that the dipolar mechanism is the contributing one to relaxation. The ratios of T_{1p}/T_{2p} are high for most complexes of Cu(II) with nitrogen ligands, such as imidazole [9]. However, for most of the ligands containing oxygen as donor atom, the value is around unity. Hence determination of T_2 values are essential to ascertain whether the relaxation mechanism is dipolar or scalar. Only then can the

TABLE II. Proton NMR transverse relaxation time data of the Cu(II)- β -cyclodextrin complex.

Signal	T_{1p}^{-1}	W_{Cu}^a	W_0	T_{2p}^{-1}	T_{1p}/T_{2p}
200 MHz ^b					
H-4	231.7	31.18	8.57	70.9	0.31
H-2	96.3	31.18	7.79	73.5	0.76
H-5	—	—	—	—	—
H-6 a&b	163.1	18.19	8.57	30.2	0.18
H-3	—	—	—	—	—
H-1	80.3	15.07	9.09	18.8	0.23
300 MHz ^c					
H-4	102.7	51.02	10.2	128.2	1.25
H-2	107.5	51.02	8.5	133.5	1.24
H-5	—	—	—	—	—
H-6 a&b	108.6	30.61	6.8	74.8	0.69
H-3	94.8	—	—	—	—
H-1	—	—	—	—	—

^a Line-width at half height: W_{Cu} – with Cu(II), W_0 – without Cu(II).

^{b,c} Same as in Table I.

Solomon–Bloembergen equation with the dipolar term be employed to determine the distances through measurement of T_1 values.

The T_2 values and the ratios T_{1p}/T_{2p} are shown in Table II. The values around unity observed for some of the BCD protons in its metal complexes show the dipolar mechanism to be the most dominant one in determining relaxation. A scalar mechanism in such an instance, with a T_{1p}/T_{2p} value around unity, can be ruled out. Besides, the non-exchangeable protons are at a considerable distance from the metal ion to carry much electron density.

The distances of glucose unit protons determined from Cu(II) at both the frequencies employed agree within an error limit of $\pm 15\%$ (Table I). Average values of about 5.0–5.9 Å were obtained for the distances of the H-2, H-4, H-6a and b, H-3 and H-1 protons from Cu(II). BCD has a cavity of 7.8 Å width at the wider end, which progressively decreases towards the narrower end. The difference in distances observed from NMR studies for H-2 and H-3 which are on the wider cavity rim on one hand and H-4, H-1 and H-6a and b on the other are not very much different, which indicates that Cu(II) should be present inside the cavity, almost certainly in the plane of the H-1 and H-4 protons (Figure 2). A value of 5.0–5.9 Å obtained indicates that the sugar protons are present at the surface of a sphere containing Cu(II) at its centre. The distances for most of the protons especially those of H-4 and H-2 after making allowance for the angles, diameter of carbon

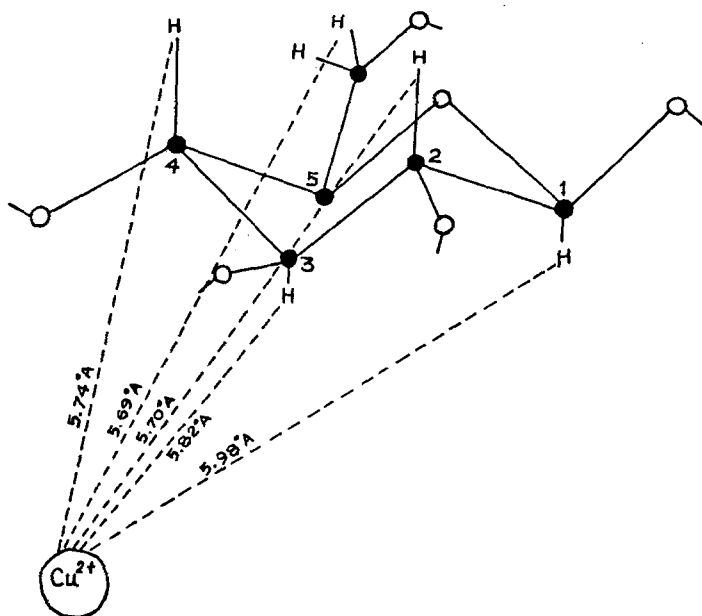


Fig. 2. Geometry of disposition of Cu(II) in β -cyclodextrin.

atoms and the C-H bond-lengths will be about 5 Å from Cu(II) (distances: C-O: 1.43 Å, Cu-O: 1.53 Å, C-H: 1.1 Å and diameter of Cu(II): 1.44 Å, [10]). The H-4 and H-2 protons project outward laterally. However, one would expect a shorter distance for the H-3 proton since 3-OH is directed towards the centre of the cavity with H-3 pointing downwards. This slight difference in distance between H-2 and H-3 is not distinctly shown in the distance measurement exercise carried out.

The effect of CuSO_4 *per se* was also examined by measuring the T_1 of BCD protons in the presence of externally added CuSO_4 to an aqueous neutral solution of BCD. The ratio of CuSO_4 : BCD used was high (0.69 : 1) resulting in very short T_1 values (< 10 ms) for the sugar protons. It was difficult to measure the T_1 values of these sugar protons accurately since most of the signals were considerably broadened.

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