Synthesis and X-Ray Crystal Structure of β-Cyclodextrin Diclofenac Sodium Undecahydrate, a β-CD Complex with a Unique Crystal Packing Arrangement

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The title complex crystallizes in the hexagonal system forming infinite helical host channels residing on crystallographic screw hexads.

Microencapsulation of drug molecules in cyclodextrins (CDs) has been extensively used in the pharmaceutical industry to produce more stable drug preparations with improved bioavailability.[1] Host–guest interactions in CD complexes include hydrogen bonding, hydrophobic binding and polar interactions, some or all of which may contribute to complex stabilization, depending on the chemical nature of the guest and that of the CD. With a view to predicting crystal packing arrangements in CD complexes, systematic analyses of available crystallographic data have been undertaken[2,3] and several general conclusions have been drawn regarding their overall packing tendencies.

We report the synthesis and structure† of a β-CD complex which not only has a unique crystal packing arrangement but is also the first example of a β-CD complex occurring in the hexagonal crystal system. The title complex crystallized as colourless needles by slow evaporation of an aqueous solution obtained by dissolving the sodium salt of the anti-inflammatory agent diclofenac, 2-[(2,6-dichlorophenyl)amino]benzeneacetic acid (56 mg), and β-CD (200 mg) in distilled water at 343 K.

Fig. 1 shows details of the host–guest interactions which include both hydrogen bonding and hydrophobic interactions between the phenylacetate residue of the drug anion and β-CD. The phenyl ring is fully inserted in the β-CD cavity while one carboxylate oxygen atom, O(18), is hydrogen bonded to a primary hydroxy group of the same β-CD molecule [O(18)···O(6G6) 2.729(6) Å]. Consequently, this primary hydroxy adopts the + *gauche* form[4] with the C(6)–O(6) bond directed towards the host cavity in contrast to the six remaining primary hydroxy groups which adopt the –gauche conformation, as usually observed. The orientation of the carboxylate group is determined by an intramolecular hydrogen bond N(3)–H(3)···O(19) [N···O 2.820(7) Å] which also occurs in the crystal structure of sodium diclofenac tetrahydrate.[5] The bulky dichlorophenyl moiety, whose minimum dimension is close to the maximum effective diameter of the apolar host cavity (7.8 Å), protrudes from the primary face of the host and is sandwiched between the β-CD molecule shown in Fig. 1 and one directly above, related by a crystallographic screw hexad. The Na^+ ion is situated at the periphery of the β-CD molecule and is approximately octahedrally co-ordinated by oxygen atoms of three water molecules [O(1W), O(6W), O(9W)], a primary hydroxy group of β-CD [O(6G6)], and two secondary hydroxy groups of a symmetry-related host molecule [$O(2G4^I)$, $O(3G4^I)$, I = 1 + *y*, 1 – *x* + *y*, –1/6 + *z*). The Na^+···O distances are in the range 2.269(6)–2.611(6) Å.

The complex units stack in a regular head-to-tail mode *via* a 6_1-axis which passes through the β-CD cavity and is nearly normal to the plane of the β-CD molecule. As shown in Fig. 2, his results in an endless helical host channel with a pitch of 51 Å. An important interaction contributing to the head-to-tail stacking is a strong hydrogen bond between carboxylate oxygen atom O(19) and the secondary hydroxy group $O(3G6^{II})$ of a 6_1-related β-CD molecule (II = *y*, –*x* + *y*, – 1/6 + *z*) with O···O 2.565(6) Å and O—H···O 171(2)°. Other stabilizing interactions between the primary face of the β-CD molecule shown in Fig. 1 and the secondary face of a 6_1-related host molecule are O(6G7)–H···O ($3G1^{II}$) with O···O 2.639(7) Å, O–H···O 175(3)°, O(6G4)···H–O($2G6^{II}$) with O···O 2.690(8) Å, O–H···O 146(11)°, and hydrogen bonds mediated by bridging water molecules, O(6G2)–H···O ($5W^{III}$) –H···O ($2G3^{II}$) (III = –1 + *x*, *y*, *z*) and O(18)···H–O(1W)–H ···O($2G7^{II}$).

The conformation of the β-CD molecule in this complex is distorted to a greater extent than is usually observed. The heptagon composed of O(4) atoms is irregular with side lengths in the range 4.238(7)–4.496(5) Å and the angles subtended at the O(4) atoms are in the range 120.1–131.6°. This distortion is partly due to the dichlorophenyl residue which rests on the secondary face of the host. The tilt angles[6] for glucose residues G1–G7 are 5.5, 4.2, 13.5, 28.7, 7.0, 11.8 and 31.7 °. The largest values, for G4 and G7, can be attributed to an intermolecular hydrogen bond O(2G4)–H···O($3G7^{IV}$) (IV = *x*, – 1 + *y*, *z*). Despite these distortions, the distances O(3G*n*)···O[2G(*n* + 1)][3] are in a relatively narrow range of 2.716(6) to 3.022(7) Å and the usual intramolecular hydrogen bonds which impart 'roundness' to β-CD appear to be largely maintained.

Columns of complex molecules, one of which is shown in

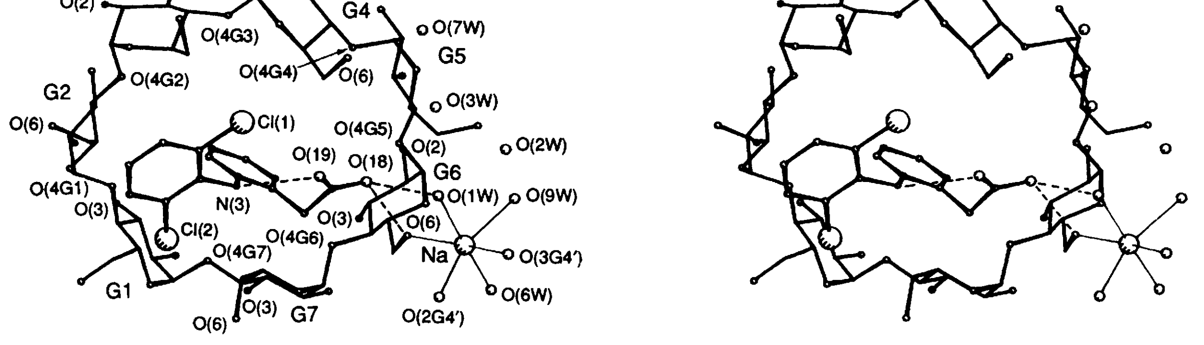

Fig. 1 Stereo drawing of the title complex viewed from the primary β-CD face. H atoms are omitted. Three of the hydrogen bonds referred to in the text are indicated by dashed lines.

Fig. 2, pack in a hexagonal array and are held together by a complex network of hydrogen bonds involving β-CD hydroxyl groups and water molecules. The title complex thus crystallizes in infinite layers (plane group p6) parallel to the (001) planes, complex molecules in each successive layer being rotated by 60 ° about the *c*-axis from those in the layer above. This arrangement is in sharp contrast to those known to occur in crystals of β-CD complexes where the preferred tendency is for host molecules to form head-to-head dimers *via* O(3)···O′(3) hydrogen bonds.[2,3] In such cases, two guest molecules are usually accommodated in the large dimer cavity and crystal space groups are confined to $C222_1$, $C2$, $P2_1$ and $P1$. Monomeric β-CD complexes occur less frequently and, with two exceptions,[6,7] adopt 'herring-bone' packing schemes in which the host cavity is blocked on either side by neighbouring complex molecules. A driving force for dimer formation appears to be the creation of a larger apolar environment for encapsulating hydrophobic guests.[3] As noted above, however, the β-CD cavity is too small to admit the dichlorophenyl residue of the anion in the title complex and we conclude that dimer formation in this case is not favoured.

We have studied the thermal decomposition of the complex by thermogravimetry (TG) and differential scanning calorimetry (DSC). The measured percentage weight loss in the temperature range 298–423 K is 12.1, which is identical to the calculated value for eleven water molecules per β-CD molecule which we located and refined in the X-ray analysis. The water molecules were exceptionally well-behaved at the low temperature of the X-ray analysis, yielding final U_{eq} values in the range 0.03–0.08 Å^2 and showing no signs of disorder. The TG trace indicated that dehydration occurs in at least four steps, each of which is accompanied by a corresponding endotherm in the DSC trace. It is possible to rationalise these observations on the basis of the different environments of the water molecules in the crystal, those involved in weak hydrogen bonds being released first and those coordinated to Na$^+$ or engaging in multiple hydrogen bonds desorbing during the later phases of mass loss. TG, DSC and thermomicroscopy indicate that on further heating, the complex does not melt but begins to decompose at approximately 473 K.

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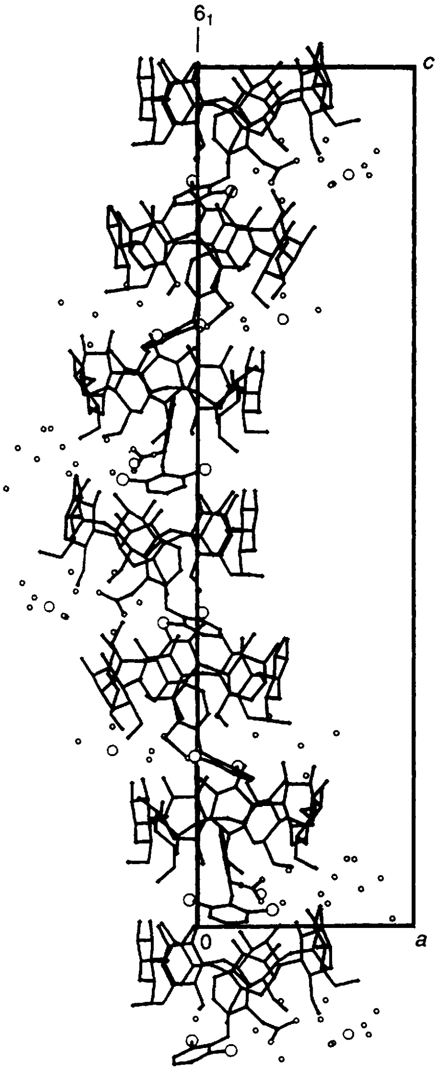

Fig. 2 (010) Projection showing the helical arrangement in one stack of complex molecules

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† *Crystal data* for $C_{42}H_{70}O_{35}\cdot C_{14}H_{10}Cl_2NO_2^-Na^+\cdot 11H_2O$, M_r = 1637.29, hexagonal, space group $P6_1$ (no. 169), a = 15.956(8), c = 50.95(1) Å, Z = 6, D_m = 1.47(1) g cm^{-3}, D_c = 1.451 g cm^{-3}, crystal size 0.38 × 0.38 × 0.45 mm. Intensity data were collected at 233 K on an Enraf-Nonius CAD4 diffractometer using Mo-Kα (λ = 0.7107 Å) radiation to θ_{max} = 25 °; 6167 unique reflections were collected. The structure was solved by direct methods using program SHELXS86[8] and the least-squares refinement (SHELX76)[9] converged to a final R = 0.056 for 5489 reflections with $I > 2\sigma(I)$: R_w = 0.051 with $w = (\sigma^2 F_o)^{-1}$. Residual electron density (max, min) = 0.57, −0.36 e Å^{-3}. All non-hydrogen atoms except carbons were treated anisotropically and hydrogen atoms were either fixed in a riding model (C–H) or refined subject to geometrical constraints (O–H). Molecular parameters with e.s.d.s were calculated with program PARST[10] and figures were drawn with PLUTO.[11] Atomic coordinates, thermal parameters, and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre. See Information for authors, Issue No. 1.

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