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^{1}H-NMR SPECTROSCOPIC EVIDENCE ON CHIRAL DISCRIMINATION OF *dl*-PIRPROFEN BY β-CYCLODEXTRIN COMPLEXATION

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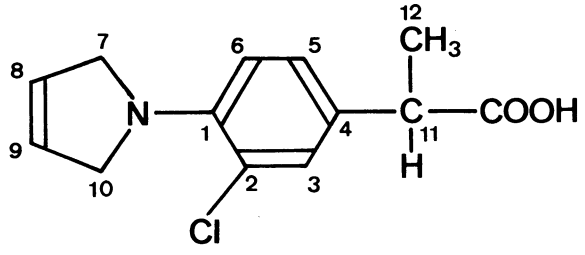
The chiral discrimination of β-cyclodextrin (β-CyD) was demonstrated by measuring 270 MHz ^{1}H-NMR spectra, using *dl*-pirprofen (PF) as a guest molecule. Upon binding to β-CyD, the induced ^{1}H-chemical shifts of PF, particularly in the phenylpropionic acid portion, were significantly different between the *d*- and *l*-isomers, while no enantiometric difference was observed in the absence of β-CyD.

Cyclodextrins (CyDs) are optically active compounds because they are built up by optically active glucose units. One of the important properties of CyDs is their ability to recognize chirality of guest molecules through inclusion complex formation. Although the intrinsic chirality of CyDs is known to be reflected in the reactivity of guest molecules[1] and in their spectroscopic properties,[2] there have been only few reports[3] on the chiral recognition of CyDs on the basis of nuclear magnetic resonance (NMR) spectroscopy. We have recently demonstrated[4] by X-ray crystallography that CyDs discriminate the chirality of biphenylylpropionic acid derivative in the crystalline state. In this brief paper, we report the chiral discrimination of β-CyD upon binding to pirprofen (PF), one of phenylpropionic acid type anti-



PF

inflammatory drugs, in aqueous solution by measuring 270 MHz ^{1}H-NMR spectra.

^{1}H-Fourier transformed NMR spectra were measured on a JEOL JNM GX-270 spectrometer (270 MHz) at 20 °C. 0.1 mol dm^{-3} DCl (pD= 1.7)[5] and 0.05 mol dm^{-3} NaOD (pD= 13.4)[5] solutions were used as solvent and the concentrations of PF and β-CyD were 2.0 x 10^{-2} and 1.5 x 10^{-2} mol dm^{-3}, respectively. ^{1}H-Chemical shifts were referenced to external sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) with an accuracy of ± 0.0012 ppm.

Figs. 1 and 2 show the ^{1}H-NMR spectra of the phenylpropionic acid portion of PF in the absence and presence of β-CyD in the DCl and NaOD solutions, respectively. The ^{1}H-resonances of C_{11}-H and C_{12}-H of PF were analyzable as A_3X-type spin system ($J_{11,12}$= 7.27 Hz), and the phenyl protons (C_3-H, C_5-H and C_6-H) were spin-coupled each other with the coupling constants of $J_{3,5}$= 1.85 and $J_{5,6}$= 8.56 Hz. The methylenic and ethylenic protons in the pyrroline ring were observed as singlet, respectively, under this experimental condition.[6] These assignments were confirmed by decoupling experiments. In the absence of β-CyD, any enantiometric differences between the *d*- and *l*-isomers of PF were not observed in the NMR spectra, which may be due to free rotation around the C_4-C_{11} bond. Upon binding to β-CyD, the ^{1}H-peaks of *dl*-PF, particularly the phenylpropionic, became more splitting with the concomitant changes in the chemical shift, which could not be simply explained by spin-spin coupling. However, it is obvious from Figs. 1 and 2 that these splittings were resulted from the difference in the induced shifts of the *d*- and *l*-isomers by β-CyD complexation. Because the magnitude of the stability constants of β-CyD complexes with the enantiomers were almost the same,[7] the observed enantiotropic shifts are attributable to the different orientation of the guest molecules within β-CyD cavity. Furthermore, the molecular motion of PF seems to be severely restricted within the cavity, yielding the independent NMR spectra of the *d*- and *l*-enantiomers. In the DCl solution, in which PF molecule exists as a pyrrolinium cation (pK_a= 3.3), the non-equivalent resonances of the enantiomers were observed in the C_3-H, C_6-H, and C_{12}-H protons. This may be due to the preferable inclusion of the phenylpropionic acid moiety of PF molecule within β-CyD cavity,[8] because this moiety is more hydrophobic than the pyrrolinium cation in the acidic region. On the other hand, the non-equivalence was observed only in the C_3-H and C_{12}-H protons in the alkaline solution, in which PF molecule exists as a carboxylate anion (pK_a= 4.3). The chiral recognition of β-CyD in alkaline solution seems to be lesser than that in acidic solution, because the pyrroline moiety, the preferable inclusion site in alkaline solution,[8] is somewhat remote from the chiral center. Further investigations are now in progress to elucidate the binding modes of *d*- and *l*-PF within β-CyD cavity along with the chiral discrimination mechanism of β-CyD.

We here demonstrated the chiral discrimination of β-CyD in aqueous solution, on the basis of NMR spectroscopy. Our present results further suggest an

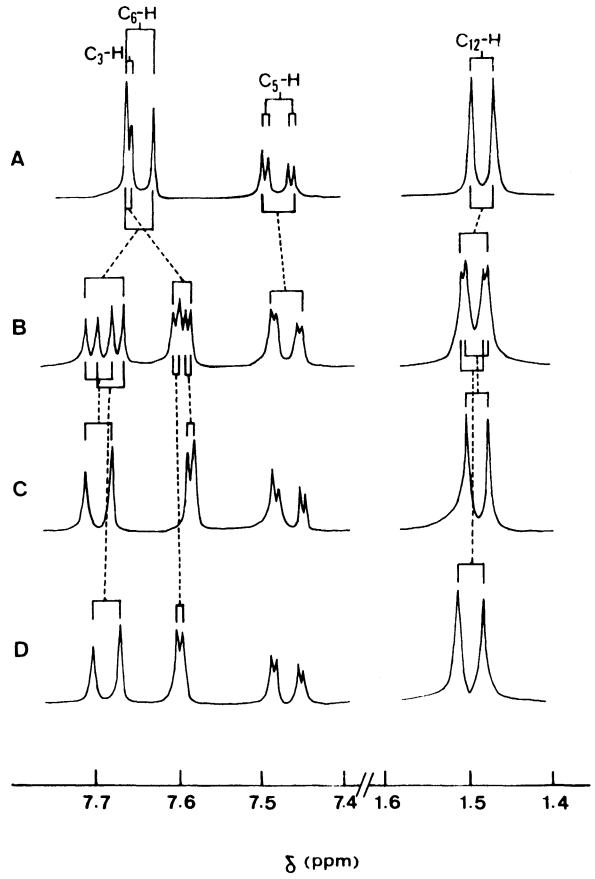


Fig. 1. ^{1}H-NMR Spectra of PF in the Absence and Presence of β-CyD in DCl (pD = 1.7).

A : PF alone,
B : *dl*-PF—β-CyD system,
C : *d*-PF—β-CyD system,
D : *l*-PF—β-CyD system.

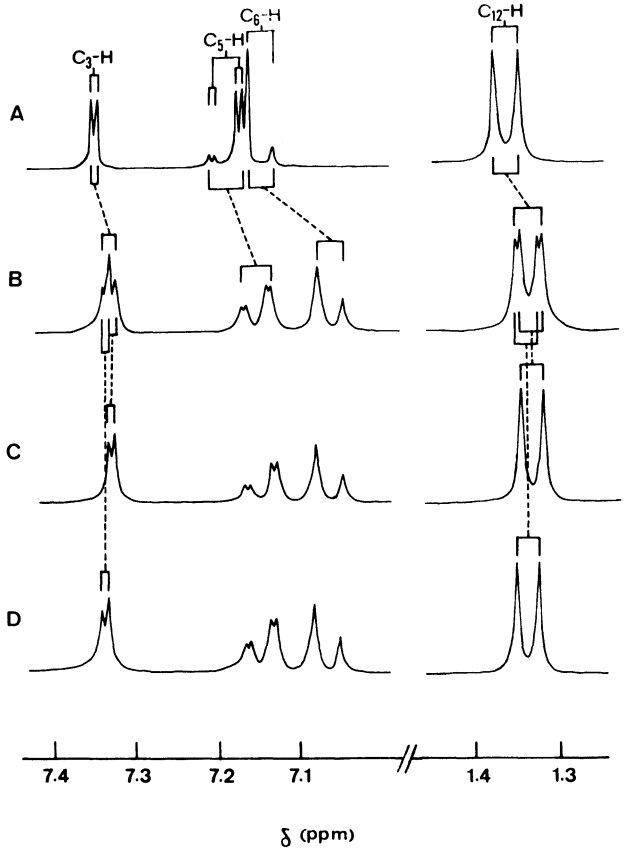


Fig. 2. ^{1}H-NMR Spectra of PF in the Absence and Presence of β-CyD in NaOD (pD = 13.4).

A : PF alone,
B : *dl*-PF—β-CyD system,
C : *d*-PF—β-CyD system,
D : *l*-PF—β-CyD system.

attractive possibility of CyDs as chiral NMR shift reagents such as chiral lanthanide ions, particularly in ultrahigh-resolution NMR spectroscopy.

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5) The pD value was estimated using the equation of pD= pH meter reading + 0.4. P.K. Glasoe and F.A. Long, J. Phys. Chem., 64, 188 (1969).
6) The ^{1}H-NMR spectra of the pyrroline ring portion are not shown here because no appreciable enantiotropic shift was observed. The C_{11}-H signal could not be accurately analyzed owing to the overlapping with the β-CyD signals.
7) The stability constants of PF-β-CyD complex were spectrophotometrically determined to be 200 and 560 dm^3 mol^{-1} in the acidic and alkaline solutions, respectively.
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