Solid-State ^{13}C Nuclear Magnetic Resonance Spectroscopic Study on Amorphous Solid Complexes of Tolbutamide with 2-Hydroxypropyl-α- and -β-Cyclodextrins

Kenya Kimura,[1] Fumitoshi Hirayama,[1] Hidetoshi Arima,[1] and Kaneto Uekama[1,2]

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Purpose. The objective of the study was to obtain structural information of inclusion complexes of tolbutamide with HP-α- and -β-cyclodextrins in amorphous state.

Method. The solid complexes of tolbutamide with HP-α- and -β-CyDs in molar ratios of 1:1 and 1:2 (guest:host) were prepared by the spray-drying method, and their interactions were investigated by solid-state ^{13}C nuclear magnetic resonance (NMR) spectroscopy.

Results. The solid 1:1 and 1:2 tolbutamide/HP-CyD complexes showed halo pattern on the powder X-ray diffractogram and no thermal change in DSC curves, indicating they are in an amorphous state. ^{13}C NMR signals of the butyl moiety were broader than those of the phenyl moiety in the HP-α-CyD solid complex, whereas the phenyl moiety showed significantly broader signals than the butyl moiety in the HP-β-CyD solid complex. As temperature increased, signals of the phenyl carbons became markedly sharper, whereas the butyl carbons only sharpen slightly in the HP-d-CyD complex. In contrast, signals of the butyl carbons became significantly sharper whereas those of phenyl carbons only slightly changed in the HP-β-CyD complex.

Conclusions. Solid state ^{13}C NMR spectroscopic studies indicated that the butyl moiety of tolbutamide is predominantly included in the HP-α-CyD cavity, whereas the phenyl moiety in the HP-β-CyD cavity in amorphous complexes.

KEY WORDS: tolbutamide; 2-hydroxypropyl cyclodextrins; inclusion complex; amorphous solid; solid-state ^{13}C NMR spectroscopy.

INTRODUCTION

Cyclodextrins (CyDs) are cyclic oligosaccharides usually consisting of six to eight glucose units which form inclusion complexes with various drug molecules both in solution and solid states, and their host/guest interactions have been investigated using a number of chemical and physical techniques such as spectroscopies, potentiometric titration, kinetics, and solubility methods, etc. (1–3). Among these techniques, nuclear magnetic resonance (NMR) spectroscopy is particularly useful for structure determination of CyD inclusion complexes in solution, because it gives detailed information of molecular dimensions (4). Whereas single crystal X-ray analysis is the definitive method for structure determination of solid complexes (5,6), CyD complexes do not always give crystals with a size suitable for single crystal X-ray analysis, often producing microcrystals or even powder. In this latter case, powder X-ray diffractometry is used for structure elucidation using the peak fitting methods such as the Rietveld method (7–9), but even at present it is difficult to apply this technique to complicated compounds such as CyD complexes, particularly in an amorphous state. Therefore, it is difficult to thoroughly characterize amorphous solid CyD complexes from a structural viewpoint, as compared with the complexes in solution or in crystalline state. Recently, solid-state NMR spectroscopy has received attention as a complementary tool to X-ray analysis for structure determination of solid compounds, because it can apply to powder samples (10,11). For example, detection and characterizations of polymorphic forms of drugs and their transformations such as polymorphic transitions, hydrations and dehydrations have been investigated using solid-state NMR spectroscopy.

2-Hydroxypropyl-β-CyD (HP-β-CyD) is a water-soluble CyD derivative that is used in two pharmaceutical preparations currently on the market, i.e., hydrocortisone mouthwash solution (Iceland) and itraconazole liquid preparation (USA and Belgium). Because HP-β-CyD is an amorphous compound, it can convert crystalline drugs to amorphous solids with higher aqueous solubility, through the inclusion complex formation (12,13). Although inclusion complex formations of HP-β-CyD with drugs in solution have been extensively studied, there are only a few reports on the structural aspect of amorphous HP-β-CyD complexes (14). Therefore, we conducted solid-state ^{13}C NMR spectroscopic studies on the complex formation of HP-α- and -β-CyD with an oral hypoglycemic agent, tolbutamide. This drug was chosen because of the presence of the alkyl and phenyl moieties that are of suitable size for the inclusion in the α- and β-CyD cavities, respectively, in a molecule (15,16).

MATERIALS AND METHODS

Materials

HP-α-CyD (degree of substitution (D.S.) 4.1) and HP-β-CyD (D.S. 4.8) were supplied by Japan Maize Co. (Tokyo, Japan). Tolbutamide was donated by Hoechst-Marion-Roussel Ltd. (Tokyo, Japan). Other chemicals and solvents were of analytical reagent grade, and deionized double-distilled water was used throughout the study.

Solubility Measurements

Solubility studies were carried out according to the method of Higuchi and Connors (17). The screw capped vials containing tolbutamide (50 mg) in an excess amount in aqueous HP-CyD solutions (3.0 ml) at various concentrations were shaken at 25°C. After equilibrium was attained (about 14 days), the solution was centrifuged at 800*g* force for 5 min and the supernatant was filtered through a membrane filter (ADVANTEC DISMIC 13CP, TOYO-Roshi, Tokyo, Japan) and the filtrate was analyzed for tolbutamide by high-performance liquid chromatography under the following conditions: a Hitachi L-6000 pump and a 635-A UV detector (Tokyo, Japan), a Yamamura YMC AQ-312 ODS column (5 μm, 6 mm × 150 mm i.d., Kyoto, Japan), a mobile phase of acetonitrile/0.05 M NaH_2PO_4 solution (45:55 v/v), and a flow rate of 1.6 ml/min, and detection of 230 nm.

[1] Faculty of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honmachi, Kumamoto 862-0973, Japan.

[2] To whom correspondence should be addressed. (e-mail: uekama@gpo.kumamoto-u.ac.jp)

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Preparation of Solid HP-CyD Complexes

Solid complexes of tolbutamide with HP-α- and -β-CyD were prepared by the spray-drying method, using a Yamato Pulvis GA32 spray dryer (Tokyo, Japan). The calculated quantities of tolbutamide and HP-CyDs corresponding to 1:1 and 1:2 (guest:host molar ratio) were dissolved in the mixed solvent of ethanol/dichloromethane (1.2:1 v/v) and then spray-dried under the following conditions: an air flow rate of 0.4 m^3/min, an air pressure of 1.0 kgf/cm^2, and inlet and outlet temperatures of 85°C and 55°C, respectively.

Powder X-ray Diffractometry and Differential Scanning Calorimetry (DSC)

Powder X-ray diffraction patterns were measured with a Rigaku Rint-2500 diffractometer (Tokyo, Japan) under the following conditions: Ni-filtered Cu-Kα radiation (1.542 Å), voltage of 40 kV, a current of 40 mA, a divergent slit of 1.74 mm (1°), a scattering slit of 0.94 mm (1°), a receiving slit of 0.15 mm, and a goniometer angular increment of 1°/min. DSC analyses were carried out using a Perkin-Elmer DSC-7 thermal analyzer (Norwalk, CT) with a data analysis system (DEC station 325C computer, USA), operated with a sample weight of 5 mg and a scanning rate of 10°C/min.

NMR Spectroscopies

^1H NMR spectra were obtained with a JEOL JNM-α 500 instrument (Tokyo, Japan) with a 5 mm inverse broad band probe, operating at 500 MHz and a sweep width of 10000 Hz, at 25°C. The concentration of tolbutamide in 0.1 M sodium borate buffer (pH 9.3) in deuterium oxide (D_2O) was 5.0×10^{-3} M, and that of HP-CyDs varied from 0 to 2.0×10^{-2} M. In the case of the continuous variation plot, the total concentration of the guest and the host was kept constant (1.0×10^{-2} M). Chemical shifts are given as part per million (ppm) downfield from that of tetramethylsilane with an accuracy of 0.005 ppm. Solid-state ^{13}C NMR spectra were taken on a JEOL JNM EX-270 spectrometer with a cross polarization/magic angle spinning (CP/MAS) accessory (Tokyo, Japan), operating at 270 MHz (^1H). The CP radio frequency field strength was about 56 kHz, the contact time was 5 ms, the repetition time of accumulation was 4 s, and the MAS was 6.2–6.4 kHz. The ^1H decoupling frequency was chosen to be 3 ppm downfield from tetramethylsilane. The ^{13}C chemical shifts were measured in ppm with respect to the methine carbon of adamantane (29.7 ppm downfield from the resonance of tetramethylsilane) as an external reference. Variable-temperature measurements were accomplished using a JEOL MVT temperature controller (Tokyo, Japan). Signal accumulation was started 20 min after the desired temperature was achieved (25–80°C). The chemical shifts of tolbutamide were assigned according to the report of Ueda *et al.* (16).

RESULTS AND DISCUSSION

Figure 1 shows the phase solubility diagrams of tolbutamide with HP-α- and -β-CyDs in water, where the solubility of the guest molecule increased as a function of CyD concentration. The solubility curve of the HP-β-CyD system deviated positively from a straight line and that of the HP-α-CyD system

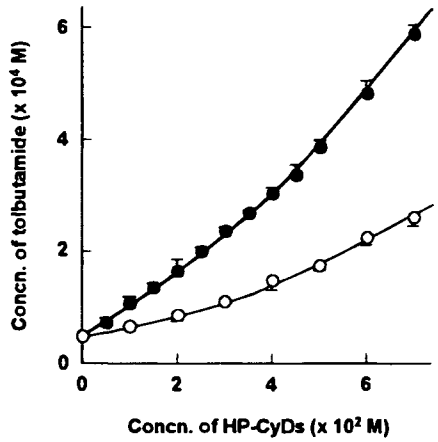

Fig. 1. Phase solubility diagrams of tolbutamide/HP-α-CyD (○) and /HP-β-CyD (●) systems in water at 25°C. Data represent the mean ± SE (n = 3–6).

deviated slightly positively. These curves were classified as A_P type (17), indicating a formation of higher order complexes. Therefore, the 1:1 and 1:2 stability constants ($K_{1:1}$ and $K_{1:2}$) of the tolbutamide/CyD complexes were calculated by analyzing the solubility curves according to the iteration method of Kristiansen (18), and were 73 (±3) and 9 (±1) M^{-1} for the 1:1 and 1:2 HP-α-CyD complexes and 194 (±8) M^{-1} and 17 (±1) M^{-1} for the 1:1 and 1:2 HP-β-CyD complexes, respectively. The fact that the 1:1 stability constant was much larger than the 1:2 stability constant, suggests that tolbutamide forms predominantly the 1:1 complex in aqueous solution and at higher CyD concentrations it forms the high order complex.

In order to gain insight into the inclusion mode of tolbutamide/HP-CyD complexes in aqueous solution, ^1H NMR spectroscopic studies were carried out. Because the solubility of tolbutamide in water (Fig. 1) was too low to measure accurately NMR spectra, the drug was dissolved in 0.1 M sodium borate/D_2O buffer (pH 9.3) where it is in ionized form (pKa 5.34). Tolbutamide gave ^1H signals of H1, H3 and H4 of toluene moiety and H9, H10, H11 and H12 of the butyl moiety at 2.31 (singlet), 7.63 (doublet), 7.29 (doublet), 2.91 (triplet), 1.28 (quintet), 1.15 (sextet), and 0.75 (triplet) ppm, respectively, in the borate buffer. Figure 2 shows changes in chemical shifts of these protons with the addition of CyDs. In the case of HP-α-CyD, ^1H signals of the butyl protons (H9-H12) markedly shifted downfield and the shift became greater at higher CyD concentrations, whereas those (H1, H3 and H4) of the toluene moiety shifted only slightly. In sharp contrast, the addition of HP-β-CyD brought about a large shift of the toluene protons, whereas those of the butyl protons shifted only slightly. These results suggested that HP-α-CyD having the smaller cavity interacts preferably with the butyl moiety of tolbutamide, whereas HP-β-CyD having the larger cavity interacts with the toluene moiety in aqueous solution. Maincent *et al.* reported (19) that the tolbutamide/parent β-CyD system gives the B_S type phase solubility diagram, where the solubility of tolbutamide increased at low CyD concentration, followed by a plateau region and then decreased with increase in CyD concentration, and that the stoichiometry of the complex is 1:2 (molar ratio of guest:host). Therefore, the stoichiometry of tolbutamide/HP-CyD complexes was estimated by the continuous variation

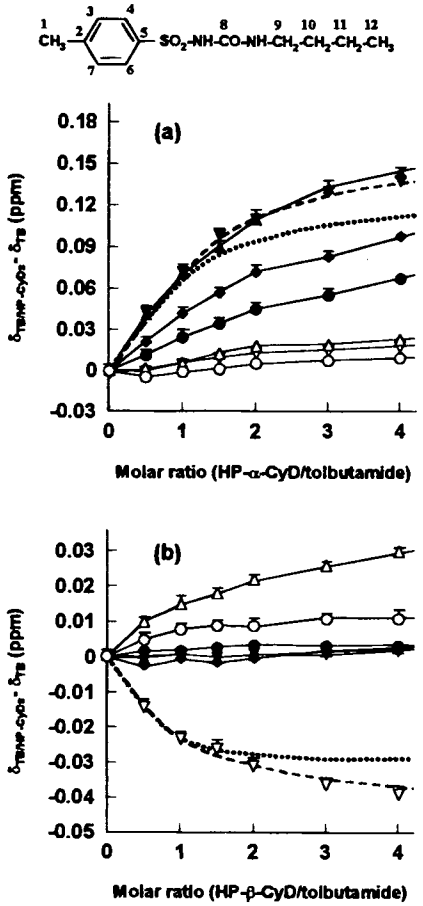

Fig. 2. Effects of HP-α-CyD (a) and HP-β-CyD (b) on ^{1}H NMR chemical shifts of tolbutamide in 0.1 M sodium borate/D_2O buffer (pH 9.3) at 25°C. (○) H1, (△) H3, (▽) H4, (●) H9, (▲) H10, (▼) H11, and (◆) H12. $\delta_{TB/HP\text{-}CyDs}$ and δ_{TB} are chemical shifts of tolbutamide in the presence and absence of HP-CyDs, respectively. Data represent the mean ± SE (n = 2–4). The dotted and broken lines represent the theoretical curves calculated on the basis of 1:1 and 1:2 complex formations, respectively, for the shift change of H11(▼) and H4 (▽) protons.

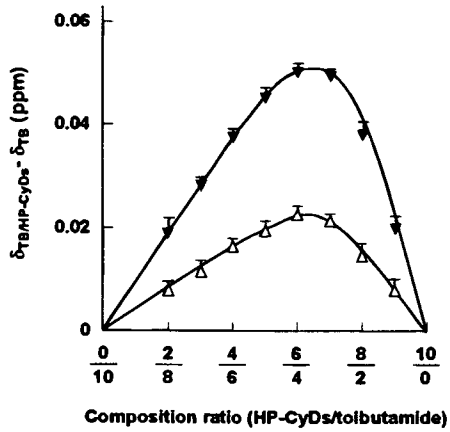

Fig. 3. Continuous variation plots for tolbutamide/HP-CyD systems in 0.1 M sodium borate/D_2O (pH 9.3) at 25°C. Chemical shifts of H11 (▼) and H3 (△) protons of tolbutamide were monitored for the HP-α- and -β-CyD systems, respectively. Data represent the mean ± SE (n = 2–3).

method (20) by monitoring the chemical shift of H3 and H11 protons. As shown in Fig. 3, both plots gave a maximum at 0.65 host/guest molar ratio, indicating that tolbutamide forms inclusion complexes with HP-α- and -β-cyclodextrins in a molar ratio of 1:2 in aqueous solution. The same stoichiometry was obtained from studies of the molar ratio method (21), i.e., an inflection point was observed at 0.35 of the guest/(host + guest) molar ratio when the signals of the H3 and H11 protons of the guest (5.0×10^{-3} M) was monitored in the range of the host concentration (0–2.0×10^{-2} M). Therefore, the NMR titration data of Fig.2 were analyzed according to the following 1:2 inclusion scheme, where $K_{1:1}$ and $K_{1:2}$ are the stability constants of the 1:1 and 1:2 complexes.

$$\text{Tolbutamide} + \text{CyD} \overset{K_{1:1}}{\rightleftharpoons} \text{Tolbutamide/CyD}$$

$$+ \text{CyD} \overset{K_{1:2}}{\rightleftharpoons} \text{Tolbutamide/(CyD)}_2$$

The changes in chemical shift of the guest in the presence of CyDs can be expressed by Eq. 1 which is in turn rearranged to Eq. 2 by combining the following equations of stability constants and mass balances. Therefore, the titration data of H4 and H11 protons of tolbutamide were treated according to Eq. 2 to obtain the $K_{1:1}$ and $K_{1:2}$ values, i.e., by setting $[CyD]_f = [CyD]_t$ as a first approximation, Eq. 2 was analyzed by a non-linear least-square method (22) and in turn $[CyD]_f$ values were calculated using the obtained apparent $K_{1:1}$ and $K_{1:2}$ values. This procedure was repeated until each stability constant converged on a constant value.

$$K_{1:1} = \frac{[TB/CyD]}{[TB]_f[CyD]_f} \quad K_{1:2} = \frac{[TB/(CyD)_2]}{[TB/CyD][CyD]_f}$$

$$[TB]_t = [TB]_f + [TB/CyD] + [TB/(CyD)_2]$$
$$= [TB]_f + K_{1:1}[TB]_f[CyD]_f + K_{1:1}K_{1:2}[TB]_f[CyD]_f^2$$

$$[CyD]_t = [CyD]_f + [TB/CyD] + 2[TB/(CyD)_2]$$
$$= [CyD]_f + K_{1:1}[TB]_f[CyD]_f + 2K_{1:1}K_{1:2}[TB]_f[CyD]_f^2$$

$$\delta_{obs} = \frac{[TB]_f}{[TB]_t}\delta_0 + \frac{[TB/CyD]}{[TB]_t}\delta_1 + \frac{[TB/(CyD)_2]}{[TB]_t}\delta_2 \quad (1)$$

$$\delta_{obs} = \frac{[TB]_t(\delta_0 + \delta_1 K_{1:1}[CyD]_f + \delta_2 K_{1:1}K_{1:2}[CyD]_f^2)}{1 + K_{1:1}[CyD]_f + K_{1:1}K_{1:2}[CyD]_f^2} \quad (2)$$

where $[TB]_t$ and $[TB]_f$ stand for total and free tolbutamide concentrations, $[CyD]_t$ and $[CyD]_f$ stand for total and free CyD concentrations, [TB/CyD] and $[TB/(CyD)_2]$ stand for concentrations of the 1:1 and 1:2 complexes of tolbutamide with CyDs, and δ_0, δ_1 and δ_2 stand for chemical shifts of tolbutamide, 1:1 complex and 1:2 complex, respectively. The optimized $K_{1:1}$ and $K_{1:2}$ values and the δ_0, δ_1 and δ_2 values of the H11 proton for the HP-α-CyD complexes were 94 (±8) M^{-1} and 12 (±5) M^{-1} and 1.152 (±0.004), 1.225 (±0.003) and 1.263 (±0.005) ppm, respectively. The optimized $K_{1:1}$ and $K_{1:2}$ values and those of the H4 proton for the HP-β-CyD complexes were 225 (±13) M^{-1} and 25 (±6) M^{-1} and 7.294 (±0.002), 7.273 (±0.002) and 7.265 (±0.004) ppm, respectively. The theoretical curves drawn using these parameters were closely fitted to the experimental data, as shown by the broken line in Fig. 2. On the

other hand, the analysis of titration data according to Eq. 3 of the 1:1 complex formation gave the following parameters, $K_{1:1}$ = 78 (±6) M^{-1} and δ_1 = 1.225 (±0.003) ppm for the HP-α-CyD complex and $K_{1:1}$ = 207 (±11) M^{-1} and δ_1 = 7.273 (±0.002) ppm for the HP-β-CyD. However, the theoretical curves drawn using Eq. 3 were deviated from the experimental data at higher CyD concentrations, as shown by the dotted line.

$$\delta_{obs} = \frac{[TB]_t (\delta_0 + \delta_1 K_{1:1}[CyD]_f)}{1 + K_{1:1}[CyD]_f} \quad (3)$$

The chemical shift of H4 and H11 protons were significantly changed in the 1:1 complex (δ_1) and only slightly in the 1:2 complex (δ_2). These results suggest that the butyl moiety of tolbutamide was preferentially included in the HP-α-CyD cavity to form the 1:1 complex, and the toluene moiety weakly interacts in the 1:2 complex at higher CyD concentrations. In sharp contrast, the toluene moiety is preferentially included in the HP-β-CyD cavity to form the 1:1 complex, and the butyl moiety weakly interacts in the 1:2 complex.

The solid complexes of tolbutamide with HP-α- and -β-CyDs in molar ratios of 1:1 and 1:2 were prepared by the spray-drying method (23). The 1:1 complex was prepared because it is a predominant species in aqueous solution. Figure 4 shows powder X-ray diffraction patterns and DSC curves of 1:1 and 1:2 complexes of tolbutamide with HP-β-CyD. The diffraction pattern of physical mixtures of the guest and host molecules was simply a superposition of each component, i.e., the patterns consisted of diffraction peaks of tolbutamide (stable form, Form I (23)) and a halo-pattern of amorphous HP-CyDs. The mixture gave an endothermic peak at 127°C due to the melting of tolbutamide (Form I) in the DSC thermograms. On the other hand, both 1:1 and 1:2 complexes gave a halo-pattern in the powder X-ray diffractogram and no thermal change in the DSC thermogram, indicating that the complexes are in an amorphous state. Same phenomena were observed for the HP-α-CyD complexes. These results suggests that tolbutamide forms amorphous solid complexes with HP-α- and -β-CyDs. However, it is very difficult to obtain information on the inclusion mode of the complexes from the halo-pattern of powder X-ray diffractograms and from the lack of thermal change on the DSC thermograms. Therefore, the interaction of the complexes in the solid-state state was investigated by solid-state ^{13}C NMR spectroscopy.

Figure 5 shows ^{13}C NMR spectra of tolbutamide/HP-α- and -β-CyD solid complexes at 25°C. It was apparent that in the 1:1 HP-α-CyD complexes, ^{13}C signals of the butyl moiety were broader than those of the phenyl moiety, i.e., the linewidths ($\Delta\nu_{1/2}$) at half-height of the C3,7, C4,6, C9 and C10 atoms were 139.8, 139.7, 194.6 and 192.5 Hz, respectively. On the other hand, in the 1:1 HP-β-CyD complex, those of the phenyl moiety were significantly broader than those of the butyl moiety, i.e., the $\Delta\nu_{1/2}$ values of the C3,7, C4,6, C9 and C10 atoms were 146.4, 145.7, 130.2 and 128.3 Hz, respectively. In the case of the 1:2 complexes, signals of the opposite inclusion sites of the guest were additionally broadened, although degrees of the broadening were less than those observed in the 1:1 complexes. The spectra of HP-α- and -β-CyDs were only changed insignificantly by the complexation with tolbutamide. Figure 6 shows the temperature dependency of ^{13}C signals of the phenyl and butyl portions of tolbutamide in the 1:1 complexes. In the case of the HP-α-CyD complex, signals of the phenyl carbons (C2–C7) became markedly narrower and sharper as temperature increased from 25°C to 80°C, whereas the butyl carbons (C9, C10 and C12) only slightly sharpened. Unfortunately, signals of methyl carbon (C1) and methylene

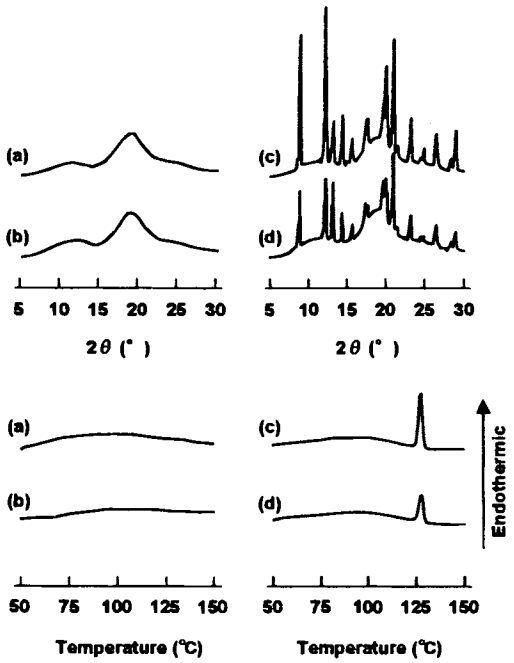

Fig. 4. Powder X-ray diffraction patterns (upper) and DSC curves (lower) of tolbutamide/HP-β-CyD systems. (a) 1:1 complex, (b) 1:2 complex, (c) 1:1 physical mixture, and (d) 1:2 physical mixture.

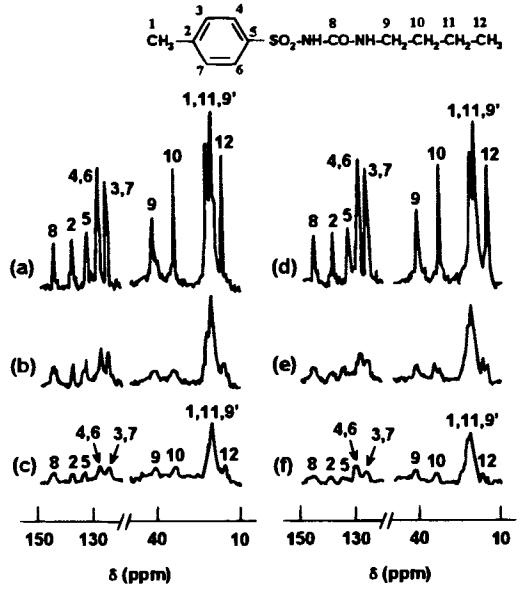

Fig. 5. ^{13}C CP/MAS NMR spectra of tolbutamide/HP-CyD systems at 25°C. (a) 1:1 physical mixture of HP-α-CyD, (b) 1:1 complex with HP-α-CyD, (c) 1:2 complex with HP-α-CyD, (d) 1:1 physical mixture of HP-β-CyD, (e) 1:1 complex with HP-β-CyD, (f) 1:2 complex with HP-β-CyD. The C11 carbon signal of tolbutamide was overlapped with HP-CyD carbon signal (C9').

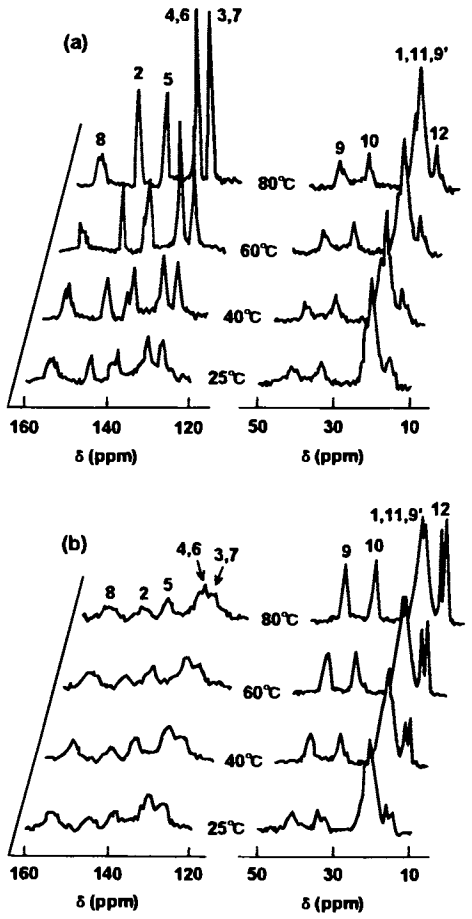

Fig. 6. ^{13}C CP/MAS NMR spectra of tolbutamide in 1:1 complexes with HP-α-CyD (a) and HP-β-CyD (b) at varying temperatures from 25°C to 80°C.

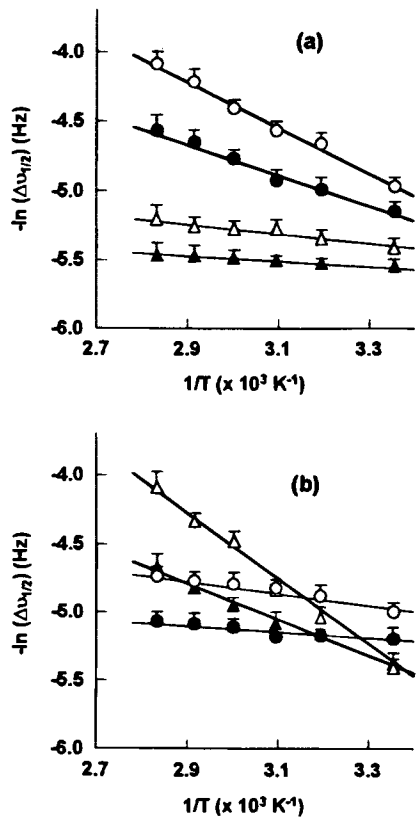

Fig. 7. Temperature dependencies of $\Delta\nu_{1/2}$ of C4,6 and C12 signals of tolbutamide in HP-α-CyD (a) and HP-β-CyD (b) complexes. (○) C4,6 in the 1:1 complex, (●) C4,6 in the 1:2 complex, (△) C12 in the 1:1 complex, and (▲) C12 in the 1:2 complex. Data represent the mean ± SE (n = 2–5).

carbon (C11) could not be analyzed because of the overlapping with signals of CyD carbons. In the case of the HP-β-CyD complex, on the other hand, signals of the phenyl carbons only changed insignificantly as temperature increased, whereas those of the butyl carbons became significantly narrower and sharper. Figure 7 shows plots of $-\ln(\Delta\nu_{1/2})$ versus the reciprocal of absolute temperature (1/T) for the C4,6 carbons of the phenyl group and the C12 carbon of the terminal butyl group in the 1:1 and 1:2 HP-α- and -β-CyD complexes. It is apparent that as temperature increased, the $\Delta\nu_{1/2}$ value of the C12 carbon was changed only slightly in both the 1:1 and 1:2 HP-α-CyD complexes, whereas that of the C4,6 carbons became markedly smaller in the 1:1 complex and moderately smaller in the 1:2 complex. On the other hand, the $\Delta\nu_{1/2}$ value of the C4,6 carbons only slightly changed in the 1:1 and 1:2 HP-β-CyD complexes, whereas that of the C12 carbon became significantly smaller in the 1:1 complex and moderately smaller in the 1:2 complex. The line narrowing or broadening in CP/MAS ^{13}C signals of the solid complexes may be attributable to both static and dynamic mechanisms (24,25). Because HP-CyDs are multi-component mixtures of the structurally related compounds with different D.S., ^{13}C signals of the guests should show a splitting due to slightly different inclusion modes. This static mechanism may contribute a certain degree to the line-broadening, particularly at lower temperatures. On the other hand, it is well known that the line-narrowing and -broadening of guests included in CyD cavities are caused by interference between the proton decoupling and the dynamic molecular reorientation of guests. In this case, the temperature dependence of line-widths is described as Eq. 4 (26,27).

$$1/T_2 = A[\tau_c(T)/(1 + \omega^2(\tau_c(T))^2)] \quad (4)$$

where T_2 is the spin-spin relaxation time, τ_c (T) is the correlation time of molecular motion and is a function of temperature, ω is the radio-frequency field strength for proton decoupling and A is a constant describing the ^1H-^{13}C dipolar interaction. The line-width corresponding to $1/T_2$ gives a maximum when $\omega\tau_c = 1$, and it becomes narrower when the molecular motion is faster ($\omega\tau_c << 1$) or slower ($\omega\tau_c >> 1$). Because the line-width of tolbutamide carbons became narrower as temperature increased as shown in Fig. 6, the molecular motion seemed to be in the condition of $\omega\tau_c << 1$ under the present experimental conditions. In this case, the line-width is proportional to τ_c as is apparent from Eq. 4, and then it is reasonable to assume that the line-width is a measure of molecular motion. Therefore, the observed temperature-dependent spectral changes of tolbutamide are indicative of the molecular motion, i.e., the butyl moiety is severely restricted in the 1:1 and 1:2 HP-α-CyD complexes, whereas the phenyl moiety is not impeded in the 1:1 complex and only moderately so in the 1:2 complex. The situation is completely reversed in the HP-β-CyD complexes,

where the molecular motion of the phenyl group is severely restricted, whereas the butyl group is in a state of high freedom. These restrictions in molecular motion can be ascribed to the inclusion of these moieties in the CyD cavity. That is, the butyl moiety of tolbutamide is preferably included in the HP-α-CyD cavity, because of the smaller size of its cavity, and the phenyl moiety interacts weakly with the second CyD molecule to form the 1:2 complex. In sharp contrast, the phenyl moiety is predominantly included in the HP-β-CyD cavity because of its larger cavity size, and the butyl moiety is loosely included in the cavity in the 1:2 complex showing a moderate molecular motion.

In this study, we showed, by means of solid-state NMR spectroscopy, that HP-CyDs form amorphous solid complexes with tolbutamide and HP-α-CyD having a smaller cavity preferably includes the butyl group, whereas HP-β-CyD having a larger cavity prefers the phenyl moiety. In general, it is very difficult to obtain structural information of amorphous CyD complexes using X-ray diffractometry and thermal analyses, because they give halo-patterns and no thermal changes. However, as shown here, solid-state NMR spectroscopy gives useful information on the inclusion complex formation, particularly in amorphous state, by monitoring temperature dependence of NMR signals. This technique may be applicable to other amorphous solid systems such as solid solutions and dispersions.

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