X-RAY STRUCTURES AND THERMAL ANALYSES OF NEW CD/DRUG INCLUSION COMPOUNDS

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ABSTRACT

Single crystal X-ray methods, thermogravimetry and differential scanning calorimetry have been used to characterize several cyclodextrin/drug complexes in order to reconcile crystal packing features with behaviour on heating.

1. INTRODUCTION

Despite the widespread use of cyclodextrins (CDs) as solubilizers for poorly soluble drug substances [1], there are relatively few studies describing comprehensive investigation of CD/drug complexes by thermal analysis and single crystal X-ray diffraction. Used in combination, thermogravimetry (TG), differential scanning calorimetry (DSC) and single crystal X-ray analysis can elucidate the nature of host-guest interactions as well as the relation between structure and thermal decomposition. With non-volatile drug guests, thermal decomposition involves crystal water loss as the first stage. Dehydration may occur in one step or in a series of steps. If the crystal structure of the complex is known, sequential water loss on heating may be correlated with the known crystal sites of hydration in favourable cases.

2. MATERIALS AND METHODS

2.1 Materials

All cyclodextrins were obtained from Cyclolab, Hungary. Diclofenac sodium was purchased from Syntex, USA, and meclofenamate sodium and (*L*)-menthol from Sigma Chemical Company, USA.

2.2 Methods

Single crystals of the CD-complexes were obtained by slow evaporation or slow cooling of aqueous solutions containing host and guest in known molar ratios. Single crystal X-ray structures were determined by direct phasing or isomorphous replacement techniques. Thermal analysis was performed on a Perkin Elmer PC7-Series Thermal Analysis system with 5-10 mg samples at a scanning rate of

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10°C min^{-1} under constant N_2-purge. Full details of crystallization conditions, X-ray structures and thermal analyses appear in the references cited.

3. RESULTS AND DISCUSSION

3.1 Crystal structures and thermal analyses

The β-CD complexes of diclofenac sodium [2] and meclofenamic acid sodium salts [3] are monomeric species crystallizing in the space groups $P6_1$ and $P2_12_12_1$ respectively with 11 and 16 H_2O molecules in the respective formula units. Structural analyses revealed that in each case the phenyl ring associated with the -COOH function is included in the host cavity from the primary hydroxyl side. In the former case, all H_2O molecules are ordered and three of them are coordinated to a Na^+ ion whose octahedral coordination sphere is completed by three O atoms from neighbouring CD molecules. Fig.1(a) shows the combined TG and DSC traces for this species. Three points of inflection are observed in the TG trace, representing successive loss of 6, 2.2, 1.8 and 1.0 H_2O molecules. The temperature range for H_2O loss (30-244°C) is considerably larger than that observed for complexes containing neutral guests and is attributed to the fact that some H_2O molecules are strongly coordinated to the Na^+ ion ($O\cdots Na^+$ 2.3(1)-2.46(1)Å). In addition to being bound to Na^+, one H_2O molecule is strongly hydrogen bonded to three other O atoms and it is suggested that loss of this molecule is reflected in the DSC endotherm B of Fig.1(a). It appears likely that just prior to this event, the other two H_2O molecules bound to Na^+ are lost (shoulder in complex endotherm A). Analogous behaviour was observed for β-CD complexes with the K^+ and Cs^+ salts of diclofenac, and for the γ-CD/diclofenac sodium complex. TG and DSC curves for the β-CD/meclofenamic acid Na^+ salt complex are shown in Fig.1(b). A point of inflection in the TG trace indicates stepwise loss of approximately 11.2 and 3.8 H_2O molecules and these events are reflected as overlapping endotherms A, B in the DSC trace. Correlation with structural data is difficult in this case due to crystallographic disorder of both Na^+ and H_2O molecules. The former is disordered over two sites 1.7Å apart with s.o.f.s 0.6 and 0.4. These sites are respectively octahedrally and tetrahedrally coordinated by O atoms. Nevertheless, we infer, by analogy with the data for the diclofenac complexes, that the H_2O molecules most strongly retained are those bound to Na^+.

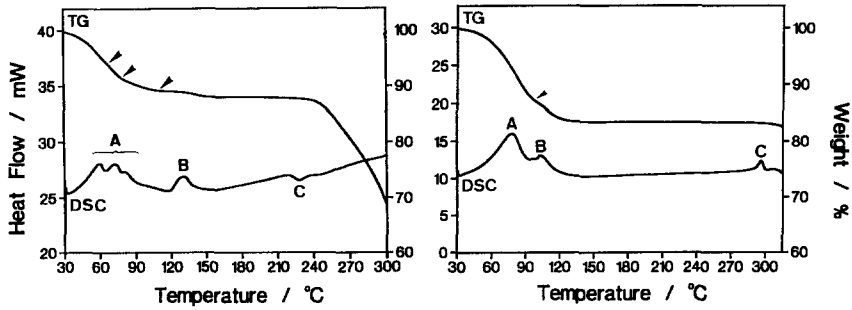

Fig.1 TG/DSC traces for β-CD complexes of (a) diclofenac sodium (left) and (b) meclofenamic acid sodium salt (right)

The β-CD/ibuprofen complex is dimeric (space group C2). X-ray analysis [4] showed that the CD molecules pack to form infinite linear channels. Severe disorder of the guests in the channel prevented their modelling by X-ray methods. However, the H_2O molecules are relatively ordered and of the 13.3 H_2O molecules per host CD (from TG analysis), nine were located outside the channels. These different environments of the H_2O molecules were again reflected as two-step H_2O losses in both TG and DSC traces. We have also determined the crystal structure of the TRIMEB/ibuprofen complex [5]. This complex contains ordered drug guest and is anhydrous. Consequently, the DSC trace shows only one sharp fusion endotherm for the complex.

(*L*)-menthol forms 1:1 inclusion compounds with β-CD ($P2_1$), TRIMEB ($P2_12_12_1$) and DIMEB ($P2_12_12_1$). X-ray analysis showed that the β-CD complex is dimeric, with the guest adopting distinctly different orientations in the cavities of symmetry-independent hosts. These orientations in turn differed from that of the guest within the cavity of TRIMEB [6]. The guest -OH group does not engage in hydrogen bonding with host O atoms in either of these complexes and the guest molecules are retained by their hosts by purely hydrophobic interactions. The DSC onset temperature for water loss from the β-CD complex is 47°C, but for the TRIMEB complex an unusually high value of 124°C was measured. The crystal structure data are consistent with these observations, revealing that in the former crystal, H_2O molecules occupy channel-like regions between columns of complex units, allowing their relatively easy escape on heating, whereas with TRIMEB as host, the H_2O molecules are enclosed in cavities formed by closely packed complex molecules.

The crystal structure of the DIMEB/(*L*)-menthol complex was not determined but the measured unit cell data are similar to those for e.g. the DIMEB/*p*-iodophenol complex [7], except that the length c is approximately doubled. The TG/DSC trace is shown in Fig.2. It differs from the traces for the other (*L*)-menthol complexes in that two weight losses, with corresponding endotherms (A, D), are observed. By chemical and ^{1}H-NMR analysis, we ascertained that these weight losses correspond to loss of H_2O followed by loss of one molecule of menthol. The traces were highly reproducible, the DSC trace showing, in addition, exothermic peaks B and C attributed respectively to a phase change for the dehydrated complex and a second phase change which possibly initiates loss of menthol.

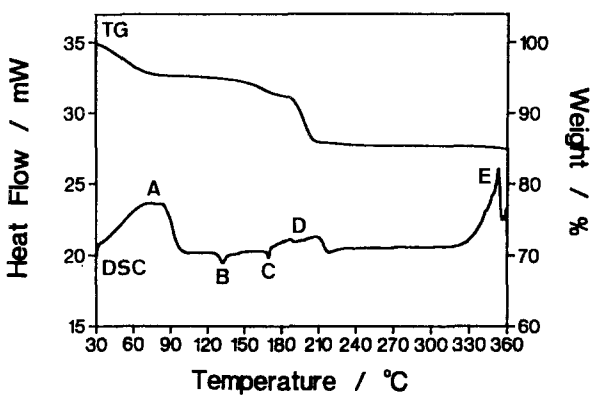

Fig. 2 TG/DSC trace for the complex between DIMEB and (L)-menthol

By analogy with the structure of the DIMEB/*p*-iodophenol complex, in which the DIMEB cavity contains H_2O molecules and the guest resides outside, it is possible that the guest (*L*)-menthol in the DIMEB complex is similarly located. This may account for the distinctly different behaviour on heating compared with that for the β-CD and TRIMEB complexes, but single crystal X-ray analysis of the DIMEB/(*L*)-menthol complex is necessary to support this explanation.

3.2 Importance of C-H···O bonds in TRIMEB

Examination of the crystal structures of TRIMEB complexes we have prepared invariably reveals the presence of host intramolecular $C(6G_n)$-H···$O(5G_{n-1})$ hydrogen bonds with C···O in the range 3.0-3.4Å . These interactions stabilise the host conformations not only in the complexes but also in TRIMEB monohydrate [8].

4. CONCLUSIONS

Interpretation of detailed features in TG and DSC curves of CD-complexes is facilitated when three-dimensional X-ray crystal structural data are available. This has been demonstrated for several CD/drug complexes.

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