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PREPARATION AND ^{13}C NMR IDENTIFICATION OF SOLID CYCLODEXTRIN INCLUSION COMPOUNDS *

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ABSTRACT. In this contribution it is shown that solid state ^{13}C NMR is a powerful technique for the identification and study of cyclodextrin inclusion compounds. From the unique splitting pattern of the host lattice spectrum, Cd compounds can be identified, and under favourable conditions information about the stoichiometry and the asymmetric unit of the crystal can be obtained. It is also shown that spherical agglomeration techniques can be used to produce Cd inclusion compounds in a particularly convenient form.

1. INTRODUCTION

Progress in the study and utilization of cyclodextrin compounds depends on the availability of efficient preparative techniques and appropriate methods of identification and analysis. Traditional preparative methods include recrystallization from solution[1,2], kneading[1,2], and more recently, spray drying[3]. Similarly, the more important techniques for the identification and analysis of crystalline inclusion compounds include X-ray powder diffraction, infrared spectroscopy, mass spectrometry and various thermal and chromatographic techniques[1,2].

In this contribution it is shown that spherical agglomeration[4,5] may be a particularly convenient method for the preparation of some types of Cd inclusion compounds. It is also shown that solid state ^{13}C NMR spectroscopy[6] can be used to good advantage for the identification of cyclodextrin inclusion compounds.

1.1. Solid state ^{13}C NMR Spectroscopy

The utility of NMR as an analytical technique depends on a one to one correspondence between the frequency and intensity of a spectral line and the number of chemically distinct nuclei of a certain kind. Complex

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*NRCC No: 28804

formation in solution has been studied extensively by NMR techniques[7] however a solution spectrum does not give any information on the stoichiometry or existence of an inclusion compound in the solid state.

A sufficient number of papers have appeared[8-12] to illustrate that it is possible to obtain well-resolved spectra for Cd inclusion compounds in a relatively modest amount of spectrometer time. The technique for obtaining spectra of the solid state differs considerably from solution techniques[6]. The presence of strong internuclear dipolar coupling between protons and carbon nuclei requires the application of strong proton decoupling fields. The tensor nature of the chemical shift in solids necessitates spinning of the sample at kHz frequencies about an axis inclined to the magnetic field at an angle of 54.7° in order to attain an isotropic chemical shift spectrum. In addition, polarization transfer from protons to carbon nuclei is used to enhance the relatively weak ^{13}C signal, and to circumvent long ^{13}C spin-lattice relaxation times which limit the repetition times used in signal averaging. Another advantage of the polarization transfer technique is that it discriminates against any signal from liquids. A disadvantage is that line intensities now depend on the cross-polarization times used. For quantitative work this relationship must be explored in detail.

In solution, due to conformational averaging only 6 lines are evident in Cd NMR spectra, one for each inequivalent carbon[7]. In the solid, conformations are locked due to steric and packing effects, and although chemically equivalent, carbon atoms may be crystallographically inequivalent. Instead of a single line for each chemically equivalent nucleus, a multiplet is observed with a multiplicity which depends on the number of carbons of that type in the asymmetric unit of the crystal. In the simplest instance, therefore, the solid state ^{13}C spectrum presents a "fingerprint", characteristic of the structure of the smallest repeat unit of the crystal. It is also possible to attempt analysis of the splitting pattern in terms of structural features for instance, the torsional angles describing the inter ring linkages[13,9,11].

A typical example of how the ^{13}C NMR spectrum is diagnostic of changes which occur in Cd compounds is provided in Fig. 1. Figure 1a shows the spectrum of α-Cd hexahydrate. The crystal structure has one molecule per asymmetric unit[14] so that the signal for each chemically distinct carbon should be split into 6 lines, one for each anhydroglucose unit. The splitting is most evident for the C_1 and C_4 carbons where 1:1:2:1:1 and 2:2:1:1 patterns are evident. As the hexahydrate loses water the structure of the compound changes. This manifests itself by the appearance of new lines in the spectrum (Fig. 1b), whereas lines for the α-Cd hexahydrate become weaker. When the transformation is complete, lines for the hexahydrate have disappeared, leaving only the lines for the lower hydrate. From the splitting pattern, this again appears to have one molecule per asymmetric unit. When ^{13}C spectral lines due to the guest molecule are observable for inclusion compounds, a particularly favourable situation arises. Figure 2a shows the ^{13}C NMR

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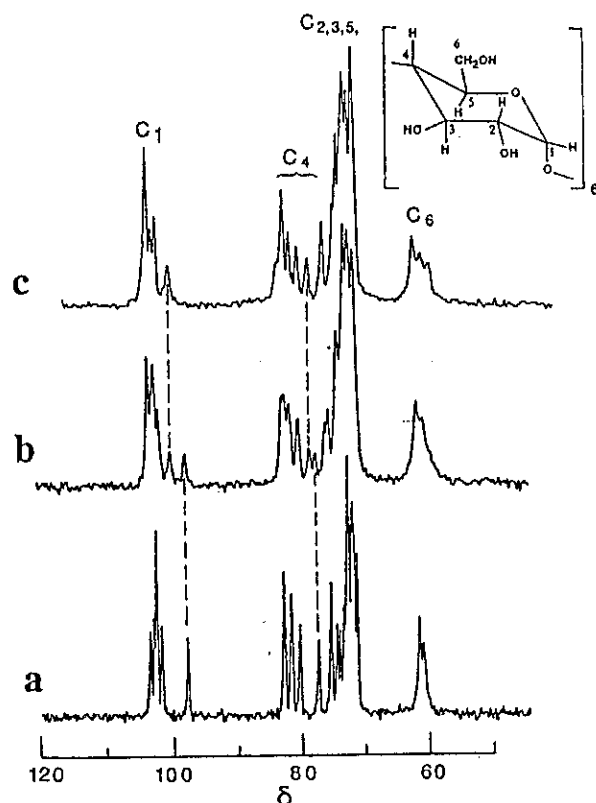Fig. 1 Solid state ^{13}C NMR spectra of (a) α-cyclodextrin hexahydrate, (b) mixed hydrate phases, (c) lower hydrate

spectrum for a toluene inclusion compound of α-Cd. On examining the C_4 region of the host lattice spectrum it is immediately evident that there is more than one host molecule in the asymmetric unit, as there are more than 6 lines visible. The toluene lines are also well resolved, and occur very near to their usual liquid chemical shift values. The integrals for the 6 guest ring carbons and the 6 C_1 host carbons are also shown and have a ratio of 1:2, and hence the stoichiometry of the compound is 2 host:1 guest. Together with the C_4 carbon splitting pattern, this suggests that there are 2 host molecules and 1 guest molecule in the asymmetric unit. Spectrum 2b shows that α-Cd compounds with toluene also occur with a different stoichiometry, in this case ~1:1.5. The spectrum is not nearly so well resolved as that in Fig. 2a. The unusual appearance of the toluene lines (128 and 20 ppm) suggest that there may be two quite distinct toluene types in the crystal, one possibly being interstitial.

     The above two cases have been relatively straightforward. However, in some instances considerable complications may occur. It is now well documented that in some cases the proton-bearing carbons of included
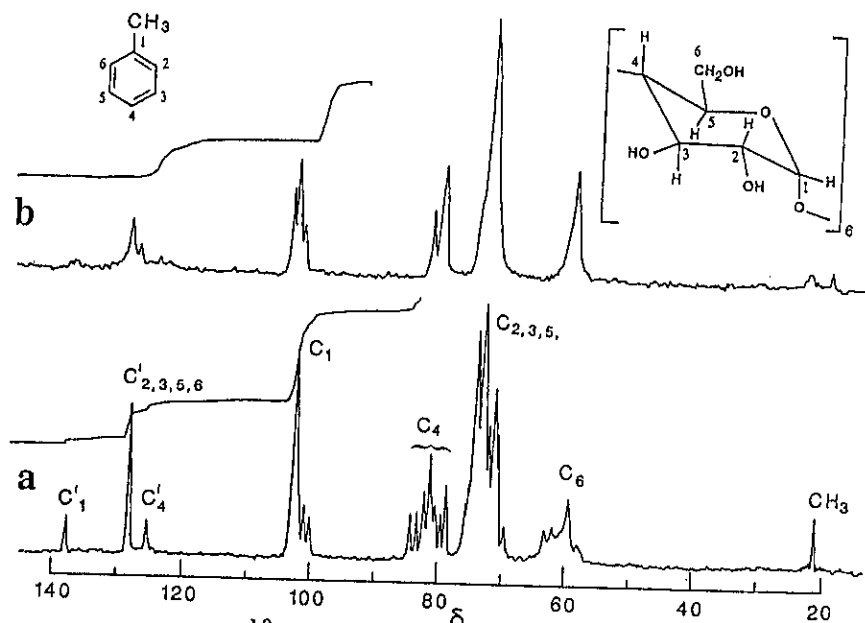
Fig. 2 Solid state ^{13}C NMR spectrum of (a) 2:1 α-Cd inclusion compound of toluene, (b) α-Cd inclusion compound of toluene with higher toluene content.

guest molecules are essentially invisible[16,17, 12]. This effect is unique to the solid state NMR experiment and occurs when there are slow guest molecule motions with frequencies of the order of the decoupling field strength (~10's of kHz)[18]. Examples are provided by the α-Cd inclusion compounds of p-nitrophenol[16] p-hydroxy benzoic acid[16] and benzaldehyde[12]. For these guests the motion is a 180° flip of the aromatic ring about the C_1-C_4 direction. A more usual spectrum can then be obtained by either raising or lowering the sample temperature and moving the motional frequency out of the critical region[12].

One example of such an anomalous spectrum is provided by the β-Cd hydrocortisone inclusion compound. Figure 3b shows the solid hydrocortisone spectrum. Figure 3c, obtained with delayed decoupling,[19] shows only the quaternary and methyl carbons. The doubling of many lines suggests that there are two hydrocortisone molecules in the crystal asymmetric unit. The β-Cd host lattice region of the spectrum (Fig. 3a) shows again that an inclusion compound has indeed been made, as it is entirely different from the β-Cd hydrate spectra[15]. However, many of the guest lines are either very broad or missing. Comparison of the guest lines with the spectrum shown in Fig. 3c shows that the best defined guest lines are either quaternary carbon or methyl group lines. The other carbons, more strongly coupled to protons, have their lines broadened considerably, presumably because of the presence of some sort of slow guest molecule motions.
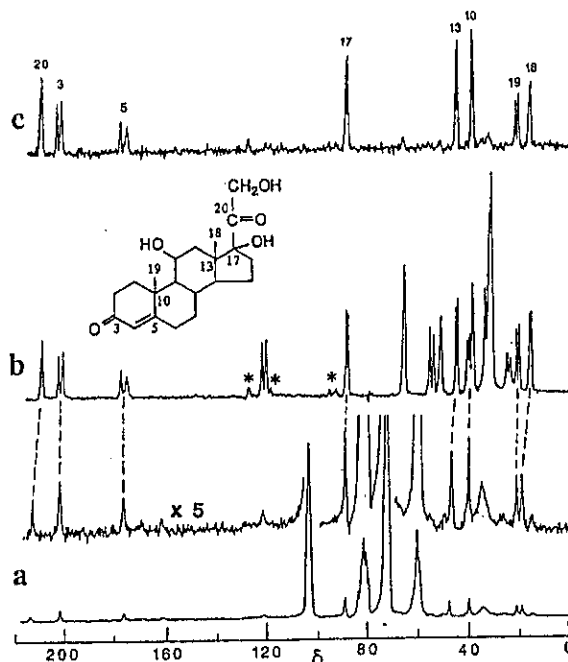
Fig. 3 Solid state ^{13}C NMR spectrum of (a) β-cyclodextrin inclusion compound of hydrocortisone, (b) solid hydrocortisone, (c) solid hydrocortisone, quaternary and methyl carbons only.

These few examples have shown that solid state ^{13}C NMR can give very useful information on Cd inclusion compounds. At worst, the host lattice spectrum, if it is different from the Cd hydrate spectra, indicates the presence of an inclusion compound. Under favourable conditions, the stoichiometry and the content of the asymmetric unit can also be obtained.

1.2 Spherical Agglomeration

Spherical agglomeration, as usually practiced, is a technique for the selective size enlargement of small particles[4,5]. If finely divided particles are suspended in a non-wetting liquid, and are agitated together with a second immiscible liquid which wets the particles, they will bridge together. The resulting product will be solid spherical pellets which are easily separated from the liquid and of a size which depends primarily on the amount of wetting liquid and the mode of agitation.

Initially attempts were made to produce agglomerates by suspending finely ground Cd hydrates in n-hexane, adding a small quantity of water, and agitating the mixture in a glass jar by using a Spex shaker. Agglomerates formed readily during a period of several minutes of agitation. Examination of the product by ^{13}C NMR showed that the agglomerates consisted of the Cd inclusion compound of n-hexane.

Some typical examples of Cd inclusion compound agglomerates are shown in Fig. 4. Evidently the inclusion compound formation accompanied the agglomeration process, although the two processes are quite distinct.
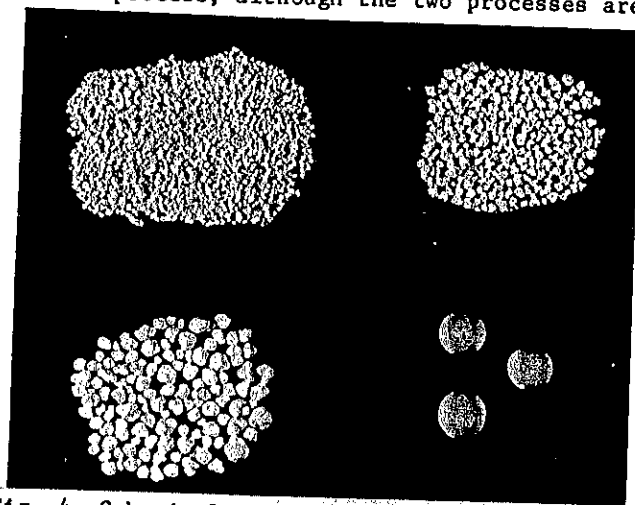

Fig. 4   Spherical agglomerates of Cd compounds.

Other water-immiscible materials such as citral, citronellal and limonene were also tried as suspending liquids. In each case the appropriate inclusion compound was formed in the form of spherical agglomerates (Fig. 4). The solid state ^{13}C NMR spectrum of the citral inclusion compound is shown in Fig. 5. All of the guest resonances are clearly visible and easily assigned. Extension of spherical agglomeration techniques to the preparation of Cd inclusion compounds of non-liquid guests is in progress.
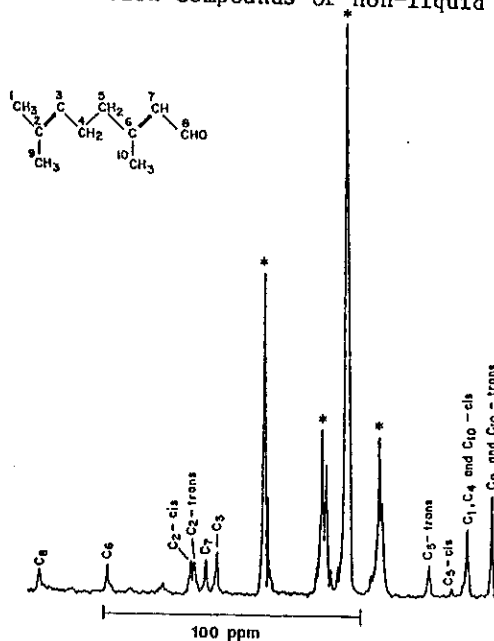
Fig. 5   Solid state ^{13}C NMR spectrum of β-Cd inclusion compound of citral prepared by spherical agglomeration. Cd peaks are starred.

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