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TWO-GUEST INCLUSION COMPLEX OF γ-CYCLODEXTRIN WITH CHLORPROMAZINE

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The interaction of chlorpromazine with γ-cyclodextrin in an aqueous solution was studied by circular dichroism and ^{1}H-NMR. γ-Cyclodextrin was found to form a 1:2 inclusion complex with chlorpromazine at a concentration higher than ca. 1×10^{-4} mol·l^{-1}. The two chlorpromazine molecules including in γ-cyclodextrin may have S-helicity.

Torus shaped oligosaccharides or cyclodextrins (CyDs) form host-guest complexes with chlorpromazine (CPZ), an important tranquilizer, in their cavities.[1] Because of its inhibition toward the photo-irradiation of CPZ and alleviation of the hemolytic effects of CPZ, CyD seems an promising admixture of CPZ. To date, no detailed information has been available in regard to the stoichiometry and the structure of the CPZ-γ-CyD complex. Chlorpromazine is present in β-CyD in a 1:1 stoichiometric ratio. Its aromatic portion is contained in the hydrophobic cavity of β-CyD, but its N-substituent interacts with the groups present on the outside of the cavity. If this orientation of CPZ with the CyD cavity is common for any CPZ-CyD system, it may be expected that two molecules of CPZ are present in γ-CyD in consideration of the large size of the cavity. Two-guest inclusions have recently been confirmed in several systems.[2-7] The present paper is concerned with the interaction of CPZ with γ-CyD, and confirmation of the existence of a one host-two guest complex by means of circular dichroism and ^{1}H-NMR.

As a result of its presence in β-CyD, optically inactive CPZ shows induced circular dichroism (i.c.d.).[1] In the presence of γ-CyD, the shape of the i.c.d. spectra changes with CPZ concentration as evident from Fig. 1A. The i.c.d. spectrum of a solution of 5×10^{-5}M (M= mol·l^{-1}) CPZ with 1×10^{-2}M γ-CyD had a positive sign in the 240-280nm region corresponding to the peak absorption of the UV spectrum

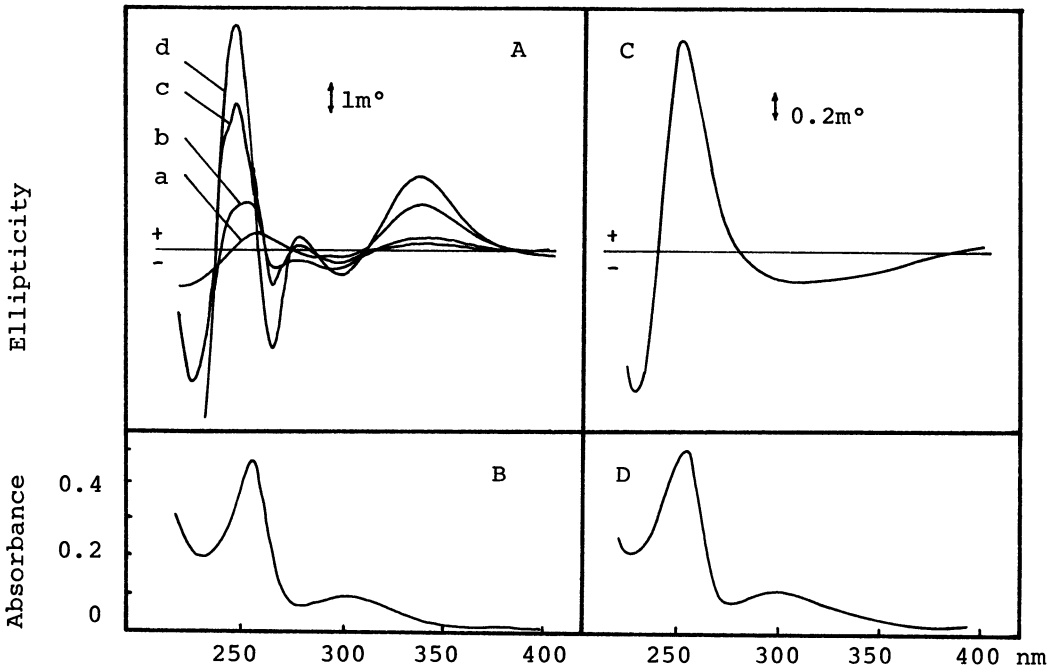

Fig.1 A) i.c.d. spectra at various concentrations of CPZ with 1×10^{-2}mol·l^{-1} γ-CyD. CPZ concentrations: a,5×10^{-5}M (M=mol·l^{-1}); b,2×10^{-4}M; c,4×10^{-4}M; d,6×10^{-4}M. B) Absorption spectrum of 5×10^{-5}M CPZ with 1×10^{-2}M γ-CyD. C) i.c.d. spectrum of 1×10^{-3}M CPZ with 1×10^{-2}M β-CyD. D) Absorption spectrum of 5×10^{-5}M CPZ with 1×10^{-2}M β-CyD.

obtained for the same solution (Figs. 1A and 1B). The i.c.d.spectrum of γ-CyD and CPZ is similar to that of the β-CyD and CPZ system.

The i.c.d. spectra for a system with a γ-CyD concentration of 1×10^{-2}M and that of CPZ exceeding 4×10^{-4}M had positive signs in the 230-255, 270-285 and 310-380nm regions and negative signs in the 215-230, 255-270 and 285-310nm regions (Fig. 1A). As can be seen from Figs. 1A and 1B, the change in the i.c.d. spectrum in the 230-280nm and 280-400nm regions is associated with transitions along the short and the long axes respectively. Those changes suggest that two molecules of CPZ are present in γ-CyD in the form of an S-helix. To confirm the stoichiometric ratio of the CPZ-γ-CyD complex at the higher CPZ concentrations described above, a continuous variation method was used. The observed ellipticity at 340nm was plotted against the composition ratio of CPZ and γ-CyD (Fig. 2). The peak of the diagram indicates that two molecules of CPZ are present together with

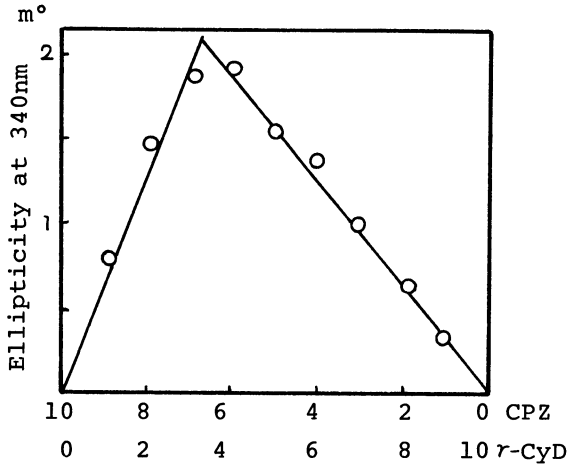

Fig.2 Continuous variation method applied to the CPZ and γ-CyD complexes.

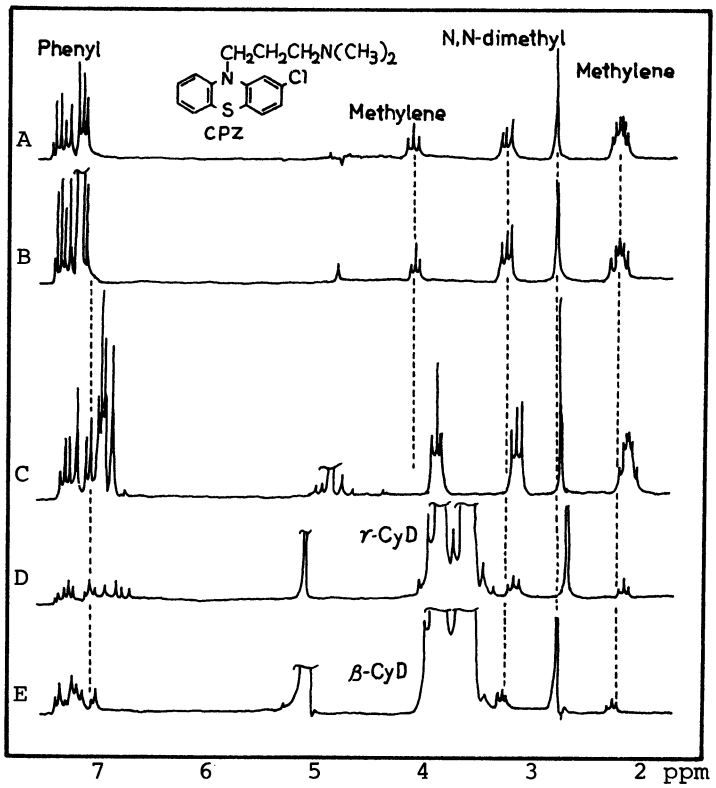

Fig.3 ^{1}H-NMR spectra of CPZ with and without γ- and β-CyD in D_2O. Concentration of CPZ is A; 5×10^{-5}M, B; 1×10^{-3}M, C; 2×10^{-2}M, D; 1×10^{-3}M CPZ with 1×10^{-2}M γ-CyD, E; 1×10^{-3}M CPZ with 1×10^{-2}M β-CyD.

one γ-CyD molecule. On the other hand, a different i.c.d. spectrum was observed at a CPZ concentrations lower than 4×10^{-4}M (Fig.1, curve a), at which a 1:1 complex may be formed.

Further confirmation was made by examining the effect of CPZ on the ^{1}H-NMR spectrum of γ-CyD. The proton H-3 located inside the cavity of γ-CyD, shifts upfield and broadens by the presence of CPZ, while exterior protons such as H-1 undergo no change. These results indicate that the aromatic moiety of the CPZ molecule is in the γ-CyD cavity and consequently,the H-3 resonance shifts upfield due to anisotropic shielding of this moiety. Similar phenomena, except for the proton H-1, have also been reported for the CPZ-β-CyD system.[1)]

To study the interaction between γ-CyD and CPZ, the ^{1}H-NMR spectra of CPZ were examined. First, the spectra of various concentrations of CPZ without CyD were measured (Figs. 3A-3C). No detectable change in the NMR spectrum of CPZ could be detected

up to 1×10^{-3}M (Figs. 3A and 3B), indicating that CPZ exists as a monomer at these concentrations. However, remarkable changes were observed at concentrations over 1×10^{-2}M (Fig.3C), i.e., the peaks of the aromatic protons spanned a relatively narrow range of 0.4ppm for 1×10^{-3}M CPZ, but were more diverse over a range of 0.6ppm for 1×10^{-2}M CPZ. This seems to indicate that self-association occurs at high concentrations of CPZ, and thereby the magnetic shielding anisotropy of aromatic groups may cause a large upfield shift of a cluster of aromatic proton peaks.

As shown in Fig.3D, in the presence of γ-CyD, the aromatic peaks of CPZ shifted upfield and broadened and the proton signals of the N-substituents of CPZ slightly shifted upfield in the ^{1}H-NMR spectrum. This indicates that, in addition to an interaction between CPZ and γ-CyD, there may be an interaction between two CPZ molecules present in γ-CyD. In the presence of β-CyD, a lower field shift of the proton signals of methylene and dimethylamino groups in CPZ, due to association with the outside groups of β-CyD cavity, was reported.[1] However, such changes in chemical shift were not observed for the CPZ-γ-CyD system.

The findings above may be concluded as conformation of the two-guest inclusion complex structure of CPZ-γ-CyD in which the phenothiazine rings of two molecules of CPZ are probably in the cavity as an S-helix and interaction of N-substituents with γ-CyD is weaker than that with β-CyD.

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