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Inclusion of the Antidepressant Paroxetine in β-cyclodextrin *

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Abstract

The X-ray structure and thermal stability of a β-cyclodextrin inclusion complex of the antidepressant paroxetine [(3S-trans)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine], with the formula (β-cyclodextrin)$_2$·paroxetine·28H$_2$O, are reported. On heating, the crystals dehydrate in two stages and begin to decompose from approximately 270 °C. An X-ray diffraction study at 173K showed that the complex crystallizes in the monoclinic system, space group P2$_1$ with $a = 15.2262(3)$, $b = 31.4771(1)$, $c = 15.6739(1)$ Å, $\beta = 104.320(1)°$ and Z = 2 formula units. Refinement on F^2 converged at R1 = 0.066, wR$_2$ = 0.182 (21478 reflections). On encapsulation within a head-to-head β-cyclodextrin dimer, the paroxetine molecule adopts an unusual 'hairpin' conformation, stabilised by intramolecular $\pi \cdots \pi$ interaction between the phenyl rings. The guest piperidine ring is located at the primary face of one host molecule of the dimer while the fluorophenyl and benzodioxole moieties respectively occupy the dimer interfacial region and the cavity of the second host molecule. Experimental and computed X-ray powder diffraction patterns for the complex are also reported. The mode of stacking of the dimeric complex units is shown to be one of at least three distinct variants which can be identified for β-cyclodextrin complexes with similar unit cell dimensions and crystallizing in the same space group.

Introduction

Paroxetine [(3S-trans)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)-piperidine, Figure1] is a well-known, potent and selective serotonin uptake inhibitor used in the treatment of depression [1]. Formulations for oral administration generally contain the drug as the hydrochloride salt. The X-ray crystal structures of paroxetine hydrochloride in the form of the hemihydrate [2, 3] and as the 1:1 solvate with propan-2-ol [3] have recently been reported. We considered it desirable to extend the structural chemistry of paroxetine beyond polymorphs and pseudopolymorphs by attempting to include the molecule in a cyclodextrin (CD). The encapsulation of a drug by a CD usually enhances its chemical stability and solubility and thus represents an alternative strategy to modifying drug performance [4]. Here we describe the preparation, thermal stability and X-ray structure of a 2:1 β-cyclodextrin-paroxetine complex. The complex is not isostructural with known β-CD inclusion complexes crystallizing in the same space group with similar unit cell dimensions. An analysis of the stacking modes in these complexes is presented, showing that significant guest-induced deviations from isostructurality occur.

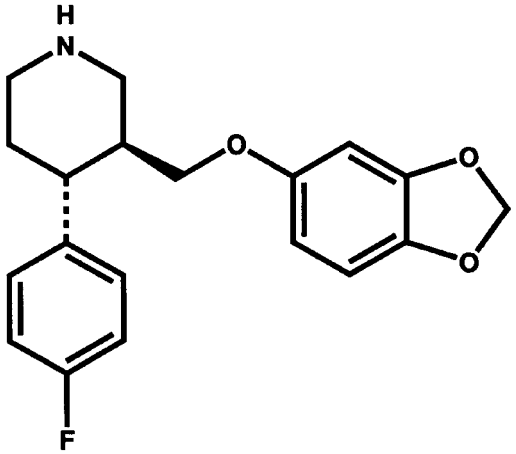

Figure 1. Chemical structure of paroxetine.

Experimental

Complex preparation and characterization

0.5 mmol β-CD (Cyclolab, Hungary) was kneaded with water in a mortar for 5 min until a paste was formed. To this was added 0.5 mmol paroxetine free base (GlaxoSmithKline, UK) without further addition of water and the mixture was kneaded for 90 min. 0.08 g of the product was dissolved in 2 mL water at 40 °C and the solution was stirred for 48 h. After filtration (0.45 μm filter) the solution was cooled

* **Supplementary Data** relating to this article are deposited with the British Library as Supplementary Publication No. SUP 82304 (27 Pages). The deposited file contains full listings of atomic coordinates, thermal parameters, details of refinement and derived molecular parameters for the title complex.

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to 20 °C and allowed to evaporate spontaneously. Prismatic colourless crystals were obtained after 10 days.

Preliminary characterization of the crystals was performed by hot stage microscopy (HSM) on a Linkam hot stage THMS600 coupled to a Linkam TP92 control unit. Thermogravimetry (TGA) and differential scanning calorimetry (DSC) were performed on a Perkin-Elmer PC7 Series thermal station. TGA and DSC scans were recorded at 10 °C/min in the temperature range 30-300 °C with sample masses in the range 1–4 mg. A nitrogen purge at 40 mL/min was used for both techniques.

Elemental analysis of fresh crystals was performed on a Fisons EA1108 CHNS-O elemental analyzer.

X-ray diffraction

Preliminary unit cell and space group data were obtained from X-ray photographs and the crystal density was measured by flotation in a mixture of chlorobenzene and carbon tetrachloride. For intensity data-collection a specimen was mounted on a fibre and covered with Paratone N oil (Exxon, U.S.A.). Data were collected on a Nonius Kappa CCD diffractometer using graphite-monochromated MoKα radiation (λ = 0.71069 Å) with the crystal cooled to 173 ± 1 K by a Cryostream cooler (Oxford Cryosystems, U.K.). A total of 30451 reflections were recorded in 394 frames using a combination of ϕ- and ω-scans whose strategies were evaluated with the COLLECT software [5]. Unit cell refinement and data reduction were performed with program DENZO-SMN [6]. Attempts to solve the structure by isomorphous replacement using trial models extracted from the Cambridge Crystallographic Database [7] failed. Routine application of direct methods with SHELXS-97 [8] did not yield a solution. The structure was solved by the Patterson-search procedure using programs PATSEE [9] and SHELXS-86 [10]. The molecular fragment used in the search comprised the non-hydrogen atom β-CD dimer skeleton occurring in the structure of the R-(−)-fenoprofen complex [11] with the primary hydroxyl O atoms removed. After optimisation of the orientation and position of the fragment, least-squares refinement followed. All remaining non-H atoms of the hosts, guests and water molecules were subsequently located by difference Fourier methods. Full-matrix refinement on F^2 followed with program SHELXL-97 [12]. Programs were run using the graphical interface X-SEED [13].

All oxygen atoms of the host molecules were treated anisotropically while the C atoms refined isotropically. Attempted anisotropic refinement of all non-H atoms of the guest molecule led to matrix singularities for six atoms. The latter were therefore treated isotropically while the remaining atoms refined anisotropically. H atoms were included in idealised positions in a riding model with U_{iso} set at 1.2 times those of the parent atoms. Hydroxyl H atoms were placed in positions of maximum electron density found by the rotating group procedure in SHELXL-97 [12]. Oxygen atoms of water molecules were located over 45 sites, 13 of which were assigned site-occupancy factors (s.o.f.'s) of 1.0 and refined anisotropically, while the remaining atoms with s.o.f.'s in the range 0.13–0.83 were assigned a constant U_{iso} equal to the average of those for the ordered oxygen atoms (0.07 Å^2). The final sum of s.o.f.'s corresponded to 28 water molecules per complex unit as deduced from thermogravimetry. In view of extensive disorder of many water molecules, no attempt was made to locate water H atoms. In the final cycles of refinement least-squares weights of the form $w = 1/[\sigma^2(F_o)^2 + (aP)^2 + bP]$, $P = [\max(F_o^2, 0) + 2F_c^2]/3$ were employed. 16 low-angle reflections were omitted owing to their truncation by the beam-stop. Residual electron density found in the region of the guest benzodioxol moiety was not considered chemically significant.

X-ray powder diffraction (XRPD) patterns were recorded with CuKα radiation (λ = 1.5418 Å) on a Philips PW1050/80 vertical goniometer equipped with a PW3710 control unit. Step scans of 0.1° and 4s counts were employed in the 2θ-range 6–40°. The theoretical XRPD pattern was computed with program Lazy Pulverix [14] which uses the formula

$$I(hkl) = mLp|F(hkl)|^2, \quad (1)$$

where $I(hkl)$ is the intensity of the reflection with indices hkl, m is the reflection multiplicity, L the Lorentz factor, p the polarization factor, and $F(hkl)$ the structure factor.

Results and discussion

Crystal composition and thermal analysis

The complex formula (β-cyclodextrin)$_2$·paroxetine·28H$_2$O is consistent with elemental analysis data (Calcd.: %C 39.86, H 7.01, N 0.45; Found: %C 39.71, H 6.70, N 0.48) and with the percentage weight loss for dehydration from TGA (Calcd. 16.3%; Found 16.5%).

Single crystals of the complex were immersed in silicone oil and examined by thermomicroscopy. The colourless crystals cracked in the temperature range 45–50 °C where evolution of bubbles indicated the commencement of dehydration. At 80 °C the sample became opaque and began to discolour only at 220 °C, eventually turning black. As shown in the TGA trace of Figure 2, dehydration evidently proceeds in two stages, occurring in the approximate ranges 30–60 and 60-105 °C. This is followed by a very gradual mass loss until the precipitous drop commences at 270 °C signifying complex decomposition. The dehydration steps appear in the DSC trace as an endothermic peak at 55 °C with a shoulder at 60 °C.

X-ray analysis

Overall description of the complex structure

Crystal data and details of the refinement are listed in Table 1. The asymmetric unit comprises two host molecules, one paroxetine molecule and 28 water molecules. As shown in Figure 3, the host molecules form a head-to-head dimer, stabilised by multiple hydrogen bonds of the type O–H···O linking their secondary faces. The stability of this dimeric motif is well established in cyclodextrin structural chemistry

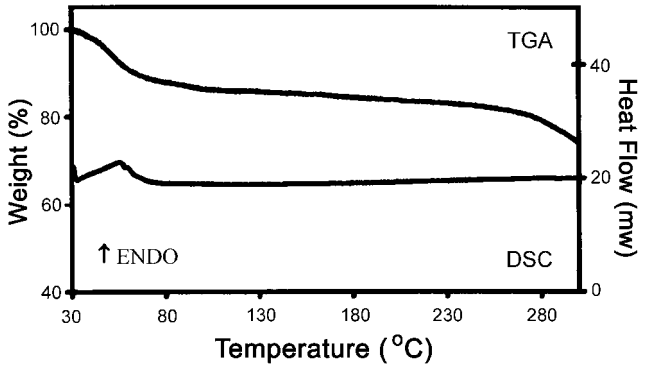

Figure 2. Combined TG and DSC trace for the complex.

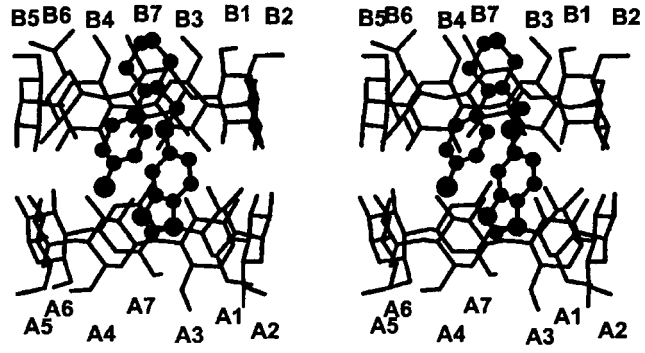

Figure 3. Stereoview showing the mode of inclusion of the paroxetine molecule in the β-CD dimer.

[15]. The paroxetine molecule is folded into a 'hairpin' conformation allowing its almost complete encapsulation by the host dimer. A key feature of the structure is the juxtaposition of the phenyl rings, indicating stabilisation of the guest conformation by $\pi \cdots \pi$ interaction.

Dimer structure and host conformations

The general features of the β-CD dimer shown in Figure 3 correspond with those listed earlier for this structural unit [15] which is known to encapsulate a large variety of guest molecules. Table 2 lists geometrical parameters for the two independent β-CD molecules A, B comprising the dimer. The glucose residues are numbered An, Bn (n = 1–7) and all fourteen residues adopt the usual $^4C_1$ conformation. In each of the host molecules A and B, one of the primary hydroxyl groups is disordered over two sites (host A: O6A2, O6C2 with s.o.f.'s 0.53, 0.47 respectively; host B: O6B6, O6D6 with s.o.f.'s 0.85 and 0.15 respectively). The majority of the primary hydroxyl groups are in a *gauche-gauche* orientation (parameter τ), exceptions occurring for glucose residues A2 (major disordered site), A3, B3, B4 and B6 (major disordered site), where a *trans*-conformation is adopted. Encapsulation of the paroxetine molecule by the β-CD dimer introduces some host distortion, evident especially in the variations in the parameters D, ϕ and α (Table 2). The O4 heptagons, however, retain their planarity (r.m.s. deviations A: 0.057, B: 0.044 Å) and are parallel (dihedral angle 1.2(1)°). Stabilization of the dimers is achieved by intermolecular O–H$\cdots$O hydrogen bonding which involves the O3 hydroxyl groups primarily (Table 3). For the 7 hydrogen bonds detected, the O3$\cdots$O3 distance range is 2.740(5)–2.895(5) Å with angles O–H$\cdots$O in the range 155-176°. Evidence for intradimer hydrogen bonding involving O3$\cdots$O3 hydroxyl groups is rare. A recent synchrotron high-resolution study revealed such hydrogen bonding in the dimeric β-CD complex with 1,12-dodecanoic acid [16].

Table 1. Crystal data, experimental and refinement parameters for the title compound

Molecular formula	$(C_{42}H_{70}O_{35})_2 \cdot C_{19}H_{20}FNO_3 \cdot 28H_2O$
M_r/g mol^{-1}	3103.77
Crystal system	Monoclinic
Space group	$P2_1$
Z	2
a(Å)	15.2262(3)
b(Å)	31.4771(1)
c(Å)	15.6739(1)
α(°)	90
β(°)	104.320(1)
γ(°)	90
V (Å^3)	7278.7(2)
D_c (g cm^{-3})	1.416
D_m (g cm^{-3})	1.40(2)
F(000)	3316
T (K)	173(1)
μ(Mo Kα) /mm^{-1}	0.128
Crystal dimensions (mm)	0.60 × 0.40 × 0.37
Range scanned θ (°)	1.67–25.39
Detector-crystal distance (mm)	55
Scan parameters (°)	ϕ 0.7, ω 0.7
Index range	h −11, 18 ; k −37, 35 ; l −18, 14
No. of reflections collected	25328
No. of unique reflections	21478
R_{int}	0.0239
No.of reflections with I > 2σ(I)	16887
No.of L.S. parameters	1430
R1 (I > 2σ(I))	0.066
wR_2 (all data)	0.182
a, b in weighting scheme	0.1017, 6.7504
S	1.036
Shift/e.s.d.,max., average	0.69, 0.01
($\Delta\rho$)max. (eÅ^{-3})	0.92
($\Delta\rho$)min. (eÅ^{-3})	−0.60

Guest conformation

Figure 4 shows the conformation of the paroxetine molecule adopted in the complex. This 'U-shaped' conformation differs significantly from the 'L-shaped' conformations assumed by protonated paroxetine molecules in known crystal structures. Table 4 lists the principal torsion angles with comparative data for the protonated species in the structures of paroxetine HCl hemihydrate (Form I, two independent cations) and the propan-2-ol solvate of paroxetine HCl [3]. As is evident from Table 4, the folded conformation of Figure 4, necessary for encapsulation of the neutral paroxetine molecule within the β-CD dimer, is attained by appropriate torsions of the L-conformation, chiefly around the C3–C7 and C7–O8 bonds. The resulting conformation has

Table 2. Geometrical parameters for the independent β-cyclodextrin molecules

Residue	D[a] (Å)	ϕ[b] (°)	d[c] (Å)	α[d] (°)	D_3^e (Å)	τ[f] (°)
CD(A)						
A1	4.33	129.2	−0.034	79.5	2.83	58
A2	4.33	125.3	−0.052	81.2	2.83	167
						67
A3	4.38	128.3	0.063	83.6	2.82	−174
A4	4.47	132.3	0.032	87.2	2.80	54
A5	4.73	127.8	−0.099	82.0	2.77	60
A6	4.38	123.6	0.040	81.0	2.78	62
A7	4.47	133.3	0.049	86.7	2.88	59
CD(B)						
B1	4.46	133.6	0.066	85.1	2.81	52
B2	4.24	129.0	−0.059	85.7	2.85	47
B3	4.40	122.1	−0.011	80.4	2.80	−172
B4	4.55	132.3	0.034	85.4	2.72	169
B5	4.27	132.2	0.022	86.4	2.79	56
B6	4.37	123.6	−0.059	81.8	2.89	−168
						55
B7	4.44	127.0	0.008	77.7	2.76	62

[a]Glycosidic O4n···O4(n + 1) distance.
[b]O4(n − 1)···O4n···O4(n + 1) angle.
[c]Deviations of atoms O4n from their least-squares planes (mean e.s.d. 0.003 Å).
[d]Dihedral angle between the mean O4n plane and the mean C2n, C3n, C5n, O5n plane of each residue (mean e.s.d. 0.1°).
[e]Inter-ring hydrogen bond O(2n)···O(3n)′ distances.
[f]Torsion angle C4n–C5n–C6n–O6n.

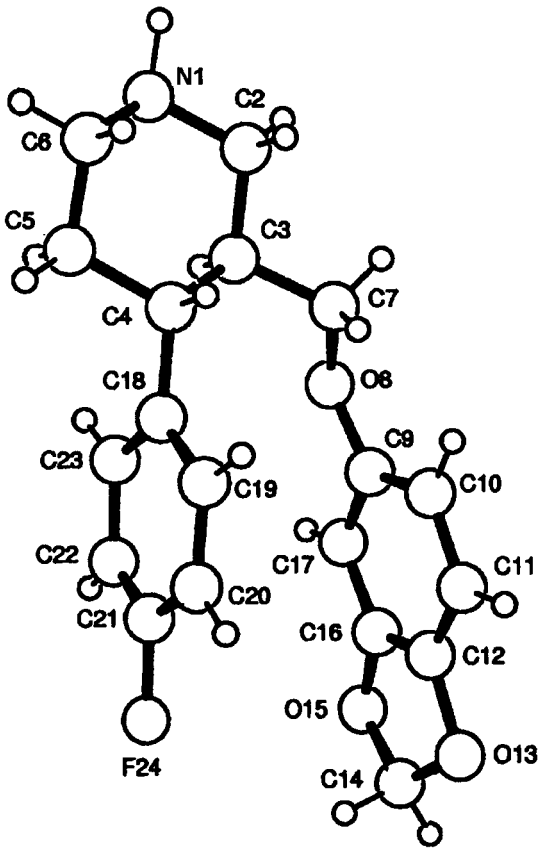

Figure 4. Conformation of the included paroxetine molecule.

Table 3. Hydrogen bond data (distances in Å, angles in degrees)[a]

Donor-H···Acceptor	H···A	D···A	D–H···A
O(2A1)–H(212)···O(3B1)	2.438	3.049(5)	130
O(2B1)–H(215)···O(3B2)	2.028	2.804(5)	153
O(2A2)–H(222)···O(3A1)	2.023	2.826(4)	159
O(2A2)–H(222)···O(4A1)	2.400	2.816(5)	111
O(2B2)–H(225)···O(3A2)	2.384	3.133(5)	148
O(2B3)–H(235)···O(3B4)	1.980	2.800(4)	165
O(2A4)–H(242)···O(3A3)	2.061	2.794(5)	145
O(2B4)–H(245)···O(13W)	1.770	2.604(8)	171
O(2A6)–H(262)···O(3A5)	2.011	2.782(4)	151
O(2A7)–H(272)···O(3A6)	2.187	2.883(5)	140
O(3B1)–H(315)···O(2B7)	1.957	2.763(6)	160
O(3A2)–H(322)···O(2A3)	2.054	2.823(6)	152
O(3B2)–H(325)···O(3A2)	1.931	2.753(5)	165
O(3A3)–H(332)···O(3B3)	2.095	2.876(5)	154
O(3B3)–H(335)···O(2B2)	2.014	2.850(4)	173
O(3B4)–H(345)···O(3A4)	1.938	2.762(5)	166
O(3A5)–H(352)···O(3B5)	2.000	2.833(5)	171
O(3B5)–H(355)···O(2B4)	1.912	2.715(5)	159
O(3A6)–H(362)···O(3B6)	2.101	2.895(5)	157
O(3B6)–H(365)···O(3A6)	2.080	2.895(5)	163
O(3A7)–H(372)···O(2A1)	2.228	2.828(4)	128
O(3B7)–H(375)···O(3A7)	1.903	2.740(5)	175
O(6B1)–H(616)···O(6W)	1.902	2.729(7)	168
O(6A3)–H(633)···O(5W)	1.924	2.751(6)	168
O(6B3)–H(636)···O(10W)	2.075	2.748(6)	136
O(6B5)–H(656)···O(2W)	1.930	2.757(5)	167
O(6B7)–H(676)···O(7W)	1.929	2.732(6)	159
O(6A4)–H(643)···O(6A7)[i]	2.040	2.816(5)	153
O(6B2)–H(626)···O(6B5) [ii]	1.976	2.784(6)	161
O(6A1)–H(613)···O(11W) [ii]	1.906	2.719(7)	163
O(2B5)–H(255)···O(2A2) [iii]	1.942	2.749(4)	160
O(2B7)–H(275)···O(2A4) [iv]	1.900	2.737(5)	173
O(2B6)–H(265)···O(13W) [iv]	2.489	3.228(8)	147
N(1) –H(1) ···O(5A6) [v]	2.53(6)	3.172(7)	121(4)
O(6B4)–H(646)···O(6A6) [v]	1.858	2.696(6)	175
O(6A5)–H(653)···O(7W) [vi]	2.233	2.806(7)	125
O(6A6)–H(663)···N(1) [vi]	1.86(6)	2.846(8)	169(5)
O(6A7)–H(673)···O(2W) [vi]	1.934	2.767(6)	170

[a]D-H distances are 0.84 Å except for N(1)–H(1) (1.02(6) Å) and O(6A6)–H(663) (0.99(6) Å).
Symmetry code: (i) −1 + x, y, z (ii) x, y, −1 + z (iii) x, y 1 + z (iv) 1 + x,y,z (v) 2 − x,1/2 + y,2-z (vi) 2 − x, −1/2+y, 2 − z.

the phenyl rings nearly parallel (dihedral angle 9.0(5)°) and in close proximity (centroid···centroid distance 3.64 Å, with perpendicular centroid···ring distances of 3.36 and 3.51 Å). These parameters indicate that the guest conformation is stabilised by intramolecular $\pi \cdots \pi$ interaction.

Crystal structure, layer stacking mode and XRPD

A stereoview of the crystal packing is shown in Figure 5 and selected hydrogen bond data are included in Table 3. Each unit cell contains a pair of 2_1-related dimeric complex units. Also shown are two important hydrogen bonds which contribute to crystal cohesion along the y-direction. These involve the guest N–H group which is located at the primary surface of one CD ring of the host dimer. In one of these

Table 4. Principal torsion angles (deg.) defining the conformations of paroxetine species

τ	Present study	Form I [3]		Form II
		A	B	
C23–C18–C4–C3	−66.0(8)	−73.1(3)	−66.3(3)	−89.9(5)
C19–C18–C4–C3	112.4(7)	104.7(3)	116.1(3)	92.0(5)
C18–C4–C3–C7	−53.1(7)	−58.7(3)	−55.6(3)	−55.6(6)
C4–C3–C7–O8	87.1(6)	−60.4(3)	179.5(2)	−54.3(5)
C3–C7–O8–C9	−131.7(6)	−174.3(2)	175.0(2)	163.4(4)
C7–O8–C9–C10	−10(1)	142.4(2)	35.4(4)	12.7(6)
C7–O8–C9–C17	168.0(6)	−42.2(4)	−149.2(3)	−166.7(4)

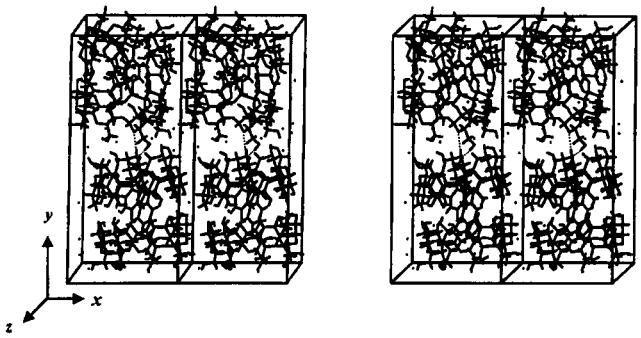

Figure 5. Stereoview of the crystal packing showing the contents of two unit cells.

interactions, the N–H group is a donor to a pyranose oxygen atom of a screw-related complex unit (N1–H1···O5A6^{v}) and in the other, the same N atom accepts a hydrogen atom from the primary hydroxyl group of the screw-related complex unit (O6A6–H663···N1^{vi}). Numerous hydrogen bonds of type O–H···O link neighbouring cyclodextrin rings either directly or via water molecule bridges. Water molecules are located mainly outside the CD cavities. Table 3 lists only those hydrogen bonds for which H atoms were placed in the structural analysis. The data include only ordered water molecules and bonds with angle D–H···A > 120°.

Failure to solve the structure by isomorphous replacement using data for an apparently isostructural complex prompted an analysis of the stacking modes of dimeric complexes in this category, details of which appear in Table 5. In a recent review of the isostructurality of CD inclusion complexes [17], compounds **1–4** were described as comprising an isostructural class, based on close correspondence of both their unit cell dimensions and their respective host atomic co-ordinates, as well as nearly superimposable XRPD patterns. Subsequent to that study, the three remaining structures in Table 5, including that of the present complex, have been reported. All seven structures belong to the screw-channel packing type defined previously [15] and all are based on stacking of layers of the type shown in the schematic of Figure 6a. The motif of two overlapping heptagons represents the connected O4 atoms of a single dimeric complex unit. Depending on the location of the 2_1-axis parallel to *b*, different stacking arrangements of such layers result. Figure 6b shows the projected layer stacking found in the isostructural series comprising complexes **1–5** listed in Table 5. This arrangement is characterised by significant overlap of the complex units of successive layers, resulting in isolated, screw-generated columns spiralling along the *y*-direction. For the paroxetine complex (**6** in Table 5), however, the dimer overlap is smaller in extent and unidirectional (parallel to *z*), as shown in Figure 6c. Finally, complex **7** has the arrangement shown in Figure 6d, characterised by negligible overlap of the dimeric motifs of successive layers. The distinct deviations of structures **6** and **7** from the strict isostructurality displayed by **1–5** are noteworthy in the context of crystal structure solution of CD inclusion complexes by isomorphous replacement. Although schematic, Figure 6 was drawn using published O4 atom co-ordinates and is therefore accurate. It shows, for example, that the 'transition' from the structure of Figure 6b to that of Figure 6c involves a displacement of overlapping dimers of ∼4 Å along *z*, which is very significant. The reason for the failure to solve the present structure (stacking of Fig.6c) using co-ordinates for compound **1** (stacking of Fig.6b) is now evident.

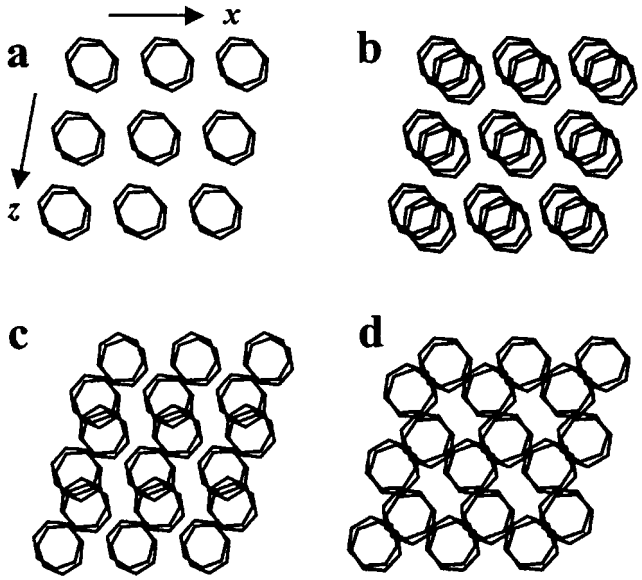

Figure 6. (010) projections of layer stacking sequences of O4 heptagons in β-CD screw-channel complexes: Key: a: a single layer; b, c and d: pairs of 2_1-related layers in each of three sets of complexes.

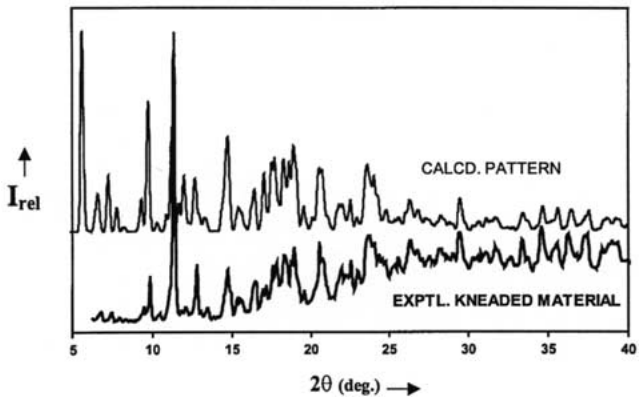

Figure 7. Comparison of the experimental XRPD trace (1:1 kneaded material) and that calculated from the single crystal X-ray analysis.

Table 5. Crystallographic data for dimeric β-CD complexes of the screw-channel type

No.	REFCODE	Ref.	a(Å)	b(Å)	c(Å)	β(°)	Guest
1	GETPAW	[11]	15.260	32.760	15.350	101.50	(R)-(−)-fenoprofen
2	GETPEA	[11]	15.310	32.124	15.277	100.76	(S)-(+)-fenoprofen
3	DUTLIN10	[19]	15.277	32.232	15.316	101.18	(RS)-fenoprofen
4	NIZGUY	[20]	15.342	32.540	15.324	102.44	(L)-menthol
5	QACXEX	[21]	15.454	31.693	15.255	102.92	p-amino-p'-nitrobiphenyl
6	Present study	–	15.226	31.477	15.674	104.32	paroxetine
7	KIFPAQ	[22]	15.428	32.545	15.437	103.56	adamantanone

A clue to the origin of these distinct layer arrangements is provided by an examination of the nature of the included guests and their modes of inclusion. Structures **1–5** all have '2:2' host-guest stoichiometry, with each β-CD cavity of a dimer occupied by one guest molecule. The paroxetine complex, **6**, has stoichiometry 2:1 with a single guest molecule folded within the host dimer. The host–guest ratio in compound **7** is formally 2:2, but the guest adamantanone molecules are disordered over three distinct regions, their centroids being located at the dimer interface for one component, and close to the primary faces of the β-CD molecules comprising the dimer for the other two components. The occurrence of grossly different guest-induced stacking arrangements of dimeric β-CD complexes is well known [15, 17] but in the present case, finer structural discrimination within an apparently isostructural series has been identified and the results may be useful for complex structure prediction. Certainly they emphasise that close correspondence of unit cell dimensions is a necessary, but not sufficient, condition for isostructurality [18].

Figure 7 shows the experimental and computed XRPD patterns for the β-CD-paroxetine complex. The former (raw data, unmodified) was recorded from the product of the host–guest kneading experiment while the latter was generated from the single crystal X-ray data. Since the kneaded phase was subsequently recrystallised to produce the single crystals, the correspondence between the patterns confirms that the complex structure was maintained during all stages of its preparation.

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