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Variable Temperature CP/MAS ^{13}C NMR Study of Cyclodextrin Complexes of Benzaldehyde*

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Abstract. Fully hydrated as well as dried benzaldehyde complexes of α- and β-cyclodextrins were studied by using CP/MAS ^{13}C NMR techniques. Variable temperature studies have shown that below ~200 K the guest is rigidly held in the complex, whereas at 328 K, only the aromatic ring performs rapid two-fold flips about the C_1–C_4 axis. In the β-Cd complex the benzaldehyde performs more general reorientation. Removal of water causes marked changes in both guest and host spectra, generally consistent with a loss of short-range order and increase in guest motional rate.

Key words: Cyclodextrin, CP MAS ^{13}C NMR, benzaldehyde, molecular motion.

1. Introduction

Recently a paper appeared in this Journal which reported results obtained for cyclodextrin complexes of benzaldehyde [1]. Studies under way at that time in our laboratory have yielded some additional information. As there are significant differences between our conclusions and those reported previously [1], results of our experiments are reported in some detail.

As more NMR results are published on cyclodextrins [2–5], it has become evident that some important points need to be addressed. For instance, although the presence of molecular motion has been inferred [1, 2], as in the case of the α-cyclodextrin-benzaldehyde complex [1], satisfactory models have not been presented. Another important aspect is the role of water in determining the detailed inclusion compound structure and guest motions, as these factors should profoundly affect the ^{13}C NMR spectrum.

Here are reported results obtained by using variable temperature CP/MAS ^{13}C NMR techniques, including dipolar dephasing, for hydrated and dried benzaldehyde inclusion complexes of α- and β-cyclodextrins.

2. Experimental Section

^{13}C NMR spectra were obtained at 45.3 MHz on a Bruker CXP-180 NMR spectrometer equipped with a variable temperature magic angle spinning (MAS) probe supplied by Doty Scientific. Single shot cross-polarization contacts [6] of 1–2 msec were used, with matched rf field amplitudes of at least 60 kHz. 2 K datum points were collected at a sweep width setting of 20 kHz, and were zero-filled to 8 K before

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Fourier transformation. MAS rates were between 3 and 5 kHz [7] and up to 2000 signals were co-added to obtain a sufficient signal to noise ratio. Dipolar dephasing was carried out by interrupting the ^1H decoupling for a 40 μsec period before data acquisition [8].

Complexes of benzaldehyde with cyclodextrins were obtained by slow cooling of aqueous solutions [9, 10]. In the case of the α-cyclodextrin–benzaldehyde complex, a hexahydrate is obtained. Spectra were obtained for fresh complexes as well as complexes dried over calcium chloride in the presence of benzaldehyde vapor. Karl Fischer titration showed that 2–3 molecules of water per formula unit were lost during the drying treatment.

3. Results and Discussions

Figure 1a shows the spectrum of the fully hydrated α-cyclodextrin complex of benzaldehyde. The spectral resolution is significantly better than that observed in the previous study [1] despite our lower resonance frequency. For instance, all six C_4 carbon resonances can be identified although 2 lines overlap almost exactly. This is consistent with the presence of a single cyclodextrin molecule in the asymmetric unit [9]. The guest spectrum is also somewhat different from that previously reported (Fig. 1b). The line assigned to $C'_{2,3,5,6}$ at 130.5 ppm is weaker, and the C'_4 line reported to be at 136.9 ppm is seen to be a doublet with lines at 136.7 and 136.2 ppm.

Dipolar dephasing [8] is often used in assigning ^{13}C spectral lines, the reduced line intensities reflecting the strength of $^{13}C—H$ nuclear dipolar interactions. With a dephasing time of 40 μsec, the lines due to methylene and methine carbons disappear, whereas quaternary carbons appear at almost full intensity in the absence of motion. Single axis rotors appear at reduced intensity depending on the detailed geometry. For rotating methyl groups the reduction is ~40%.

The guest spectrum obtained under these conditions is shown in Fig. 1c. The weaker component of the doublet disappears, whereas the stronger component has its full intensity. This allows assignment of the stronger component at 136.7 ppm to C'_1, the line at 136.2 ppm to C'_4. The line due to $C'_{2,3,5,6}$ appears at about half intensity, and the aldehyde carbon line at 193.5 ppm disappears almost completely. The interesting conclusion of the dipolar dephasing results is that the aldehyde portion of the guest molecule is fixed except, perhaps, for small amplitude librations. The reduced intensity of the $C'_{2,3,5,6}$ line suggests therefore that the ring is moving. The complete disappearance of the C_4 line suggests that the C—H dipolar interaction for this carbon is unchanged, or nearly so. This is the case when the C'_4—H bond lies approximately along the rotation axis.

The NMR results therefore support a model where the aromatic ring rotates about an axis which lies approximately along the $C'_1—C'_4$ direction whilst the aldehyde group is fixed in the lattice. The X-ray structure [9] shows a guest molecule essentially fixed in the lattice with the aromatic ring fitting in the secondary hydroxyl side of the cyclodextrin molecule, and the aldehyde group protruding into the primary hydroxyl side of an adjacent host molecule. Steric hindrance must lock the aldehyde group into place. The ring rotation then takes place as a 180° flip about an axis through the C'_1 and C'_4 carbons.

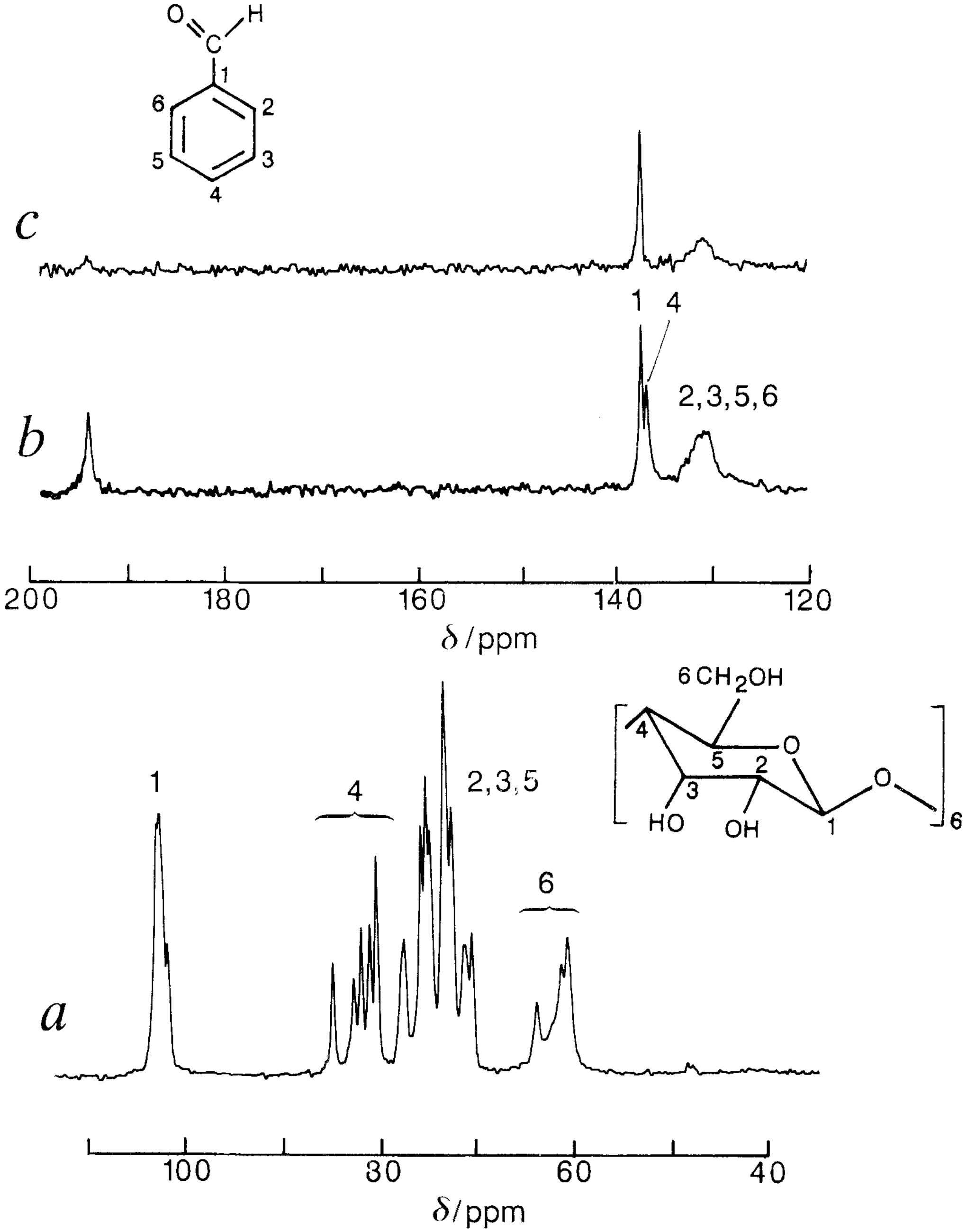

Fig. 1. CP/MAS ^{13}C NMR spectrum of hydrated α-cyclodextrin complex of benzaldehyde: (a) host lattice spectrum, (b) guest spectrum, (c) guest spectrum with dipolar dephasing.

The lack of spectral intensity for $C'_{2,3,5,6}$ suggests that the molecular motion is of some intermediate rate, with the exact criteria which should be applied to the spectral broadening as yet undefined. These should become apparent on either raising or lowering the temperature. The guest spectrum at various temperatures

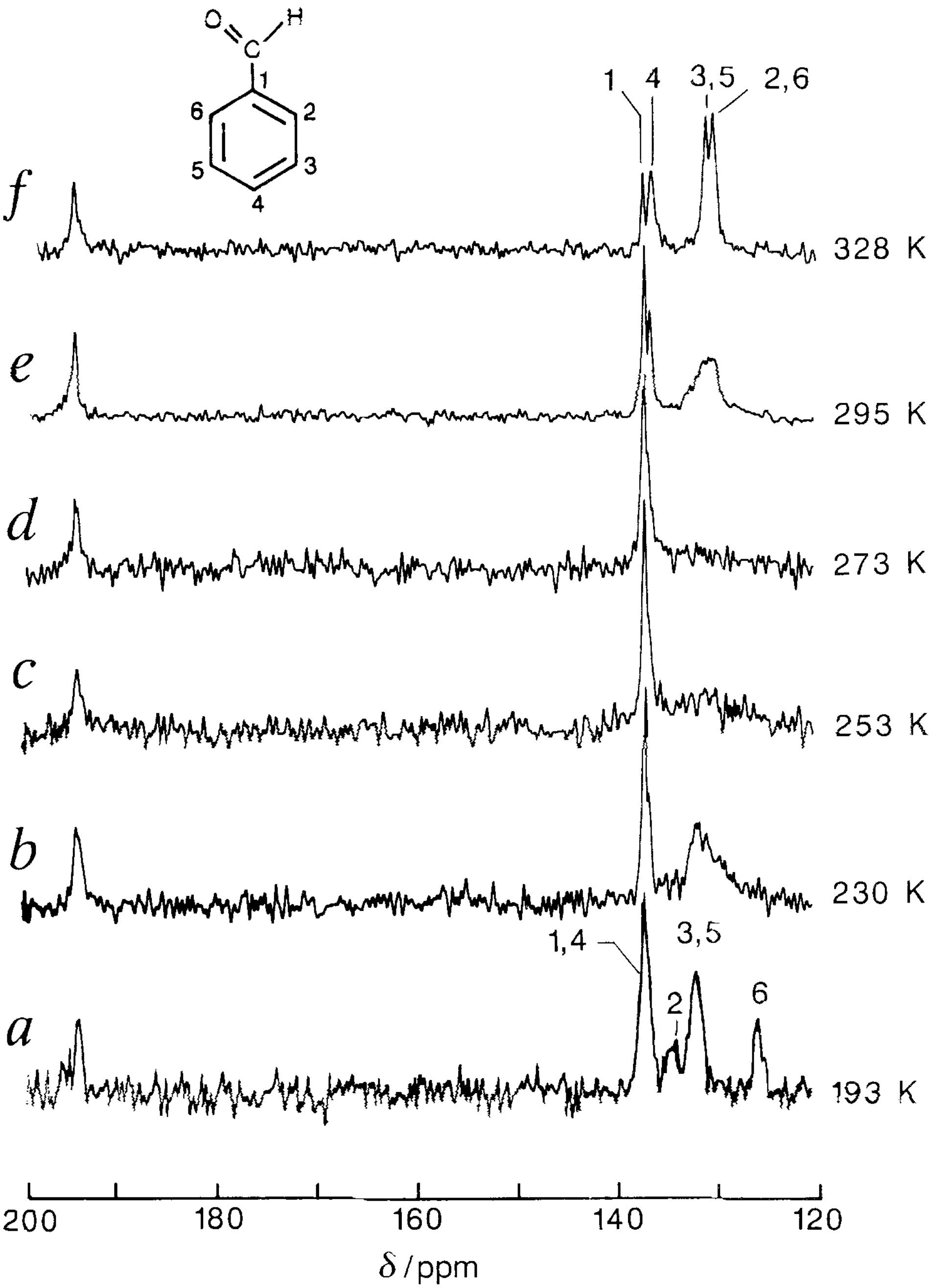

Fig. 2. CP/MAS ^{13}C NMR spectrum of hydrated α-cyclodextrin complex of benzaldehyde – guest region as a function of temperature: (a) 193 K, (b) 230 K, (c) 253 K, (d) 273 K, (e) 295 K, (f) 328 K.

is shown in Figs. 2a–f. At 273 K, the $C'_{2,3,5,6}$ resonance has essentially disappeared, and at 253 K the line is again discernible above noise level. Below 210 K, the lines sharpen again, and at 193 K, all 7 benzaldehyde carbons can be accounted for. The C'_1 and C'_4 lines are not individually resolved at 136.3 ppm, C'_3 and C'_5 occur at 132.0

ppm and the ortho carbons C_2' and C_6' occur at 134.2 and 126.0 ppm, respectively. This is consistent with a rigidly held benzaldehyde [11] guest in the cyclodextrin complex. On the other hand, on increasing the temperature to 328 K, the guest lines are again well resolved, with C_4' at 137.1 ppm, C_1' at 136.2 ppm, $C_{2,6}'$ at 130.1 ppm and $C_{3,5}'$ at 130.8 ppm. This spectrum therefore confirms the presence of rapid twofold flips about the C_1'–C_4' direction. The dipolar dephasing spectrum (not shown) confirms the assignment.

Line broadening due to motional effects has several origins, each with different criteria. First of all, twofold flips of the benzaldehyde ring average the C_2', C_6' and C_3', C_5' chemical shift differences, with maximum line broadening setting in when motional rates occur at some 10s to 100s of Hz [12].

Secondly, there is line broadening when motional flips give rise to dephasing of spin packets under magic angle spinning conditions when the main line broadening mechanism is the anisotropic chemical shift [13]. Finally, line broadening occurs in dipolar coupled systems when motional rates have frequencies comparable to the strength of the decoupling field [14], ~60 kHz in our case. These latter two broadening mechanisms can be expected to occur for the benzaldehyde $C_{2,3,5,6}'$ carbons for motional correlation times between $\sim 10^{-3}$ and 10^{-7} sec. The net effect is that the protiated aromatic carbons of benzaldehyde have anomalous width for over a hundred degree temperature range.

At intermediate temperatures the aldehyde carbon line does not show the severe line-broadening seen for the protiated aromatic carbons, and hence, rotations or other large amplitude motions are ruled out for this group.

It is to be noted that this picture of the benzaldehyde motion differs markedly from that proposed in the previous study [1]. Rapid large amplitude motions were deemed to be absent because of the presence of spinning sidebands for the benzaldehyde carbons. However, the limited motional averaging produced by single axis rotations such as two-fold flips of an aromatic ring apparently reduce the width of the shielding tensor pattern minimally, so that spinning sidebands still appear when moderate (2–3 kHz) spinning rates are used.

The spectrum of the host lattice also is temperature dependent (Fig. 3). There is relatively little difference on going up to 55 °C from room temperature. However, with decreasing temperature extra features can be observed especially for the C_4 carbon band. At 193 K, both the C_1 and C_4 regions appear more complicated than at higher temperatures. If the sharp component at the high field side of C_1 is an indication of peak height for a single carbon in the asymmetric unit, then it must be concluded that this unit must include rather more than a single molecule. There is a hint of this also from the low temperature guest spectrum where the broad nature of the lines may well hide doublet or other multiplet splitting. Of course a disordered structure cannot be ruled out.

Some other interesting trends in the temperature dependent spectra can be seen in the C_4 and C_6 bands. At 55 °C all C_4 carbons in the unit cell have more or less equal intensity and linewidth. At room temperature the line at 84.8 ppm and especially the line at 82.7 ppm have greater linewidth, and this trend continues with decrease of temperature. This may be connected with the disorder observed in the X-ray structure [9]. Whereas 4 primary hydroxyls are in the *gg* configurations (here O(6) is gauche with respect to O(5) and C(4)), one hydroxyl is in a *gt* configuration, and one is disordered. The lines for the 4 *gg* C_6 carbons can be seen at 60.6

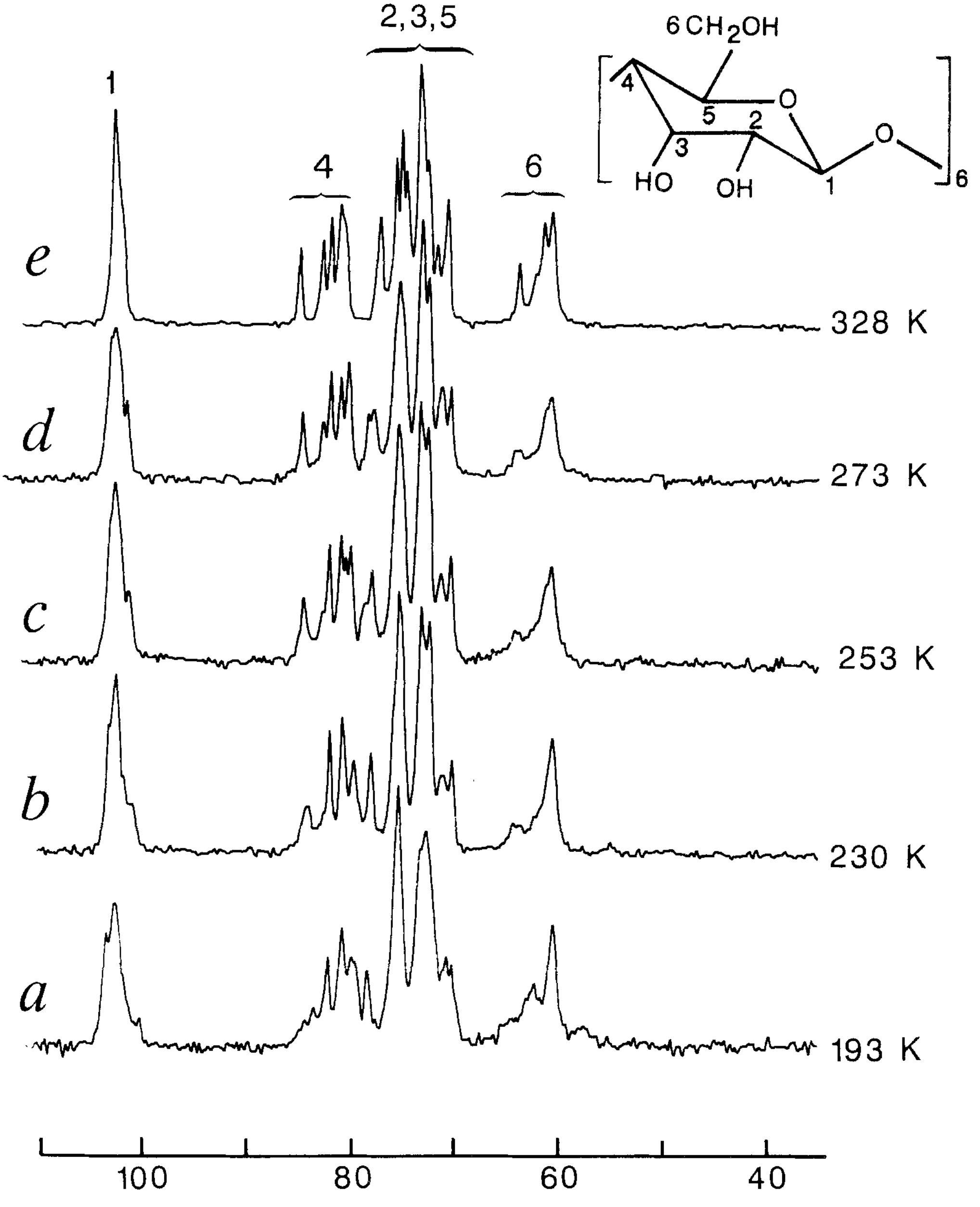

Fig. 3. CP/MAS ^{13}C NMR spectrum of hydrated α-cyclodextrin complex of benzaldehyde – host region as a function of temperature: (a) 193 K, (b) 250 K, (c) 253 K, (d) 273 K, (e) 328 K.

and 61.3 ppm, the ordered *gt* C_6 carbon at 63.9 ppm. The shoulder at 62.1 ppm could then be assigned to the disordered carbon if exchange between the disordered positions takes place at a rate approaching the fast motion limit. A decrease in temperature then causes a freezing of the disorder which manifests itself both in the C_4 and

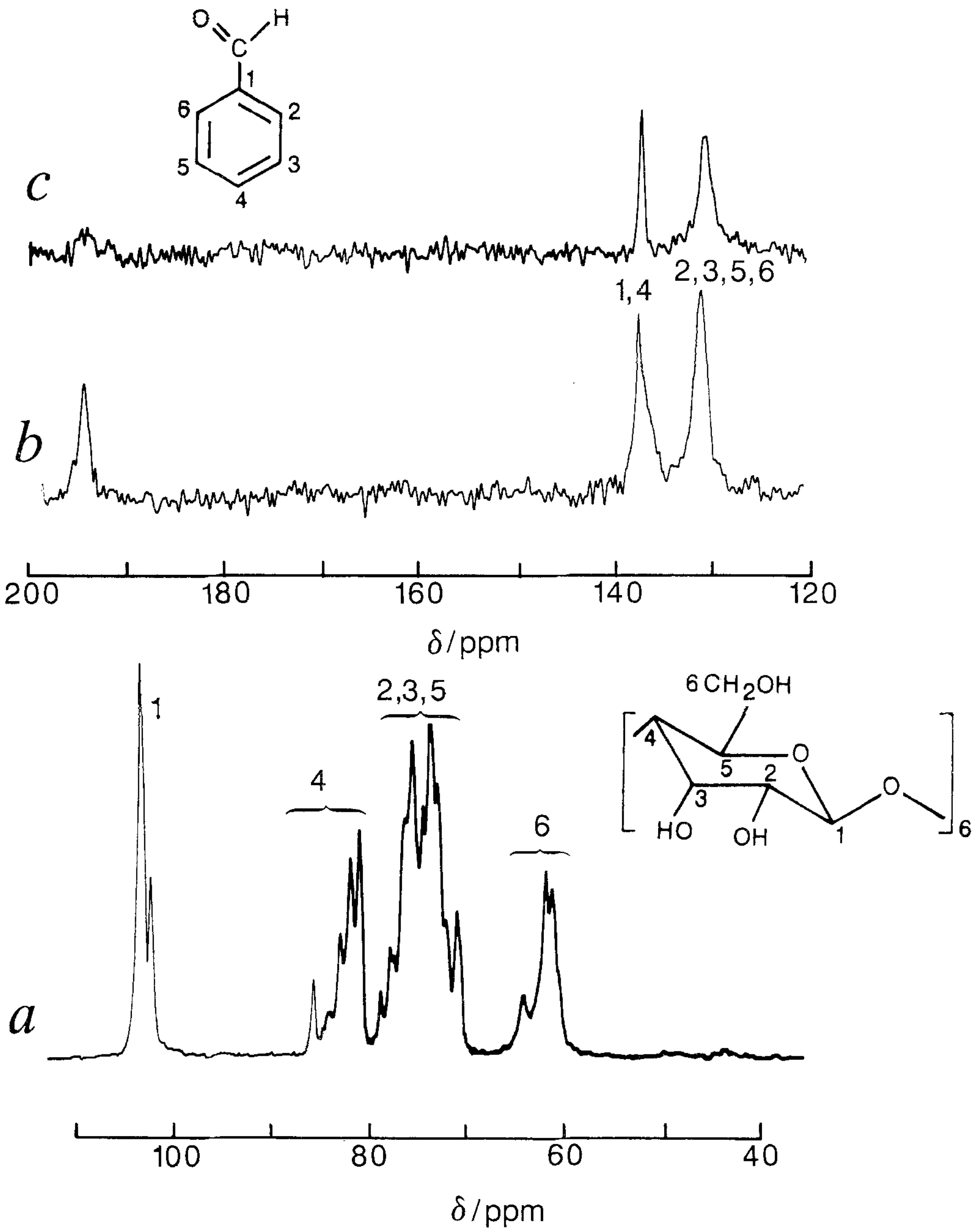

Fig. 4. CP/MAS ^{13}C NMR spectrum of the dried α-cyclodextrin complex of benzaldehyde: (a) host lattice spectrum, (b) guest spectrum, (c) guest spectrum with dipolar dephasing.

C_6 regions. At low temperatures (193 K) there again is extra intensity in the centre of the C_6 band, so that this simple explanation no longer holds.

From the X-ray study of the α-cyclodextrin complex of benzaldehyde [9], water molecules play a critical role in filling space between host molecules and imposing

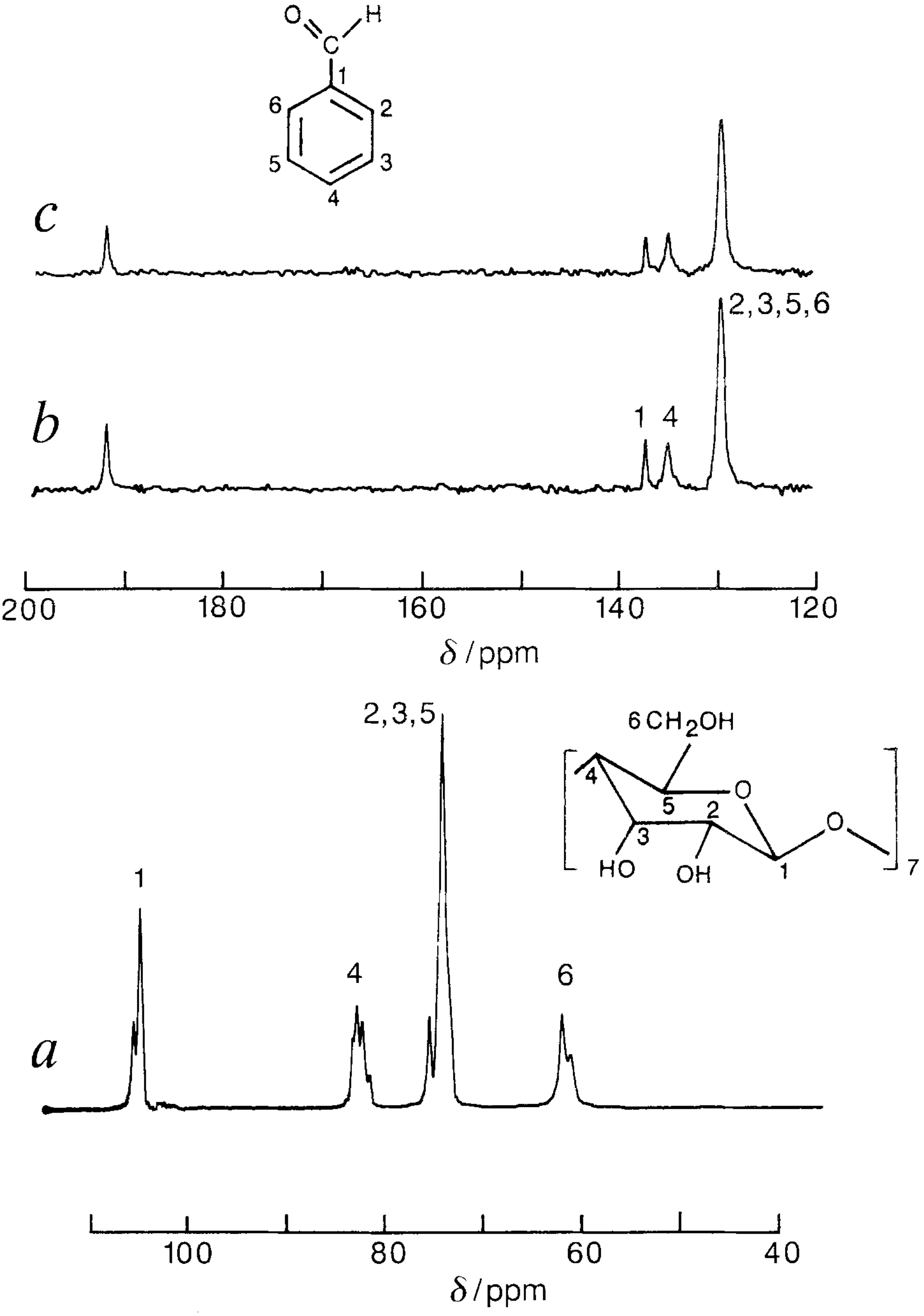

Fig. 5. CP/MAS ^{13}C NMR spectrum of the fully hydrated β-cyclodextrin complex of benzaldehyde: (a) host lattice region, (b) guest spectrum, (c) guest spectrum with dipolar dephasing.

short range order in the structure by establishing a hydrogen bonding network. Removal of some or all of this water should result in loss of short range order, and perhaps some loosening of the structure.

Figure 4a shows the host lattice spectrum of the α-cyclodextrin–benzaldehyde complex after drying over calcium chloride. In order to preserve included benzaldehyde, drying was carried out in the presence of benzaldehyde vapour, and Fig. 4b and c show that benzaldehyde is indeed still present. The ^{13}C spectrum of the host region (Fig. 4a) for the dried sample is more complicated than for the fully hydrated sample. It is not obvious if the extra structure merely indicates a doubling of the asymmetric unit size, or on the other hand a more general lack of short range order in the lattice.

Evidently guest motions are also affected by loss of water (Fig. 4b, c). One difference between hydrated and dried samples is the lack of resolution of the C'_1 and C'_4 resonances which results on drying. Also, for the dried sample the $C'_{2,3,5,6}$ line is much more intense. As the intensity loss was attributed to intermediate motional effects for the fully hydrated sample, the intensity gain on drying can be attributed to a closer approach to the fast motion limit. The dephased spectrum (Fig. 4c) shows that the same lines disappear as for the hydrated sample, so that the type of motion does not change, only the frequency. The faster two-fold flip rate on drying is then consistent with a loosening of the lattice.

In order to contrast the behaviour of the α-cyclodextrin complex, some data are also reported for benzaldehyde trapped in the β-cyclodextrin inclusion compound. The host lattice spectrum, for the fully hydrated complex is shown in Fig. 5a. It is completely different from that reported in the previous study [1] presumably because of the drying treatment of that sample. No structural information on this compound is available, so that a detailed interpretation of the spectrum is not possible. However, the relatively narrow chemical shift range for the chemically equivalent, but crystallographically inequivalent carbons suggests a much more regular structure of the cyclodextrin torus for the β-cyclodextrin than for the α-cyclodextrin.

Figures 5b and 5c show ^{13}C spectra, normal and dephased, respectively, for the benzaldehyde guest. From the relatively small intensity losses on dipolar dephasing there is more general reorientation of the guest molecule than is the case for the α-cyclodextrin complex. There is no unusual line-broadening, so that the motion is in the fast limit. The line positions also indicate that there is internal rotation of the aldehyde group with respect to the ring.

The benzaldehyde chemical shift values for the complexes and chloroform solution are summarized in Table I. The most general trend observable is the progressive low field shift on going from solution to β-cyclodextrin to α-cyclodextrin.

Table I. Benzaldehyde carbon chemical shifts (ppm)

Carbon	α-Cyclodextrin	β-Cyclodextrin	Chloroform Solution[a]
C=O	193.5	192.0	192.0
C_1	137.1	137.3	136.4
C_4	136.2	135.0	134.2
C_2 C_6	130.1	129.9	129.5
C_3 C_5	130.8		128.9

[a] Ref. [16].

4. Conclusions

The main conclusions of this study are summarized as follows.

The benzaldehyde ring in the α-cyclodextrin complex performs twofold flips about the C_1'–C_4' direction at rates of some 10–100 kHz at room temperature whilst the aldehyde group is fixed in the lattice. Most likely, this twofold ring flip motion also occurs for other mono and para disubstituted benzenes in the α-cyclodextrin complexes. As an aside, this makes benzene itself not a very useful probe for detailed molecular motion in cyclodextrin complexes. A recent ^{2}H NMR study [15] showed that motion of the benzene ring in various cyclodextrin complexes could best be described as a 6-fold rotation about the ring symmetry axis. In the presence of such a motion, neither the ^{13}C chemical shift tensor nor the ^{2}H quadrupole coupling tensor is then sensitive to twofold flips about an axis in the molecular plane.

Benzaldehyde in the β-cyclodextrin complex performs much more general reorientation involving both ring and aldehyde group. As well, there is relative rotation of the two moieties.

In the event detailed interpretations of the chemical shifts are attempted for the cyclodextrin host-lattice spectrum in terms of torsional angles obtained from crystal structure data, some caution must be exercized that indeed the same material is being studied. Although in the case of the α-cyclodextrin–benzaldehyde complex the fully hydrated material appears to give the best resolved spectrum, lower hydrates may also yield well-defined spectra. Apparently, loss of water has an effect both on macrocycle conformation and guest molecule motion. In the case of the α-cyclodextrin–benzaldehyde complex there appears to be a loss of short range order and an increase in guest motional rate.

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