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Structure and Molecular Dynamics of Solid-State Inclusion Complexes of Cyclodextrin and Permethylated Cyclodextrin with Benzaldehyde Studied by High-Resolution CP/MAS ^{13}C NMR

FU-HUA KUAN, YOSHIO INOUE★, and RIICHIRO CHŪJŌ
Department of Polymer Chemistry, Tokyo Institute of Technology, O-okayama 2-chome, Meguro-ku, Tokyo 152, Japan

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Abstract. The structure and molecular dynamics of the benzaldehyde inclusion-complexes with α- and β-cyclodextrins and permethylated α-cyclodextrin in the solid state have been studied by high-resolution cross-polarization/magic angle sample-spinning ^{13}C NMR spectroscopy. It is shown that the guest benzaldehyde molecule undergoes motion in the host cyclodextrin cavity and the rate of motion depend on the cavity size. In the α-cyclodextrin complex, compared to β- and permethylated α-cyclodextrin complexes, the benzaldehyde motion is severely restricted, but under high-vacuum benzaldehyde is released more easily from the cavity.

Key words: Cyclodextrin, inclusion complex, benzaldehyde, ^{13}C NMR, molecular motion.

1. Introduction

Cyclodextrins (CD) are cyclic oligosaccharides composed of at least six (1→4)-linked α-D-glucosyl residues, which have the shape of a hollow, truncated cone with primary and secondary hydroxyl groups crowning the narrower and the wider rims, respectively. In the solid state as well as in solution, they can form inclusion complexes with a variety of guest molecules, in which the guest molecule is held within the cavity of the host macrocycle [1,2]. Recently, chemically modified cyclodextrins have received considerable attention in many fields [3–10] because their physicochemical properties are more or less different from those of the unmodified cyclodextrins. For example, some modified cyclodextrins called 'capped cyclodextrins' have been synthesized to enhance the hydrophobicity of the host cavity and to improve their complex-forming abilities [11,12].

Selectively and completely methylated cyclodextrins are quite simple derivatives for investigating the effect of substituents on the properties of cyclodextrins and their inclusion complexes. The synthetic procedure and the chemical and physical properties have been reported [13,15]. Methylated cyclodextrins can also form inclusion complexes with several guest compounds, some of which are more stable than the corresponding unmodified cyclodextrin complexes [14,16].

Cyclodextrins have been extensively applied to improve the physicochemical properties of various drugs [2,10]. For example, a potent anticancer agent, benzaldehyde [17,18], is used as inclusion complexes with α-, β-, and γ-cyclodextrin [19]. Needless to say, benzaldehyde is an oily liquid and has some unfavorable properties, such as instability to air and light, low

★ Author for correspondence.

solubility in water, stimulating odor, and so on. Thus, it requires some device for use as an orally acceptable drug. On complexation with cyclodextrins benzaldehyde is powdered and can be conveniently manufactured as tablets without significant loss of its antitumour activity. Further, it was reported that the stability of benzaldehyde against oxygen is improved by complexation with β-CD [20].

It is of great interest to compare the molecular structure and the stability of the modified-cyclodextrin inclusion complexes with those of the unmodified-cyclodextrin complexes. The crystalline inclusion-complexes of benzaldehyde with α-CD [5] and with hexakis-(2,3,6-tri-O-methyl)-α-cyclodextrin (α-TMCD) [9] have been characterized by the X-ray diffraction method. In the solid-state, benzaldehyde was found to form 1 : 1 inclusion complexes with both α-CD and α-TMCD, but the orientation of the guest molecule in the inclusion complexes is inversed, i.e., in the α-CD complex the benzene ring of benzaldehyde is located at the center of the α-CD cavity and its carbonyl group protrudes from the O(2), O(3) side of the cavity, while in the α-TMCD complex the benzaldehyde molecule is almost fully included within the α-TMCD cavity and its carbonyl group is located at the center of the cavity.

Recently, high-resolution solid-state cross-polarization (CP)/magic-angle sample spinning (MAS) ^{13}C NMR spectroscopy has proved useful in the study of the structure and the molecular dynamics of the cyclodextrin inclusion-complexes [21–26]. We now report on the study of the structure and the stability of inclusion-complexes of benzaldehyde with α-CD, β-CD, and α-TMCD.

2. Materials and Methods

Guaranteed grade of α-CD, β-CD, and benzaldehyde were purchased from Nakarai Chemicals, Ltd, Kyoto. α-TMCD was synthesized from α-CD [27] and recrystallized twice from hot water. The structure and purity of α-TMCD was confirmed by ^{1}H- and ^{13}C-NMR measurements in $^{2}HCCl_3$ or $CDCl_3$ and $^{2}H_2O$ solutions as well as by thin-layer chromatography. The crystals of the inclusion complexes were prepared according to the reported method [5,9], crystallized from water, and dried under vacuum.

High-resolution CP/MAS ^{13}C NMR spectra were recorded with JEOL JNM FX-200 and GX-270 spectrometers operated at 50 and 67.5 MHz, respectively. The instrumental conditions were MAS rate, 3.5 kHz; CP contact time, 2 ms; proton-decoupling field strength, 50–55 kHz. The details of the CP/MAS NMR operations have been reported [24]. ^{1}H NMR spectra of solution samples were recorded with a JEOL JNM PS-100 spectrometer at 100 MHz. UV spectra were measured with a Beckman 25 spectrometer.

3. Results and Discussion

3.1. CP/MAS ^{13}C NMR SPECTRAL FEATURES

Figure 1 shows the high-resolution CP/MAS ^{13}C NMR spectra of solid-state β-CD and β-CD/benzaldehyde complex. The assignments for β-CD resonances are based on those found in the literature [21–26]. Although the resolution in the solid-state is not as good as that in solution, the benzaldehyde resonances observed in the solid-state complex were readily assigned as shown in Figure 1b due to its close resemblance to those obtained in chloroform solution [27]. The two ortho-(C-2′,6′) and two meta-carbons (C-3′,5′) are magnetically equivalent. Upon complexation with benzaldehyde, there is only one (C-1) significant change in the β-CD resonances.

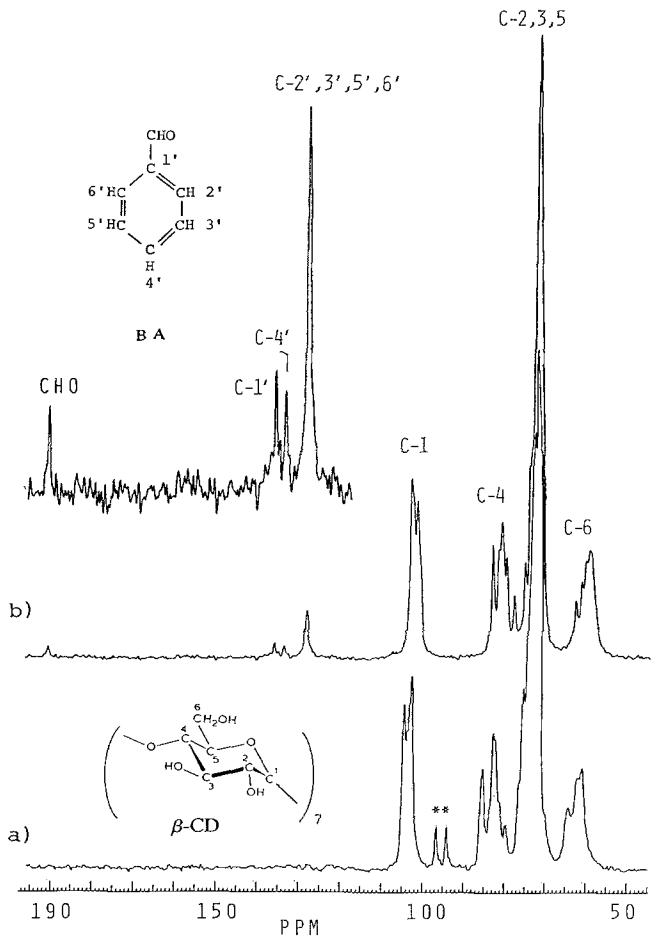

Fig. 1. CP/MAS ^{13}C NMR spectra of (a) β-CD (500 scans; contact time, 2 ms; repetition time, 5 s) and (b) β-CD-benzaldehyde (BA) inclusion-complex after 8 h drying at 25°C and about 5 mmHg (1185 scans; contact time, 2 ms; repetition time, 5 s). Unidentified peaks are indicated by '*'.

The CP/MAS ^{13}C NMR spectra of solid-state α-TMCD and α-TMCD/benzaldehyde complex are shown in Figure 2. The assignments of α-TMCD resonences are based on those for solution [16]. Upon complexation, as in the β-CD/benzaldehyde complex, the C-1 resonance of α-TMCD shows significant changes in its appearance. In the spectra of the α-TMCD/benzaldehyde complex, the resonances of the ortho carbons (C-2′,6′) and the meta carbons (C-3′,5′) of benzaldehyde are well resolved, unlike in the case of the β-CD/benzaldehyde complex.

In Figure 3 are shown the CP/MAS ^{13}C NMR spectra of α-CD and the α-CD/benzaldehyde complex in the solid state. The analysis of the ^{13}C spectra of crystalline α-CD hexahydrate has been reported [26]. Upon complexation, there are changes in the C-4 as well as the C-1 resonances of α-CD. Due to some ambiguities the assignments of the C-2′,6′ and C-4′ resonances of benzaldehyde are not conclusive. The spinning side-bands from the resonances of the aromatic ring-carbons at 136.9 and 130.5 ppm clearly appeared at 187.8

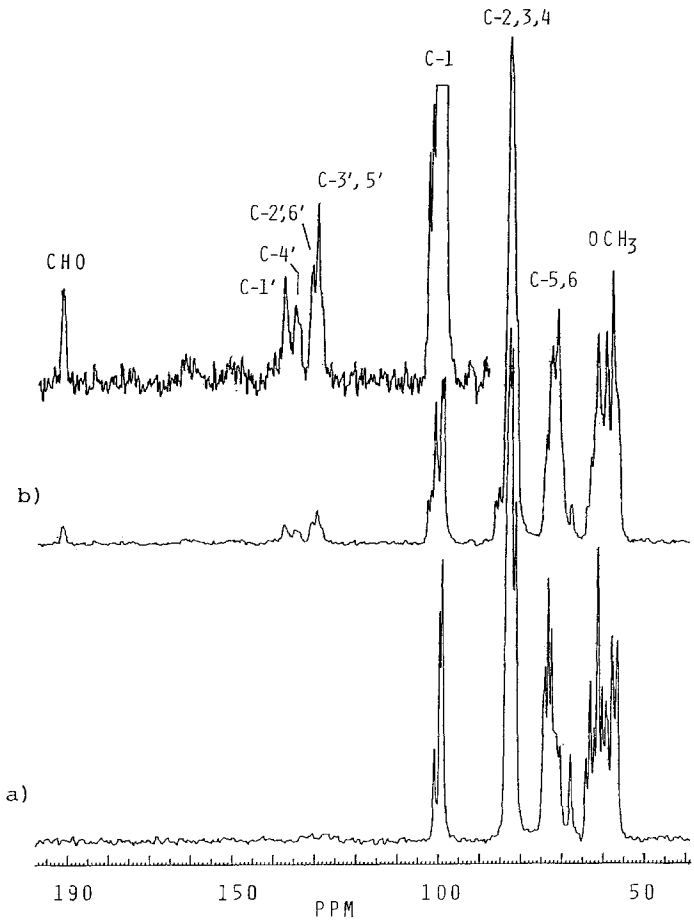

Fig. 2. CP/MAS ^{13}C NMR spectra of (a) α-TMCD (200 scans; contact time, 2 ms; repetition time, 5 s) and (b) α-TMCD/benzaldehyde inclusion-complex after 48 h drying at 60 °C and about 5 mmHg (500 scans; contact time, 2 ms; and repetition time, 5 ms).

and 181.0 ppm, respectively. The corresponding side-bands were not found in the spectra of the β-CD/benzaldehyde and the α-TMCD/benzaldehyde complexes.

Table I contains the ^{13}C chemical shifts of benzaldehyde in the solid state, and for comparison, those for solution [27,32] as well as for neat liquid [28].

3.2. CONFORMATION OF HOST CYCLODEXTRINS

In a previous paper [26], we have analysed the ^{13}C chemical shift variations of the C-1 and C-4 resonances of solid-state α-CD and its inclusion complexes and have indicated that the ^{13}C shifts of both resonances are sensitive to the conformational change of the glycosidic linkage and that the most plausible source of the solid-state ^{13}C shift variation of these resonances was the diversity of conformations about the glycosidic linkage. Thus, the conformational change is reflected in the line-shape and chemical shifts of C-1 and C-4 resonances. As shown in the preceding section, the C-1 and C-4 resonances of α-CD, β-CD, and α-TMCD changed their appearances, more or less, upon complexation with benz-

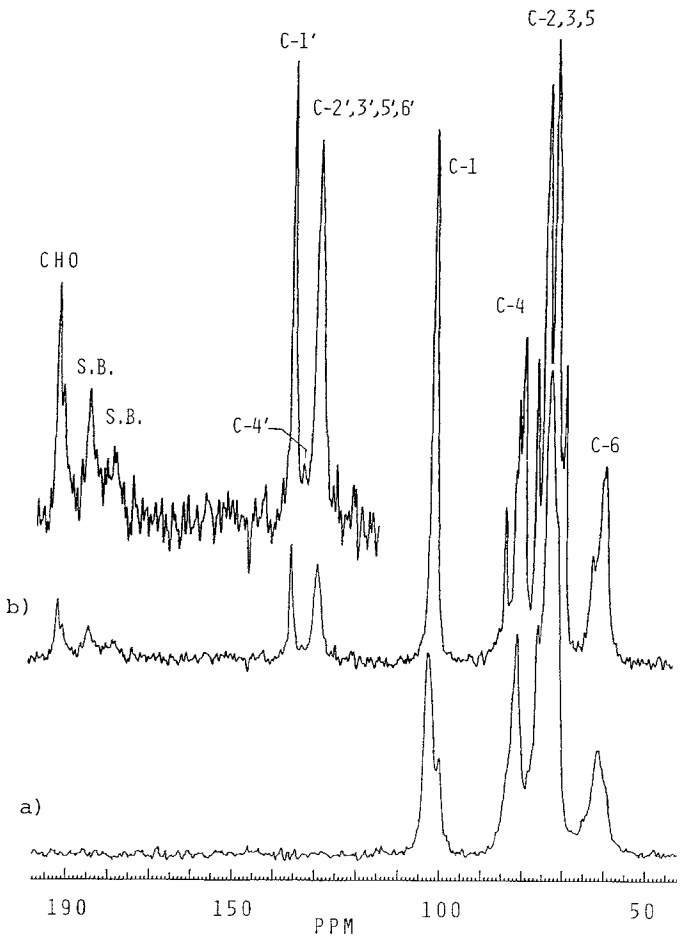

Fig. 3. CP/MAS ^{13}C NMR spectra of (a) α-CD (400 scans; contact time, 2 ms; repetition time, 5 s) and (b) α-CD/benzaldehyde inclusion-complex after 8 h drying at 25°C and about 5 mmHg (495 scans; contact time, 2 ms; repetition time, 5 s). Obvious side bands are indicated by 'S.B.'.

Table I. Carbon-13 chemical shifts[a] of benzaldehyde in the free and complexed states with α-CD, β-CD, and α-TMCD

State	Carbon atom				
	C-1'	C-2',6'	C-3',5'	C-4'	CHO
Neat liquid[b]	137.5	129.7	129.7	134.5	–
C^2HCl_3 solution[c]	136.4	129.5	128.9	134.2	192.0
Dimethylether solution at −134°C[d]	137.1	125.8 134.8	129.4 129.7	135.3	–
Solid complexed with β-CD	136.1	129.5	129.5	134.8	192.0
Solid complexed with α-TMCD	138.1	131.2	129.9	135.6	191.8
Solid complexed with α-CD	136.9	130.5[e]	130.5	134.1[e]	193.5

[a] In ppm downfield from Me_4Si. Experimental error, ± 0.5 ppm.
[b] Ref. [28]. [c] Ref. [27]. [d] Ref. [32].
[e] Assignments are not conclusive.

aldehyde, indicating that the conformational changes were induced on including benzaldehyde into these host cavities. The host cavity may change its conformation to accommodate the guest and/or to make a stable inclusion complex. The small changes in C-1 and C-4 resonances on going from β-CD to the β-CD/benzaldehyde complex suggest that the conformation of the β-CD macrocycle is only slightly perturbed by benzaldehyde compared to the conformations of the α-CD and α-TMCD macrocycles. This may be due to the fact that crystalline β-CD dodecahydrate has an open, round macrocycle with a symmetrical conformation [29], having the optimum cavity size to form inclusion complexes with benzene derivatives. The macrocyclic conformations before and after the inclusion of benzaldehyde may not be so different from each other.

Opposed to β-CD, the crystalline α-CD hexahydrate has a collapsed less symmetrical macrocyclic-conformation [30]. Upon inclusion of the planar benzaldehyde molecule, the hexagonal α-CD macrocycle changes its conformation to an elliptically distorted one [5]. The relatively large change in the C-1 resonance of α-CD on inclusion of the benzaldehyde molecule may be induced by these large conformational changes. Strictly, the rotational state about the glycosidic linkage is specified by four angles ϕ_1, ϕ_1', ϕ_2, and ϕ_2', which specify, respectively, the torsion angles O-5–C-1–O-4′–C-4′, C-2–C-1–O-4′–C-4′, C-1–O-4′–C-4′–C-3′, and C-1–O-4′–C-4′–C-5′ [31], where primed and unprimed atoms indicate atoms of adjacent glucopyranose units. The six sets of four angles $[\phi_1 : \phi_1' : \phi_2 : \phi_2']$ for the α-CD hexahydrate are widely distributed as follows [88.2 ~ 112.8, $\sigma = 8.9$; −126.5 ~ −151.9, $\sigma = 9.0$; 116.6 ~ 170.4, $\sigma = 17.6$; −69.3 ~ −123.7, $\sigma = 19.7$], compared to those for the α-CD/benzaldehyde complex, i.e., [90.6 ~ 109.4, $\sigma = 6.3$; −130.5 ~ −147.4, $\sigma = 5.7$; 126.2 ~ 142.9, $\sigma = 5.3$; −94.6 ~ −114.6, $\sigma = 6.5$ [5], where σ is the standard deviation from the simple average. As observed for the C-1 resonances of α-CD and the α-CD/benzaldehyde complex, it may be qualitatively said that the smaller the distribution of these four angles, the narrower is the ^{13}C shift distribution, but it is very difficult to correlate quantitatively these angles with the ^{13}C shifts. At present, we cannot refer to the conformations of the β-CD/benzaldehyde complex and α-TMCD, because we have no X-ray crystallographic structural information for them.

3.3. ^{13}C CHEMICAL SHIFTS OF GUEST BENZALDEHYDE

Some of the most useful information available from the solid state NMR spectra result from the different chemical shifts of single atoms within different sites. Substantial deviations between solid and solution chemical shifts are observed in many samples. Differences in conformation, in sites of association, and in complexation equilibria, which are mostly averaged in solution spectra, can often be resolved in the solid spectra. In general, the ^{13}C chemical shifts of solid samples measured by the CP/MAS technique reflect frozen geometries, as well as molecular packing effects and such fixed interactions as hydrogen bonding.

It is noteworthy that the ^{13}C chemical shifts for benzaldehyde resonances in the solid-state α-CD/benzaldehyde complex agree well, within a probable experimental error of 0.5 ppm, with the corresponding chemical shifts for chloroform solution, as seen in Table I. This result indicates that the benzaldehyde molecule in the α-CD complex is subjected to a low-polar environmental effect similar to that in the chloroform solution. Also the steric perturbation of the host cavity on the included benzaldehyde molecule may be small. The most outstanding result is that, in spite of the solid state, both the two ortho-(C-2′,6′) and the two meta-carbons (C-3′,5′) of benzaldehyde in all three complexes are magnetically equivalent. This is similar

to the situation in the neat liquid or in chloroform solution at ambient temperature, rather than in the dimethyl ether solution at low temperature [32], where the two ortho- and meta-carbons show magnetic non-equivalence of 9.0 and 0.3 ppm, respectively. The magnetic non-equivalence in the latter solution arises by freezing the internal rotation about the phenyl-formyl bond. This will be discussed in the following section.

Earlier ^{13}C NMR studies of cyclodextrin inclusion complexes with substituted benzenes in the solid state [24] as well as in solution [33] showed that the chemical shifts of the resonances of ipso- and corresponding para-carbons of the guests are sensitive to whether they are included in the cyclodextrin cavity or not. The chemical shift displacements induced by the complexation for these resonances are used to identify the guest–host orientation in the complex. For the β-CD inclusion-complex with benzaldehyde, there are no crystallographic data. But the CP/MAS ^{13}C data suggest that, in the solid state, benzaldehyde is included in the β-CD cavity in the same manner as for α-CD [5]. Namely, the phenyl ring is located at the center of the CD cavity and its carbonyl group is orientated toward the outside of the cavity, since the ^{13}C shifts of the C-1′ and C-4′ resonances of benzaldehyde in the β-CD complex are quite similar to those in the α-CD complex.

In contrast, the C-1′ and C-4′ resonances of benzaldehyde in the α-TMCD complex appear at lower field compared to those in the α- and β-CD complexes. These clear differences must be due to the oppositely oriented guest in α-TMCD/benzaldehyde as found by X-ray methods [5,9]. According to the X-ray crystallographic structures, the benzaldehyde carbonyl group in the α-CD/benzaldehyde complex is in van der Waals contact with the primary hydroxyl side of the next α-CD, while in the α-TMCD/benzaldehyde complex it is located at the center of the cavity. The relatively large down-field shift of the carbonyl resonance of benzaldehyde in the α-CD complex compared to the shift in the α-TMCD complex may reflect this geometrical difference.

In the α-TMCD complex, the benzaldehyde resonance C-2′,6′ showed a larger down-field shift (1.7 ppm) than that of the C-3′,5′ (1.0 ppm), referenced to the shifts in chloroform solution. This difference may be explained by the structure of the complex, i.e., the carbons 2′,6′ reside inside the α-TMCD cavity while the carbons 3′,5′ are located outside.

These results show that the isotropic ^{13}C shifts of guests observed by the CP/MAS method can provide information concerning the guest–host geometry of the cyclodextrin inclusion-complexes.

3.4. DYNAMICS OF BENZALDEHYDE

The aromatic carbon region of the CP/MAS ^{13}C NMR spectra of the solid-state α-CD/benzaldehyde complex has very unusual patterns. The C-2′,6′ resonance cannot be observed separately from the other resonances. A plausible explanation for this is that the C-2′,6′ resonance has shifted to and is overlapped by the broad C-3′,5′ resonance as found in the spectra of the β-CD/benzaldehyde complex. This explanation is a possibility, but it cannot explain the significant reduction in total intensity of the resonances of protonated aromatic carbons compared to the intensity of the C-1′ resonance. The disappearance of the C-2′,6′ resonance can be more reasonably explained by the restricted intramolecular reorientation of the phenyl ring and/or the formyl moiety about the phenyl–formyl bond. This will bring about the exchange of the aldehyde carbonyl group between the two stable positions, i.e., O-*cis* and O-*trans* relative to one of two ortho carbons C-2′,6′. Evidence of restricted rotation of the –CHO moiety has been obtained by ^{1}H and ^{13}C NMR spectroscopy in a number of aromatic aldehydes [32,34]. In the frozen state, the carbonyl group is restricted to one of two stable

positions and as a result both the two ortho- and meta-carbons become magnetically non-equivalent. The non-equivalence amounts to 9.0 and 0.3 ppm for the ortho- and meta-carbon chemical shifts, respectively, of the benzaldehyde molecule in the frozen state in solution at $-134°C$ [32].

In general, if the exchange is fast enough compared to the chemical shift difference between two chemically but not magnetically equivalent carbons, then a single peak would be seen for these carbons, and two lines might be discerned for slow exchange. For an intermediate exchange rate, i.e., when the rate is near the chemical shift difference, the resonances are broadened and actually disappear from the spectrum. This rate is about 500 Hz for the ortho carbon resonances of the benzaldehyde molecule. This explanation is consistent with the fact that the C-3′,5′ resonance is affected little by the exchange process, because the chemical shift difference between these carbons is quite small in the frozen state [32]. Unfortunately, however, the intensity loss of the C-4′ resonance is not explained by the same exchange process and the reason is not clear at present.

Evidence indicating the rotational motion of benzene compounds included in the α-CD cavity has been observed by CP/MAS ^{13}C NMR spectroscopy [24,25]. Thus it may be reasonable to deduce that the intramolecular reorientation which induces the exchange process considered here is the restricted librational motion of the phenyl ring. The mobility of the aldehyde moiety might be limited due to van der Waals contact with the primary hydroxyl side of the next α-CD unit in the solid, but the motion of this moiety cannot be fully denied as the cause by the present data.

The appearance of clear spinning side bands from the benzaldehyde aromatic carbon resonances in the spectrum of the α-CD/benzaldehyde complex (Figure 3) indicates the absence of a large-amplitude motion of the benzaldehyde molecule, faster than $10^3 \sim 10^4$ Hz, since typical values [35] for the chemical shift anisotropy for aromatic carbons are in the range of $150 \sim 200$ ppm. In contrast, there are no detectable spinning side bands in the spectra of β-CD/benzaldehyde (Figure 1) and α-TMCD/benzaldehyde (Figure 2) complexes, although those were not removed artificially, indicating the benzaldehyde phenyl ring is undergoing faster motion in these complexes than in the α-CD complex.

According to the theory [36] for the line-width of a solid-state resonance for a ^{13}C spin coupled to a proton spin through a dipolar mechanism under conditions of random rotational motion and proton decoupling, the line-widths is reduced more efficiently by faster motion in the short correlation limit, $\omega_1 \tau_c < 1$, where ω_1 and τ_c are the frequency of proton decoupling and the correlation time of molecular motion, respectively. The line-widths of the benzaldehyde resonances in the spectrum of the β-CD complex (Figure 1) are narrower than those of the α-TMCD complex, suggesting that the molecular motion of the benzaldehyde molecule is faster in the former complex than in the latter.

The expectation that the benzaldehyde molecule has the largest mobility in the β-CD complex followed by α-TMCD and then by the α-CD complexes is consistent with the order of cavity size of the host cyclodextrins. An X-ray crystallographic study [9] has shown that the size of the secondary hydroxyl side of the cavity is widened by methylation of all hydroxyl groups, so that the guest molecule can be more loosely bound in α-TMCD than in α-CD.

The line-width of the benzaldehyde carbonyl resonance in the ^{13}C spectra of β-CD and α-TMCD complexes is narrower than that in the spectrum of the α-CD complex, indicating that the formyl moiety is also reorientating in the β-CD and α-TMCD cavities.

In conclusion, the CP/MAS ^{13}C NMR spectra clearly indicate that the guest benzaldehyde molecule included in the cyclodextrin cavity undergoes molecular motion even in the solid state and its rate and mode are dependent on the cavity size.

3.5. STABILITY OF THE COMPLEXES

Figure 2 shows that α-TMCD is capable of holding the volatile benzaldehyde molecule in its cavity even under the condition of 48 h drying at 60 °C in a vacuum of about 5 mmHg. Under the same conditions, however, α-CD released almost all the benzaldehyde as shown in Figure 4. No benzaldehyde resonances could be found even after a longer contact time of 10 ms but the characteristic UV signal of benzaldehyde could be observed for this sample dissolved in water. The drying condition of the crystal sample of the α-CD/benzaldehyde complex, used for the measurement of its CP/MAS ^{13}C spectrum shown in Figure 3, was milder, i.e., at 25 °C and 5 mmHg for 8 hours. These results indicate that α-CD has a lower capability of holding the benzaldehyde molecule than α-TMCD, even though it is more tightly included and its motion is more severely restricted in the α-CD cavity than in the α-TMCD cavity. The capability of holding volatile guest molecules in the CD cavity may depend on several factors such as cavity size, strength of host–guest interaction, and crystal morphology of the complex. The permethylation of α-CD is effective for holding the volatile benzaldehyde molecule in the cavity.

The ^{13}C spectra of α-CD shown in Figure 4 has a very different appearance from that shown in Figure 3, indicating that releasing of the guest molecule induces drastic conformational changes in the α-CD molecule. This is the first observation of the ^{13}C spectrum of the empty α-CD.

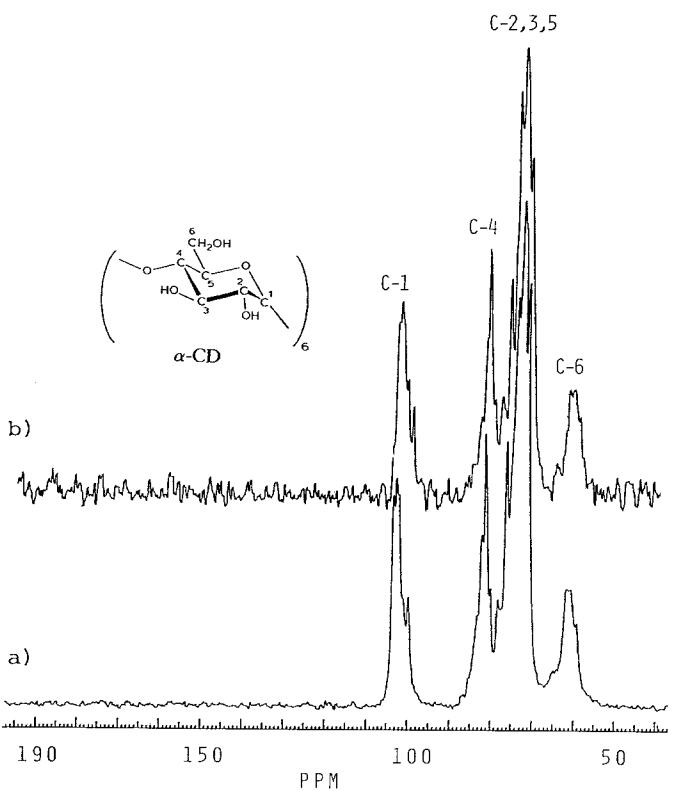

Fig. 4. CP/MAS ^{13}C NMR spectra of α-CD/benzaldehyde inclusion complex after 48 h drying at 60 °C and about 5 mmHg. (a) 600 scans, contact time 2 ms, and repetition 5 s. (b) 1100 scans, contact time 10 ms, and repetition time 5 s.

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