High field solid state $^{13}$C NMR spectroscopy of cucurbituril materials

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Solid state $^{13}$C NMR spectra of several cucurbituril materials, CB[$n$] where $n$ = 5, 6, 7 and 8, have been analysed in detail. Where crystal structures are known the complex splitting patterns for the C=O, CH and CH$_2$ resonances can be directly related to the different site symmetries imposed on the CB molecule by the crystal. Conversely, where the structure is not known the NMR splitting patterns can be used to suggest possible symmetries for the CB, and these could conceivably aid in solving crystal structures. The fact that each structure produces a uniquely different $^{13}$C NMR splitting pattern makes it a useful fingerprinting tool which can be used to detect new phases.

Introduction

In a previous paper we presented a comprehensive solid state study of the separation, purification and characterization of solid compounds of the cucurbituril macrocycles CB[$n$], $n$ = 5, 6, 7 and 8, where $n$ refers to the number of glycoluril units linked together by bridging methylenes to form the ring. CB[6] is illustrated in Scheme 1.

The pumpkin-shaped cucurbiturils have become the focus of a rapidly expanding branch of macrocyclic host–guest supramolecular chemistry with many potential uses (see an extensive list of articles in ref. 1) both in solution and the solid state, and as derivatized molecules, and there have been a number of recent reviews. A very recent paper suggests a use for a CB derivative as a molecular "velcro".

In past work with $t$-butyl-calix[4]arene inclusion compounds we found it very useful to screen samples using solid state $^{13}$C NMR spectra as a fingerprinting tool, to determine which of several structural types was formed with different guests under various conditions. Here we show that this technique may be just as useful for the characterization of cucurbituril compounds. This fingerprinting relies on the fact that carbon atoms which are chemically equivalent in the undistorted isolated molecule can become inequivalent in the solid state. In the previous paper we made the observation that the multiplicities seen in the $^{13}$C spectra for the crystalline materials could be correlated with their crystal structures. In this current paper we show in detail how these correlations can be made, and how they relate to the different symmetries encountered.

One concern with the solid state $^{13}$C NMR spectroscopy of cucurbiturils is that every carbon atom is attached to two quadrupolar $^{14}$N atoms, which at lower fields can give rise to a splitting and broadening of the $^{13}$C resonances. This is due to residual $^{14}$N-$^{13}$C dipolar interactions which are not removed under MAS. Such splitting can confuse the interpretation of spectra considerably. However, this problem can be eliminated at high fields, for example as was recently shown in a study of caffeine polymorphs. Another advantage of high field is that it often gives greater dispersion, i.e. more chemical shift resolution.

Experimental

Samples

The labelling and details of the various samples studied by solid state NMR are given in Table 1. The preparation of samples CB[5]-1, CB[6]-1, CB[6]-2, CB[6]-3, CB[7]-1 and CB[8]-1 were described in detail in earlier papers. The procedure to get CB[6]-4 was adapted from the method reported for the...
preparation and separation of the main members of the CB[n]
family:1 after the reaction that afforded a mixture of CB[5],
CB[6], CB[7], and CB[8] as the main macrocycles, the solvent
was removed under reduced pressure yielding a sticky yellow
solid from which CB[8] was extracted with a formic acid
solution. The resulting filtrate, containing CB[6] as the major
product, was again evaporated to dryness before dissolution
in a water–sulphuric acid mixture. Acetone was then slowly
diffused into this mixture, leading to the formation of large
colorless crystals of CB[6]-4 that were collected and washed
diffused into this mixture, leading to the formation of large

11.74 T for comparison. Solid state cross-polarization magic

instruments, mainly at 21.14 T, with some repeated at

are rather stringent. Consequently we ran spectra on modern

groups between 154–160 ppm, (ii) CH groups between 67–77 ppm, and (iii) CH2 groups between 48–58 ppm. Fig. 2 shows a comparison of spectra for two samples run at 21.14 T and 11.74 T. For CB[6]-3 the only difference is that two lines in the 11.74 T spectrum, which clearly consist of overlapped lines, each begin to show a slight resolution into two peaks at 21.14 T. For CB[6]-4, on the other hand, the higher field has a definite advantage and provides more information, clearly showing that the CH3 region has a 2:4:4:2 quartet whereas the lower field shows only a doublet of asymmetric peaks.

Although the focus in this paper is largely on the resonances of the CB[n], solid state 13C NMR spectra are useful in other

Results and discussion

13C CP/MAS NMR spectra are shown in Fig. 1–4, with details in Table 1 pertinent to the discussion below. Note that the compositions from the crystal structures given in Table 1 indicate unusual stoichiometries. This is a common feature of host–guest systems where variable stoichiometry is often possible depending upon the degree of occupancy of the guest sites. The figures show expansions of the chemical shift regions corresponding to the three chemically distinct carbon functionalities: C=O, CH and CH2, and the intensities have been arbitrarily scaled just for clarity. The first striking observation is that the spectra are quite different for each compound and that each shift region often shows multiple sharp lines: (i) C=O groups between 154–160 ppm, (ii) CH groups between 67–77 ppm, and (iii) CH2 groups between 48–58 ppm. Fig. 2 shows a comparison of spectra for two samples run at 21.14 T and 11.74 T. For CB[6]-3 the only difference is that two lines in the 11.74 T spectrum, which clearly consist of overlapped lines, each begin to show a slight resolution into two peaks at 21.14 T. For CB[6]-4, on the other hand, the higher field has a definite advantage and provides more information, clearly showing that the CH3 region has a 2:4:4:2 quartet whereas the lower field shows only a doublet of asymmetric peaks.

Table 1 Details of the cucurbituril materials studied and the numbers of expected and observed 13C NMR linesa

<table>
<thead>
<tr>
<th>Sample</th>
<th>Space group</th>
<th>Composition (unit cell volume (Å3))</th>
<th>Crystallogr. unique</th>
<th>13C NMR resonances expected (lines observed)</th>
</tr>
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<tbody>
<tr>
<td>CB[5]-1</td>
<td>Pbam</td>
<td>CB[5]-3.75HCl-10.88H2O (9867.5)</td>
<td>12,10,12</td>
<td>C=O, CH, CH3</td>
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<tr>
<td>CB[5]-2</td>
<td>Unknown</td>
<td>CB[5]HCl/KCl/H2O</td>
<td>4 × 1, 8 × 2</td>
<td>4 × 1, 8 × 2</td>
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<tr>
<td>CB[6]-1</td>
<td>P6/mmm</td>
<td>CB[6]-2HCl-36H2O (1901.5)</td>
<td>1,1,1</td>
<td>1 × 12 (12)</td>
</tr>
<tr>
<td>CB[6]-2</td>
<td>Cmc21</td>
<td>CB[6]-1acetone-8H2O (4900.4)</td>
<td>8,6,6</td>
<td>4 × 1, 4 × 2</td>
</tr>
<tr>
<td>CB[6]-3</td>
<td>R3</td>
<td>CB[6]-4.66H2O (11036.7)</td>
<td>6,6,6</td>
<td>4 × 6</td>
</tr>
<tr>
<td>CB[6]-5</td>
<td>None</td>
<td>Amorphous CB[8]</td>
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<td></td>
</tr>
<tr>
<td>CB[8]-1</td>
<td>4H/a</td>
<td>CB[8]-4HCl15-1H2O (17299.2)</td>
<td>8,8,8</td>
<td>8 × 2 (4:8:4)</td>
</tr>
<tr>
<td>CB[8]-2</td>
<td>Unknown</td>
<td>CB[8]H2O 100 ºC/48 h</td>
<td>(Poor resol.)</td>
<td>(2:6:6:2)</td>
</tr>
</tbody>
</table>

respects: (a) they can be used to verify the presence of guest species in the solid materials, e.g. the full spectra of samples CB[6]-2 and CB[6]-4 show sharp lines due to the CH₃ and C==O groups of guest acetone (at 204.4 and 28.9 ppm in the latter).

Fig. 1  Solid state ¹³C CP-MAS spectra of CB[6] materials at a field of 21.1 T focusing on the isotropic chemical shift ranges of the three chemically distinct carbons: (a) CB[6]-1, P6/mmm, CB[6], 2HCl, 36 H₂O, shortly after removal from mother liquor and already showing additional resonances from a decomposition product, the three single resonances of P6/mmm are indicated by * (4 mm probe, 9.5 kHz spin rate); (b) CB[6]-2, Cmc₂₁, CB[6], 1 acetone, 8 H₂O (3.2 mm probe, 14 kHz spin rate); (c) CB[6]-3, R̅₃, CB[6], 4.66 H₂O (3.2 mm probe, 14 kHz spin rate); (d) CB[6]-4, unknown structure from H₂SO₄/acetone preparation (4 mm probe, 6 kHz spin rate). The three regions are shown at the same shift scale expansion. The intensities of the spectra have been arbitrarily scaled in each region simply for clarity.

Fig. 2  Comparison of solid state ¹³C CP-MAS spectra of CB[6] materials at fields of 21.1 T and 11.72 T: (a) and (b) CB[6]-3, R̅₃; (c) and (d) CB[6]-4, the unknown structure from H₂SO₄/acetone preparation. (a) and (d) at 21.1 T, 3.2 mm probe, 14 kHz spin rate for (a), 4 mm probe, 6 kHz spin rate for (d). (b) and (c) at 11.72 T, 3.2 mm probe, 20 kHz spin rate.
(b) They can show if the bulk material prepared corresponds to the small single crystal that was pulled out for structure determination. (c) They can also indicate if the material is amorphous or crystalline. (d) Dipolar dephasing (also known
as interrupted decoupling) spectra\textsuperscript{13} can show whether or not there is molecular reorientation, e.g. as mentioned previously\textsuperscript{1} the complete suppression of the CH and CH\textsubscript{2} resonances indicated that in samples CB\textsuperscript{[5]}-1, CB\textsuperscript{[6]}-4, CB\textsuperscript{[7]}-1 and CB\textsuperscript{[8]}-1 there is no reorientation of the cucurbitril molecules. On the other hand, it is anticipated that guest molecules will be dynamic at room temperature, and indeed the lines for acetone are extremely sharp and its CH\textsubscript{3} resonance appears in the dipolar dephased spectrum.

We can envisage that in the isolated state CB\textit{n} molecules adopt their high symmetry conformation, defined by the principal \textit{n}-fold axis, the equatorial mirror plane perpendicular to this axis and \textit{n} mirror planes perpendicular to the equatorial plane. In this situation all the C=O are identical, as are the CH and CH\textsubscript{2} groups, and there would be a single NMR resonance for each of these chemically distinct carbon atoms. When the molecule is situated in a crystal lattice, the requirements of the crystal packing usually mean that the molecular symmetry is lowered, and as a consequence chemically equivalent C atoms may have different environments and hence slightly different NMR chemical shifts. (It is interesting to note that both CB\textsuperscript{[5]} and CB\textsuperscript{[7]} may be highly symmetric in isolation, but in the solid state will inevitably lose this symmetry because 5-fold and 7-fold axes are not compatible with crystal packing. However, retention of high symmetry in a solid phase may be possible for CB\textsuperscript{[6]} and CB\textsuperscript{[8]}.)

The number of crystallographically distinct atoms determines the maximum possible number of distinct resonances that might be seen in the spectrum (though unfortunately they will not necessarily all be resolved), and the number of atoms of each crystallographic type in the CB\textit{n} molecule determines the intensity of the resonance for that type.

**Analysis of spectra of materials for which the structure is known**

We begin with the simplest case CB\textsuperscript{[6]}-1. In this \textit{P6\textsubscript{1}mmm} structure the CB\textsuperscript{[6]} molecule sits with its principal axis on a 6-fold crystal axis and retains the very high symmetry that it would have in the isolated state. Consequently there is only one crystallographic type for each of the chemically distinct C atoms, i.e. all 12 C=O carbons are equivalent; similarly for the 12 CH carbons and 12 CH\textsubscript{2} carbons. So the \textsuperscript{13}C NMR spectrum, Fig. 1a, should show a single resonance in each region. The single strongest sharp feature in each region can be assigned to C=O at 157.9 ppm, CH at 71.6 ppm and CH\textsubscript{2} at 52.6 ppm (the other features of the spectrum are due to dehydration products which will be discussed later).

CB\textsuperscript{[6]}-2. For CB\textsuperscript{[6]} in this \textit{Cmc2\textsubscript{1}} structure there is no equatorial mirror plane, but there is one mirror plane perpendicular to this which divides the molecule into left and right halves. One of these halves is shown in Scheme 2a. There are 20 crystallographically distinct C atoms. Those atoms in the mirror plane occur once while those which sit off the plane have a mirror image twin. So it can be readily seen that for C=O there are 4 single and 4 paired carbon atoms, for CH there are 6 pairs and for CH\textsubscript{2} 6 pairs, and there could be up to 8 NMR resonances for C=O, and up to 6 each for CH and CH\textsubscript{2}. The observed lines, Fig. 1b, and associated intensities are entirely consistent with this (see Table 1). For example, for the C=O resonances there are 3 lines with intensities 1:3:8, which because of overlaps could correspond to 1 single, 3 singles, and 4 doubles respectively, or alternatively 1 single, 1 single plus one double, and 2 singles plus 3 doubles.

CB\textsuperscript{[6]}-3. In the \textit{R3} structure the CB\textsuperscript{[6]} has 18 crystallographically distinct C atoms, Scheme 2b, in one half of the molecule, and every atom is related to an equivalent one by an inversion centre, so that for C=O there are 6 pairs of C atoms, and likewise for CH and CH\textsubscript{2}. So there could be up to six lines of equal intensity for each of the three chemical types. Again the observed spectrum, Fig. 1c, is quite compatible with this when overlaps are considered, for example the four lines for CH\textsubscript{2} with intensities 2:2:4:4 correspond to one double, one double, two doubles and two doubles respectively.

CB\textsuperscript{[5]}-1. The structure of CB\textsuperscript{[5]}-1 is more complex in that there are two distinct molecules, though both possess a non-equatorial mirror plane relating one half of the molecule to the other. This results in two sets of 17 crystallographically distinct carbon atoms, Scheme 3. In each molecule, for C=O there are 2 single and 4 paired C atoms, likewise for CH\textsubscript{2}, whereas for CH there are 5 paired C atoms. Accounting for both molecules there is then the potential for as many as 12 lines in the C=O and CH\textsubscript{2} regions and up to 10 lines in the CH region. The spectrum, Fig. 3a, is not resolved in the CH\textsubscript{2} region, though there is underlying structure, and the other regions show multiple components with many overlaps, but the intensity distributions are nevertheless compatible with the structural analysis.

CB\textsuperscript{[7]}-1. The spectral regions of sample CB\textsuperscript{[7]}-1 are also shown here, Fig. 3c, to show what happens when the material is truly amorphous, and to compare this with the crystalline materials. A smooth distribution of intensity over a relatively broad region is observed. The most plausible explanation of this behaviour is that there is a distribution of very many slightly different environments each with its own chemical shift.

CB\textsuperscript{[8]}-1. In the \textit{I4\textsubscript{1}/a} structure the CB\textsuperscript{[8]} has 24 crystallographically distinct C atoms in half of the molecule related to equivalents by an inversion centre (analogous to the CB\textsuperscript{[6]} \textit{R3} case), so that each of the three chemical carbon types has 8 pairs of inequivalent C atoms. The spectrum, Fig. 3d, is not as clean because of multiple overlaps and unresolved structure for the CH\textsubscript{2} region, but it is nevertheless compatible with the structure: the intensities for the C=O lines of 4:8:4 would correspond to two doubles, four doubles and two doubles respectively, and the approximately 2:2:8:4 intensities for the CH region would correspond to one double, one double, four doubles and two doubles respectively.
After analyzing all spectra with known structures, it can be seen that the NMR results are entirely consistent with the associated crystal structures and show that the bulk materials are also largely single phase materials.
Spectra of materials for which the structure is not known

It was seen above how the different symmetries give rise to distinct patterns of splitting. The question now arises as to whether we can work backwards to suggest symmetry from the splittings for a material of unknown structure?

CB[6]-4. This spectrum, Fig. 1d, is quite intriguing since it appears to be relatively simple, but it does not resemble any of the spectra obtained for known structures. We have not yet been able to determine the crystal structure by single crystal X-ray diffraction. The intensity distribution among the resonances for each chemical type, for each of which there are 12 C atoms in the CB[6] molecule, Table 1, are C−O 8:4, CH 4:8 and CH2 2:4:4:2. The relative simplicity of the spectrum suggests there is likely only one distinct CB[6] molecule. We must now consider the possible symmetries which could give rise to this combination of peaks and intensities. Table 2 summarises the predicted number of lines and intensities for CB[6] with one or a combination of two symmetry elements. From this it can be seen that certain combinations of symmetry elements (marked by asterisks in Table 2) reduce the number of possible CH2 peaks to three, and therefore are incompatible with the observation of four. Also incompatible are combinations of three or more symmetry elements, since these reduce the number of possible CH2 peaks to no more than two. Unfortunately we are left with several possibilities which could be compatible, and of these five have exactly the 2 × 2 and 2 × 4 combination.

CB[6] dehydration spectra. Earlier we reported that the CB[6]-1 P6/mmm hydrated channels structure readily undergoes dehydration and after heating at 100 °C for 48 h it converts to the R3 structure. In Fig. 4a the dehydrated product R3 spectrum shows much less resolution than the spectrum of CB[6]-3 R3, Fig. 4b. The loss of resolution is most likely due to poor crystallinity upon dehydration, i.e. many defects, but may possibly also be due to varying degrees of residual hydration. The R3 framework appears to be a quite robust configuration of CB[6] molecules which is capable of hosting a variety of molecules with variable stoichiometries, including H2O, HCl, C2H2, CH4, Xe and CO2 but it can also be empty.14,15 Kim14 has reported several CB[6] R3 structures: CB[6]-10.88 H2O, which can be converted to CB[6]-2H2O by heating at 100 °C for 48 h, CB[6]-2.3H2O 2C2H2, CB[6]-1.1HCl11.3H2O and CB[6]-1.2H2SO4·6.4H2O. (Note CB[6] also forms very similar R3 structures.15,16)

Dehydration of CB[6]-1 P6/mmm under milder conditions (in the atmosphere at room temperature) produces yet another phase. In fact it appears to be very difficult to isolate the P6/mmm structure in bulk under ambient conditions because of the ease of loss of guest water as soon as the mother liquor is removed, Fig. 4d, resulting in a mixture of P6/mmm crystals and the new phase. Taking into account the presence of the simple three line 13C NMR spectrum due to P6/mmm, it is clear in Fig. 4c that there is another component with a more complicated spectrum of sharp lines. This spectrum definitely does not match the R3 spectrum (compare Fig. 4b with c) nor the other CB[6] spectra (see Fig. 1b and d) and thus must represent an unknown structure.

CB[5]-2. From the patterns of multiple, and in some cases quite sharp, lines in the spectrum of this sample, Fig. 3b, it would appear to be a well-formed crystalline material. The CH region shows five peaks and at least three other features are discernible, and the CH2 region, though less well resolved, shows at least seven features. Since one CB[5] molecule has only 10 CH and 10 CH2 the large number of observed features means that the structure either has only one distinct molecule with no symmetry (10 inequivalent atoms for each type), or two distinct molecules (conceivably more) which could have some symmetry. As discussed earlier, the 5-fold symmetry axis of isolated CB[5] is not compatible with crystal packing. We note also that once CB[5] distorts and loses its 5-fold symmetry, then there are only two symmetry elements still possible, namely the equatorial mirror plane and the mirror plane perpendicular to this which bisects the molecule; an

<table>
<thead>
<tr>
<th>Equatorial mirror plane</th>
<th>xz mirror plane</th>
<th>zy mirror plane</th>
<th>Inversion centre</th>
<th>2-Fold principal axis</th>
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<td>X</td>
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</table>

* The xz mirror plane refers to a plane perpendicular to the equatorial plane, with four of the CH2 groups in the plane. Similarly for the zy plane, except that there are four C−O groups in the plane.
inversion centre and 2-fold rotation about the principal axis are not feasible.

**CB[8]-2.** Based on comparison of PXRD data the first solid CB[8] material produced by formic acid treatment of the initial CB[n] mixture was found to have the same basic structure as the HCl-containing CB[8]-1, and indeed this is confirmed by NMR (not shown) which shows a very similar spectrum to that of CB[8]-1 with an underlying, possibly amorphous, component. PXRD also indicated that heat treatment of both of these materials produced a new phase. The spectrum of CB[8]-2, Fig. 3e, confirms this, as the pattern of lines is quite distinct from that of CB[8]-1. While some lines are well resolved others are not, even though there is clearly a lot of structure, which makes it difficult to say much about this phase. However, the fact that the CH resonances cluster into 2:6:2:6:2 suggests the possibility of either a mirror plane perpendicular to the equatorial plane, a 2-fold rotation axis or an inversion centre acting on 8 unique CH atoms.

Previously reported *ab initio* DFT calculations on isolated CB[n] molecules were accurate in reproducing experimental 13C isotropic chemical shifts observed in CB[n] solutions and in high symmetry crystalline phases. DFT calculations support an experimentally observed trend of increasing 13C chemical shifts for CH and CH2 moieties with increasing CB[n] size (n = 5, 6, 7, 8). For practical reasons, most CB[n] compounds in the solid state are much less amenable to quantum chemical calculations due to extremely large unit cell volumes (see Table 1), often exceeding 5000–10 000 Å3, and disordering of guest molecules. How to handle this disorder is particularly problematical. Some computation work in this area is underway in our lab.

**Conclusion**

We can conclude that, with the correct experimental approach, solid state 13C NMR is a valuable tool for the investigation of crystalline cucurbiturils. One might have anticipated such a conclusion from previous comprehensive NMR studies on other macrocyclic supramolecular materials, *e.g.*, those based on p-t-butylcalix[4]arene. However, there are some key differences. Whereas the calixarenes could be classified into a limited number of families of structures, the cucurbiturils appear to be far more diverse in terms of structural types. As well, complex disorder and crystal twinning often provide additional challenges for solving high quality crystal structures. In this paper we have demonstrated that in each case there is consistency between the 13C NMR spectrum and the crystal structure in the case of known structures and that the symmetry of the cucurbituril in the solid state can be constrained by using the 13C NMR spectrum. Also, because each structure produces a unique 13C chemical shift pattern, the NMR can be used as a fingerprinting tool and for detecting new phases. This does require special consideration as at low magnetic fields the spectral resolution is limited by coupling of 13C to 14N, and because the structures are quite rigid, there are large dipolar couplings between the methylene 13C atoms and the attached protons requiring adequate high power decoupling. Thus high magnetic fields and strong decoupling fields will give the best results and are likely to give spectra that are useful in providing structural information. The ability to obtain high quality NMR spectra is also the first step towards the utilization of crystal engineering approaches to obtain more extensive structural information.

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