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Syntheses and Structural Aspects of Cyclodextrin/Dialkylamine Inclusion Compounds

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Abstract. We report the syntheses and structural aspects of cyclodextrin host–guest inclusion compounds containing linear secondary alkylamines (dipropyl, dibutyl, dipentyl, dihexyl, and dioctyl) at 25 °C. Elemental analysis, ^{13}C CP-MAS NMR spectroscopy, and powder X-ray diffraction analysis confirm the inclusion process. The basic host structure of the products is similar to that of typical cyclodextrin inclusion systems. ^{13}C MAS NMR experiments show a different resonance pattern for the confined guest molecules with respect to the amine in the liquid phase. The presence of different resonance signals for the homologous carbon atoms of both dialkylamine branches is evidence for the non-symmetric location of the amine in the cyclodextrin channels.

Key words: inclusion compounds, cyclodextrins, dialkylamines, CP-MAS NMR.

1. lntroduction

The most thoroughly investigated monomolecular inclusion compounds are those formed by the cyclodextrins [1–6]. Molecules of suitable size and shape can be held within the cavity of a particular cyclodextrin principally by van der Waals forces [2]. The structure of the cyclodextrin inclusion compounds in solution and in the crystalline state differ significantly. In solution, the guest molecule occupies the cavity of the cyclodextrin host and the entire complex is surrounded and solvated by water molecules. In the crystal, however, the guest may be enclosed in a void space of a lattice and not necessarily by individual cyclodextrin molecules [1].

The cyclodextrins and their inclusion compounds can be crystallized from water and examined by X-ray crystallography as empty molecules or as inclusion complexes. Depending on the size and ionic or molecular character of the substrate, ‘channel’ or ‘cage’ structures are formed in which the cyclodextrin molecules are stacked [1].

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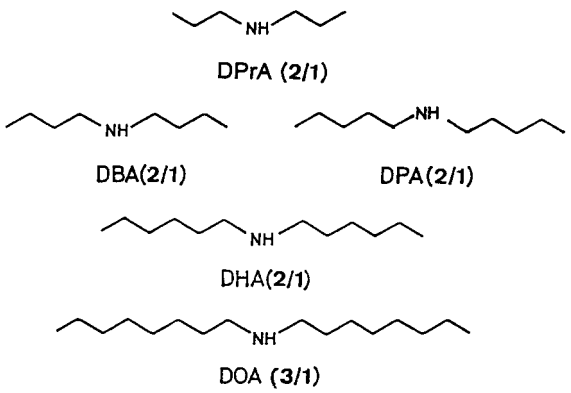

Figure 1. Guest species in cyclodextrin inclusion compounds discussed in this paper and the host–guest ratios (identical for the α- and γ-cyclodextrin complexes). DPrA = dipropylamine, DBA = dibutylamine, DPA = dipentylamine, DHA = dihexylamine, DOA = dioctylamine.

Recently we reported the synthesis and structural properties of urea/dialkylamine polymolecular inclusion compounds [7]. In these compounds the amine molecules are located within infinite channels formed by the urea matrix molecules. In order to compare the effect of a monomolecular matrix such as cyclodextrins on the interactions with amine, we have investigated the formation of inclusion compounds and powder X-ray diffraction and ^{13}C MAS NMR studies with a series of secondary alkylamines.

2. Experimental

Commercially available reagents were used as received. The products were obtained from amine and saturated solutions of cyclodextrins in water at room temperature. The amine to cyclodextrin molar ratios used in the experiments were always somewhat greater than the stoichiometric relation found for the products. Microcrystals were separated immediately, washed with hot acetone and dried under vacuum at 50 °C. Cyclodextrin : amine ratios reported in Figure 1 were determined by both elemental microanalysis (Perkin Elmer 24 °C microanalyzer) and ^{1}H-NMR spectroscopy of dimethyl-d_6 sulfoxide solutions. Crystal inspection by optical polarizing microscopy showed colorless thin layers.

Solution ^{1}H and ^{13}C high resolution NMR spectra were recorded on a Bruker AMX-300. The ^{13}C cross-polarization magic angle spinning (CP MAS) NMR spectra were recorded on a Bruker MSL-400 spectrometer at a frequency of 100.63 MHz for ^{13}C. The number of scans varied between 200 and 2100 with 5.5 μs 90° pulses, 1 ms cross-polarization contact time, 41 ms acquisition time during proton decoupling and 5 s recycle delay. The polycrystalline powder samples were spun at a frequency of 4 kHz using a Bruker CP MAS probe. The chemical shifts are given relative to tetramethylsilane (TMS), determined via the use of internal standard. Powder X-ray diffractograms were recorded in the range $2° < 2\theta < 30°$

Table I. Lattice parameters of the hexagonal structures at room temperature.

Inclusion compound	a (Å)	b (Å)	c (Å)
DBA-(2αCD)·12H_2O	27.38	27.38	16.24
DPA-(2αCD)·14H_2O	27.27	27.27	15.78
DHA-(2αCD)·30H_2O	27.30	27.30	15.81
DOA-(3αCD)·8H_2O	27.62	27.62	16.07
DPrA-(2γCD)·28H_2O	37.02	37.02	16.45
DBA-(2γCD)·24H_2O	37.21	37.21	16.51
DPA-(2γCD)·10H_2O	37.18	37.18	16.50
DHA-(2γCD)·18H_2O	37.23	37.23	16.81
DOA-(3γCD)·30H_2O	37.28	37.28	16.89

on a Siemens D-5000 diffractometer using Cu-K_α radiation (40 KV, 30 mA) and a graphite monochromator (λ =1 .5418 Å). Samples were ground to a fine powder in order to reduce the likelihood of the crystallites exhibiting a preferred orientation. For all the products apart from amine-(β-cyclodextrin) and DPrA-(α-cyclodextrin), the diffractograms indicate the absence of any other crystalline phases than those of the reported inclusion compounds. For amine-(β-cyclodextrin) and DPrA-(α-cyclodextrin) the diffractograms principally exhibit the pattern corresponding to the pure cyclodextrin phase [8].

3. Results and Discussion

Analytical as well as further characterization of the products clearly shows that secondary amines $CH_3(CH_2)_nNH(CH_2)_nCH_3$ with n = 2, 3, 4, 5, and 7, can be accommodated by α- and γ-cyclodextrin matrices to form stable inclusion compounds with channel structures at room temperature which are similar to those obtained from the inclusion of other guests [8]. The lattice parameters of the host obtained from X-ray analysis of polycrystalline samples of the products are reported in Table I. All peaks in the diffractograms, independent of the included amine, can be indexed on the basis of a hexagonal lattice with parameter values close to $a = b \approx 27$ Å, $c \approx 16$ Å, $\alpha = \beta = 90°$ and $\gamma = 120°$ for α-cyclodextrin and $a = b \approx 37$ Å, $c \approx 16$ Å, $\alpha = \beta = 90°$ and γ = 120° for γ-cyclodextrin. A typical indexed diffractogram, that for the compound DPA-(2α-cyclodextrin) is shown in Figure 2. Depending on the guest molecular length, it must occupy either two or three cyclodextrin units.

The cyclodextrin molecules takes on the shape of a cone with the C2 and C3 hydroxyls located around the larger opening and the more reactive C6 hydroxyl aligned around the smaller opening. The arrangement of C6 hydroxyl opposite the

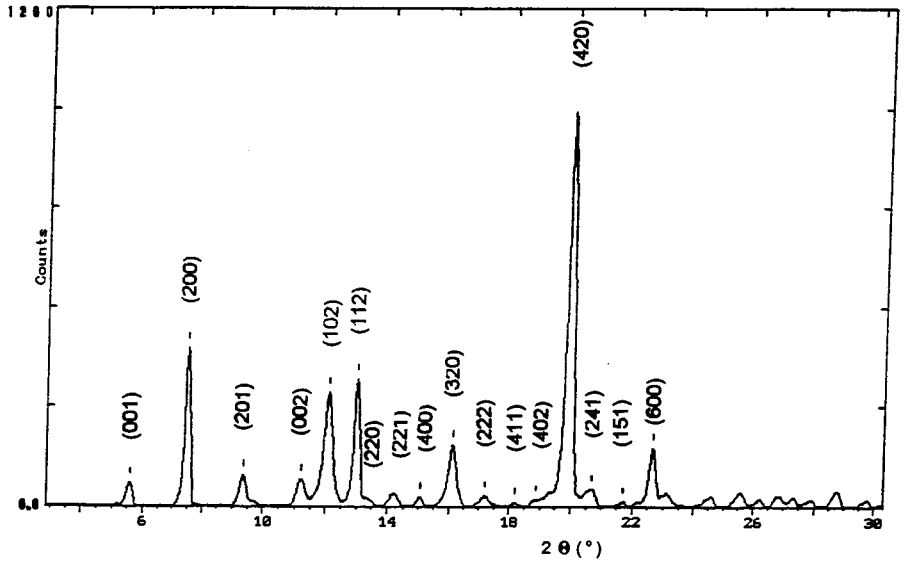

Figure 2. Indexed powder X-ray diffractogram for the matrix in the DPA-(2α-CD) inclusion compound at 296 K (CuK_α radiation).

Table II. Chemical shifts (ppm) of dipentylamine inserted in the urea and α- and γ-cyclodextrin matrices compared with those of the amine in other media.

Assignment	Guest in urea matrix	Guest in α-CD	Guest in γ-CD	Guest in CCl_4 (10% v/v)
C_α1(1)	52.58	51.88	52.01	49.51
C2(2)	32.65	32.71	32.82	29.62
C3(3)	31.17	31.20 sh	30.95	29.15
		30.70		
C4(4)	24.51	24.28	24.05	22.13
		23.06		
C5(5)	14.58	15.24	14.83	13.23
		14.51		

sh = shoulder.

hydrogen bonded C2 and C3 hydroxyl forces the oxygen bonds into close proximity within the cavity, leading to an electron rich, hydrophobic interior. In cyclodextrin inclusion compounds the matrix channel is formed by these cone units which interact through van der Waals forces and are ordered to encounter the similar end of neighboring units (larger opening–larger opening, smaller opening–smaller opening).

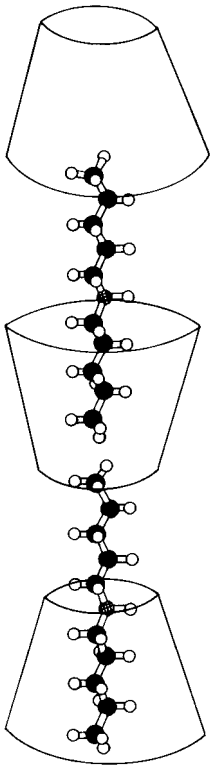

Figure 3. Schematic representation of the inclusion of dipentylamine in cyclodextrins.

The behavior of organic dialkylamine molecules placed in such environments is expected to differ from those of the same molecules in other phases. It is known that dialkylamines as guests in urea acquire their most extended linear conformation [7]; a similar behavior is shown by *n*-alkanes in the same matrix [9]. In this work, the ^{13}C CP MAS NMR spectra of α-CD included dipentylamine were analyzed in some detail (Table II).

In the inclusion of the secondary amine the —NH— group of the guest could be located at the extreme boundary of a cyclodextrin unit, with one of the alkyl branches in the apolar and poor electron density zone of the cyclodextrin cavity and the other branch outside, in the rich electron density space, O(2)H, O(3)H, O(6)H, O′(2)H, O′(3)H and O′(6)H groups, between two cyclodextrin units (Figure 3). This arrangement could produce different magnetically anisotropic environments for each alkyl branch of the included secondary amine, which would be evidenced in the ^{13}C-CP MAS NMR spectra, Figure 4. Two different kinds of signals were observed for the same type of C atoms of the dipentylamine guest. The other α- and γ-cyclodextrin inclusion compounds showed wide signals in the NMR spectra and splittings were not observed (Table III). The two kinds of signals indicate that the guests are aligned on the channel matrix axis and that these guests do not rotate

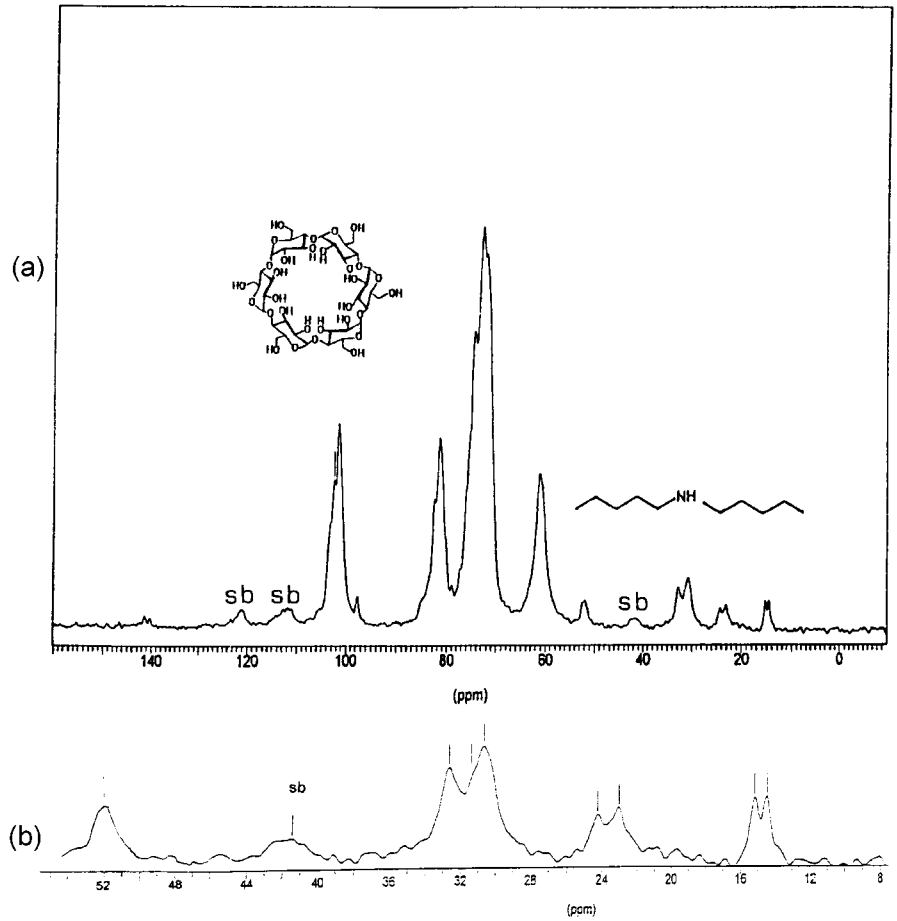

Figure 4. ^{13}C CP MAS NMR spectrum of the DPA-(2α-CD) at room temperature and at 100.63 MHz (a) and amplification of the resonance lines corresponding to the guest (b). sb = side band.

end-to-end in this magnetically anisotropic medium. The higher chemical shift signal corresponds to the amine carbon atom directed to the inside of the cavity and the lower chemical shift signal corresponds to the carbon atom located in the gap between the cyclodextrin units (Table II). Only one signal is observed for the α- and β-carbon atoms however, probably due to both α- and β-carbon atoms being located near to the edge of a cyclodextrin. The two different carbon signals could also stem from two non-equivalent guest molecules (i.e., two species per unit cell) if the guests present a clew shaped conformation. Such an interpretation could be excluded by the stoichiometry of the compounds.

The ^{13}C MAS NMR spectra of a secondary amine included in the urea matrix presents only one signal for each kind of carbon atom (Table II), because the hexagonal channels of the urea matrix constitute a continuous and homogeneous

Table III. Chemical shifts (ppm) of dialkylamines inserted in the α- and γ-cyclodextrin matrices.

Assignment	Guest in α-cyclodextrin	Guest in γ-cyclodextrin
Dipropylamine		
C$-\alpha$1(1)		53.0
C2(2)		23.8
C3(3)		12.2
Dibutylamine		
C$_\alpha$1(1)	49.5	51.7
C2(2)	32.2	32.9
C3(3)	20.6	20.8
C4(4)	14.0	14.3
Dihexylamine		
C$_\alpha$1(1)	51.2	53.1
C2(2)	31.9	32.8
C3(3)	30.5	31.4
C4(4)	27.2	28.0
C5(5)	22.7	23.1
C6(6)	14.0	14.3
Dioctylamine		
C$_\alpha$1(1)	51.7	53.1
C2(2)	33.2	34.1
C3(3)	31.8	32.6
C4(4)	31.8	32.6
C5(5)	31.8	32.6
C6(6)	29.6	30.1
C7(7)	24.4	24.7
C8(8)	14.4	14.9

medium different from the heterogeneous and discontinuous channels of cyclodextrins. Similar effects of a magnetically anisotropic environment on the guest are observed in other inclusion compounds, for example, hemicarceplexes with several kind of guests [10].

From the results discussed above it can be concluded that cyclodextrins, in the presence of secondary amines form normal inclusion compounds accommodating the guests in channels, which are possibly preferential places for the amine group and for each branch of the guest.

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References

1. W. Saenger: *Angew. Chem. Int. Engl.* **19**, 344 (1980).
2. S..G. Frank: *J. Pharm. Sci.* **64**,1585 (1975).
3. R. Bishop and I. Dance: *Top. Curr. Chem.* **149**, 137 (1988).
4. K. Takemoto and N. Sonoda: in J.L. Atwood, J.E.D. Davies, and D.D. MacNicol (eds.), *Inclusion Compounds*, Academic Press, New York (1984).
5. L. Song and P. William: *Chem. Rev.* **92**, 1457 (1992).
6. F. Vögtle: *Supramoleculare Chemie*, B.G. Teubner, Stuttgart (1989).
7. P. Jara, N. Yutronic, and G. Gonzalez: *J Incl. Phenom.* **22**, 203 (1995).
8. K. Takeo and T. Kuge: *Agric. Biol. Chem.* **36**, 2615 (1972).
9. K.D.M. Harris and J.M. Thomas: *J. Chem. Soc. Faraday Trans.* **86**, 3135 (1990).
10. D.J. Cram, MT. Blanda, K. Paek, and C.B. Knobler: *J Am. Chem. Soc.* **114**, 7765 (1992), and references therein.