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X-ray Structural Comparison of the Modes of Inclusion of Meclofenamate Sodium and Diclofenac Sodium by β-cyclodextrin

MINO R. CAIRA*, VIVIENNE J. GRIFFITH and LUIGI R. NASSIMBENI
Department of Chemistry, University of Cape Town, Private Bag, Rondebosch 7701, South Africa

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Abstract. The X-ray structure of the 1 : 1 meclofenamate sodium-β-cyclodextrin complex has been determined. It crystallises in the orthorhombic system, space group $P2_12_12_1$, D_x = 1.440 g·cm^{-3}, D_m = 1.44(1) g·cm^{-3}, a = 15.087(2) Å, b = 17.967(2) Å, c = 29.634(4) Å and Z = 4. Refinement yielded a final R-value of 0.076 for 5349 observed reflections. The mode of inclusion of the non-steroidal anti-inflammatory drug in β-cyclodextrin is compared with that of its structural isomer diclofenac sodium, as determined in an earlier crystallographic study. The latter indicated a 1 : 1 diclofenac sodium-β-cyclodextrin complex belonging to the hexagonal system, space group $P6_1$, with a = 15.956(8) Å, c = 50.95(1) Å and Z = 6. Gross features of the modes of inclusion of meclofenamate sodium and diclofenac sodium are similar, but there are several weak host-guest interactions in the complex with diclofenac sodium which are not observed in the other complex. The crystal packing arrangements are different, that of the diclofenac sodium complex being unique and having a layered appearance while that of the meclofenamate sodium complex resembles the arrangement observed in the majority of known heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin complexes.

Key words: β-cyclodextrin, non-steroidal anti-inflammatory drug (NSAID), inclusion complex, X-ray crystal structure

Supplementary Data relating to this article are deposited with the British Library as Supplementary Publication No. 82242 (50 pages).

1. Introduction

The therapeutic properties of the non-steroidal anti-inflammatory drugs (NSAIDs) are characteristic of the prototype aspirin (acetylsalicylic acid) and include analgesic and antipyretic effects in addition to the anti-inflammatory effect. The action of these drugs is attributable to the inhibition of prostaglandin synthesis [1]. Non-steroidal agents other than salicylates are often preferred to aspirin to relieve painful conditions such as osteoarthritis, rheumatoid arthritis and gout, since high doses of aspirin are needed for a significant anti-inflammatory effect [1]. Although NSAIDs are very widely used, they are well known for causing gastrointestinal ulceration and bleeding. Complexation of these drugs with cyclodextrins is a pos-

* Author for correspondence.

sible way of reducing local irritation in the gastrointestinal tract by promoting more rapid absorption and therefore shorter exposure to the drug [2]. This has already been demonstrated for β-cyclodextrin complexes with piroxicam [3] and naproxen [4]. Diclofenac is an arylacetic acid derivative and an advantage of this drug is that therapeutic effects are elicited at lower doses than for most other NSAIDs [5]. Meclofenamic acid is a structural isomer of diclofenac and belongs to the aminoaryl carboxylic acid derivative class of NSAIDs [6]. The interaction of both of these drugs with β-cyclodextrin in solution has been studied by phase solubility, UV and circular dichroism techniques [7–9], which yielded stoichiometries of 1 : 1 for both complexes and stability constant data under various conditions. We have given a brief description of the crystal structure of the diclofenac sodium-β-cyclodextrin undecahydrate complex in a previous communication [10] and now report the preparation and detailed crystal structure of the meclofenamate sodium-β-cyclodextrin decahexahydrate complex with further details of the structure of the former complex for comparison. This report is motivated by the fact that opportunities for detailed comparison of the modes of inclusion of closely related guests in a cyclodextrin are rare and, furthermore, by the fact that the guests involved here are potent NSAIDs.

2. Experimental

2.1. MATERIALS

β-Cyclodextrin and meclofenamate sodium were obtained from Sigma Chemical Company, U.S.A and were used as received.

2.2. COMPLEX PREPARATION

Crystals of the meclofenamate sodium-β-cyclodextrin complex (**1**) were grown by slow cooling over about 3 days of a filtered solution made by dissolving 0.13 mmol of meclofenamate sodium and 0.16 mmol of β-cyclodextrin in 4 mL of distilled water at 70 °C. Complex **2** was prepared as described previously [10].

2.3. CRYSTAL STRUCTURE SOLUTION

Reflection intensity data for the meclofenamate sodium-β-cyclodextrin complex (**1**) were collected on an Enraf-Nonius CAD-4 diffractometer using graphite-monochromated MoKα radiation (λ = 0.71069 Å) from a crystal mounted on the end of a thin glass rod and coated with quick-setting cyanoacrylate glue. Accurate cell dimensions were obtained by least-squares analysis of the setting angles of 24 reflections in the range $16° \leq \theta \leq 17°$. Intensity data were collected by the ω-scan technique to $(\sin\theta/\lambda)_{max}$ = 0.595 Å^{-1} with a forced scan for all reflections. Three standard reflections were checked periodically during data collection to detect any

crystal decay and orientation control was performed after every 200 measured reflections. During data collection, there was a period of fairly rapid decay following which the standard reflections remained constant. Therefore a linear decay correction was applied only over the period of decay and all the remaining reflections were corrected by a constant factor. The structure was solved by direct methods (program SIR92 [11]) and the model was refined using SHELX93 [12]. All the non-hydrogen atoms of the host and guest, except the Na^+ ion, were located in the direct methods solution. Hydrogen atoms attached to carbon atoms on both the host and guest were inserted at idealised positions in a riding model (C—H = 1.00 Å). All hydrogen atoms of each glucose residue and all the hydrogen atoms of the guest were assigned common variable isotropic temperature factors. The non-hydrogen atoms of the host and guest anion were then assigned anisotropic temperature factors. There were still many peaks of relatively high electron density in the difference Fourier map representing water molecules and the sodium cation. However, the position of the sodium ion was not obvious from the peak heights. A search of the Cambridge Structural Database (CSD) [13] for $Na^+ \cdots O$ contacts revealed a minimum distance of 2.1 Å and an average of approximately 2.4 Å. The sodium ion was then assigned on the basis of $Na^+ \cdots O$ distances and geometry. The isotropic temperature factor of the assigned sodium ion was abnormally high, indicating disorder, and there was a peak 1.7 Å away from it. Since this distance is too short for a $Na^+ \cdots O$ contact and chemical analysis for sodium indicated one sodium ion per 1 : 1 complex unit, the peak was assigned as an alternative location for Na^+ with site occupancies of 0.6 for the former peak and 0.4 for the latter peak. Thermogravimetric analysis of the complex gave a mass loss which corresponded to sixteen water molecules per 1 : 1 complex unit [14]. Twelve water molecules were placed with full site occupancy. A further eight sites for water molecules were found; their temperature factors were fixed at 0.2 $Å^2$ (average of those for the water molecules with full site occupancy) and their site occupancies were refined. This accounted for a total of 15.5 water molecules. Water molecules O(1W), O(2W), O(3W) and O(4W) were then assigned anisotropic temperature factors. The hydrogen atoms of the hydroxyl groups of the host, except that of the disordered group, were found and inserted with geometrical constraints (O—H = 0.98 Å, σ = 0.05 Å or 0.005 Å in some cases, C$\cdots$H = 1.99 Å, σ = 0.05 Å or 0.005 Å). No attempt was made to locate the hydrogen atoms of the water molecules. Table I lists refined atomic coordinates and thermal parameters for complex **1**.

The crystal structure of the diclofenac sodium-β-cyclodextrin complex (**2**) was solved as previously described [10]. Atomic coordinates are available in the CSD [13] (compound refcode HEHJEJ). Table II lists crystal data, experimental and refinement parameters for the meclofenamate sodium-β-cyclodextrin (**1**) and diclofenac sodium-β-cyclodextrin (**2**) complexes.

Table I. Refined atomic coordinates ($\times 10^4$) and isotropic or equivalent isotropic thermal displacement parameters (Å^2 $\times$ 10^3) for complex **1**. U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor

	x	*y*	*z*	U_{eq}/U_{iso}*
Cl(1)	112(2)	3579(2)	3234(1)	76(1)
Cl(2)	311(2)	3979(2)	1432(1)	76(1)
N(3)	961(5)	3434(4)	2299(3)	59(2)
C(4)	118(6)	3735(4)	2318(3)	54(2)
C(5)	−285(6)	4016(5)	1928(3)	58(2)
C(6)	−1135(6)	4330(4)	1921(3)	58(2)
C(7)	−1585(6)	4347(5)	2330(3)	63(2)
C(8)	−1197(7)	4112(5)	2725(3)	63(2)
C(9)	−353(6)	3832(5)	2719(3)	57(2)
C(10)	1200(5)	2720(4)	2450(3)	48(2)
C(11)	2078(6)	2510(4)	2435(3)	52(2)
C(12)	2334(7)	1832(5)	2616(4)	71(3)
C(13)	1689(11)	1349(6)	2787(5)	106(4)
C(14)	838(8)	1539(6)	2779(5)	88(3)
C(15)	588(7)	2212(5)	2620(3)	65(2)
C(16)	−1564(8)	4572(7)	1499(4)	87(3)
C(17)	2788(6)	2981(4)	2216(3)	49(2)
O(18)	3531(4)	3009(4)	2407(3)	73(2)
O(19)	2608(5)	3282(3)	1849(2)	66(2)
C(1G1)	772(6)	1052(4)	4887(2)	42(2)
C(2G1)	121(6)	412(5)	4952(3)	50(2)
C(3G1)	−452(6)	345(4)	4528(3)	47(2)
C(4G1)	−915(5)	1065(4)	4429(2)	43(2)
C(5G1)	−266(6)	1719(4)	4418(3)	48(2)
C(6G1)	−741(7)	2464(5)	4430(4)	76(3)
O(2G1)	591(5)	−259(4)	5039(2)	70(2)
O(3G1)	−1072(5)	−236(4)	4604(2)	72(2)
O(4G1)	−1314(3)	990(3)	4001(2)	47(1)
O(5G1)	297(4)	1721(3)	4810(2)	48(1)
O(6G1)	−92(6)	3032(4)	4397(3)	86(2)
C(1G2)	−2234(5)	1128(5)	3948(3)	52(2)
C(2G2)	−2639(6)	443(5)	3732(3)	55(2)
C(3G2)	−2276(5)	336(4)	3263(3)	49(2)
C(4G2)	−2429(5)	1029(4)	2991(3)	44(2)
C(5G2)	−2024(5)	1708(4)	3223(3)	44(2)
C(6G2)	−2252(6)	2428(4)	3001(3)	56(2)
O(2G2)	−2501(5)	−197(4)	4004(3)	82(2)
O(3G2)	−2724(5)	−245(3)	3029(2)	68(2)
O(4G2)	−2020(4)	927(3)	2558(2)	47(1)

Table I. Continued

	x	*y*	*z*	U_{eq}/U_{iso}*
O(5G2)	−2384(4)	1758(3)	3682(2)	52(1)
O(6G2)	−3177(4)	2487(3)	2918(2)	60(2)
C(1G3)	−2539(5)	1103(5)	2180(3)	48(2)
C(2G3)	−2608(5)	423(5)	1868(3)	51(2)
C(3G3)	−1709(5)	237(4)	1668(3)	45(2)
C(4G3)	−1306(5)	908(4)	1454(3)	44(2)
C(5G3)	−1279(6)	1563(5)	1779(3)	55(2)
C(6G3)	−951(8)	2270(5)	1567(3)	73(3)
O(2G3)	−2977(4)	−186(4)	2103(2)	63(2)
O(3G3)	−1826(4)	−348(3)	1348(2)	63(2)
O(4G3)	−420(3)	720(3)	1334(2)	45(1)
O(5G3)	−2169(4)	1709(3)	1940(2)	58(2)
O(6G3)	−1382(8)	2459(5)	1158(3)	107(3)
C(1G4)	−119(6)	877(5)	889(3)	51(2)
C(2G4)	218(5)	151(5)	695(3)	47(2)
C(3G4)	1001(6)	−114(4)	954(3)	46(2)
C(4G4)	1707(5)	475(4)	977(3)	43(2)
C(5G4)	1306(5)	1208(4)	1164(3)	47(2)
C(6G4)	1968(7)	1842(5)	1137(5)	79(3)
O(2G4)	−467(4)	−396(4)	682(2)	64(2)
O(3G4)	1349(4)	−774(3)	748(2)	56(2)
O(4G4)	2392(3)	218(3)	1267(2)	41(1)
O(5G4)	549(4)	1411(3)	898(2)	53(1)
O(64A)	1566(8)	2526(7)	1170(4)	70*
O(64B)	2174(11)	2071(9)	748(5)	70*
C(1G5)	3238(5)	142(4)	1075(2)	44(2)
C(2G5)	3626(6)	−604(4)	1229(3)	46(2)
C(3G5)	3741(5)	−597(4)	1736(2)	41(2)
C(4G5)	4297(5)	54(4)	1879(2)	39(2)
C(5G5)	3919(6)	779(4)	1703(2)	42(2)
C(6G5)	4447(6)	1463(4)	1799(3)	52(2)
O(2G5)	3037(4)	−1177(3)	1086(2)	61(2)
O(3G5)	4140(4)	−1287(3)	1872(2)	58(2)
O(4G5)	4296(3)	56(3)	2363(2)	41(1)
O(5G5)	3793(4)	731(3)	1218(2)	47(1)
O(6G5)	5302(5)	1369(4)	1608(2)	69(2)
C(1G6)	5112(5)	91(4)	2580(2)	41(2)
C(2G6)	5128(5)	−508(4)	2948(3)	41(2)
C(3G6)	4425(5)	−366(4)	3303(3)	45(2)

Table I. Continued

	x	*y*	*z*	U_{eq}/U_{iso}*
C(4G6)	4546(5)	418(4)	3474(2)	42(2)
C(5G6)	4570(5)	989(4)	3098(2)	43(2)
C(6G6)	4746(6)	1770(5)	3249(3)	52(2)
O(2G6)	4997(4)	−1224(3)	2741(2)	50(1)
O(3G6)	4482(5)	−881(3)	3657(2)	60(2)
O(4G6)	3815(3)	565(3)	3766(2)	49(1)
O(5G6)	5245(4)	793(3)	2781(2)	44(1)
O(6G6)	5564(4)	1813(3)	3503(2)	61(2)
C(1G7)	3978(6)	941(6)	4181(3)	65(3)
C(2G7)	3738(6)	448(6)	4559(3)	68(3)
C(3G7)	2726(6)	288(5)	4548(3)	55(2)
C(4G7)	2250(5)	1018(5)	4571(3)	49(2)
C(5G7)	2569(5)	1542(5)	4190(3)	53(2)
C(6G7)	2200(7)	2327(6)	4206(4)	76(3)
O(2G7)	4201(5)	−266(5)	4528(2)	85(2)
O(3G7)	2476(5)	−167(4)	4914(2)	78(2)
O(4G7)	1327(4)	888(3)	4523(2)	45(1)
O(5G7)	3518(4)	1619(4)	4200(2)	63(2)
O(6G7)	2526(6)	2713(4)	4601(3)	86(2)
Na(1A)	291(10)	3668(8)	−17(5)	161(4)*
Na(1B)	886(19)	3235(14)	391(8)	163(7)*
O(1W)	768(5)	2243(4)	5785(2)	69(2)
O(2W)	1130(6)	3255(5)	5085(2)	91(2)
O(3W)	4045(6)	3440(5)	4213(3)	97(2)
O(4W)	−3863(6)	2635(4)	1981(3)	103(3)
O(5W)	3785(8)	3524(6)	1148(4)	132(4)*
O(6W)	3381(8)	3460(7)	3346(4)	132(4)*
O(7W)	−1893(10)	189(9)	5672(5)	167(5)*
O(8W)	6054(11)	232(10)	4695(5)	180(6)*
O(9W)	5633(13)	1011(10)	714(6)	198(6)*
O(10W)	2143(21)	1680(18)	−247(11)	312(14)*
O(11W)	−3179(15)	2784(13)	1119(7)	241(8)*
O(12W)	4178(19)	1993(15)	596(9)	277(11)*
O(13W)	−845(29)	2851(22)	339(12)	200*
O(14W)	7106(32)	−644(25)	5169(15)	200*
O(15W)	5071(36)	3238(27)	202(17)	200*
O(16W)	1603(28)	3131(22)	227(13)	200*
O(17W)	1251(29)	2835(24)	−379(13)	200*
O(18W)	4199(38)	3405(29)	213(17)	200*
O(19W)	2967(28)	3441(24)	42(14)	200*
O(20W)	−23(33)	2840(24)	480(13)	200*

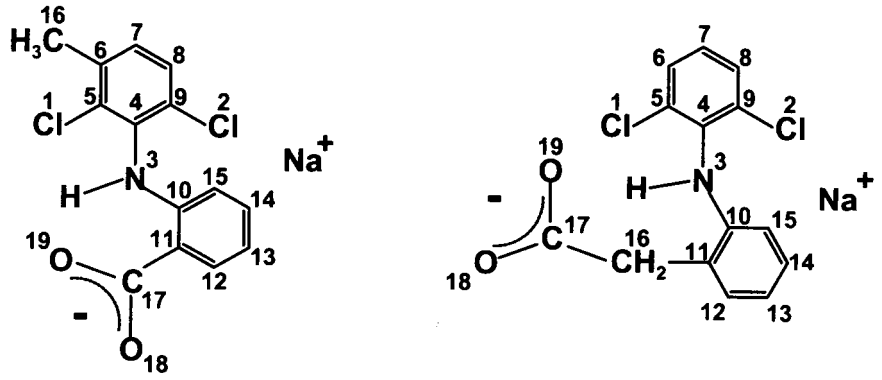

Figure 1. Structures and numbering schemes for meclofenamate sodium (left) and diclofenac sodium (right).

3. Results and Discussion

Figure 1 shows the structures and numbering schemes for the guests meclofenamate sodium and diclofenac sodium. The numbering scheme for the host, β-cyclodextrin, is the same as that used in the sulfathiazole-β-cyclodextrin complex [15]. Figure 2 is a stereodiagram of complex **1** in which the glucose residues have been numbered. All glucose residues are in the $^4C_1$ chair conformation. Atom O(6G4) is disordered over two sites with site occupancies of 0.57 and 0.43. The C(6)–O(6) bonds of all the glucose residues are directed away from the cavity in the (−)-*gauche* conformation [16], except those of G1 and the major site of O(6) in G4, which point inwards towards the cavity in the (+)-*gauche* conformation. O(6G1) is hydrogen bonded to O(2G4) of a screw-related cyclodextrin molecule and O(64A) is within hydrogen bonding distance of O(19) of the guest and is coordinated to the minor position of the Na^+ ion, Na(1B). Table III lists values for the O(4)···O(4′)···O(4″) angles of the O(4) heptagon, O(4)···O(4′) distances, radii of the O(4) heptagon [17], tilt angles of the glucose residues [17] and the deviations of the O(4) atoms from their least-squares plane for both complexes. Comparison of these geometrical data shows that the conformation of the cyclodextrin molecule in **1** is not as distorted as that in **2**. O(2)···O(3′) distances of adjacent glucose residues in **1** are in the expected range of 2.77(1)–2.89(1) Å, consistent with the usual intramolecular hydrogen bonding and with the average O(2)···O(3′) distance in β-CD dodecahydrate [18]. In contrast, this parameter has a wider range of 2.716(6)–3.022(7) Å in **2**. That the conformation of the host in **1** is closer to that of the 'round' conformation of uncomplexed β-CD is also confirmed by the narrower ranges of the parameters listed in Table III. In addition, the r.m.s. deviation of atoms from the O(4) heptagon is very similar in **1** and uncomplexed β-CD (0.16 and 0.18Å respectively), whereas in **2** it is 0.27Å.

Figure 3 is a stereodiagram of **1** viewed perpendicular to the axis of the host. The phenylcarboxylate ring of the drug anion is included in the host cavity from the pri-

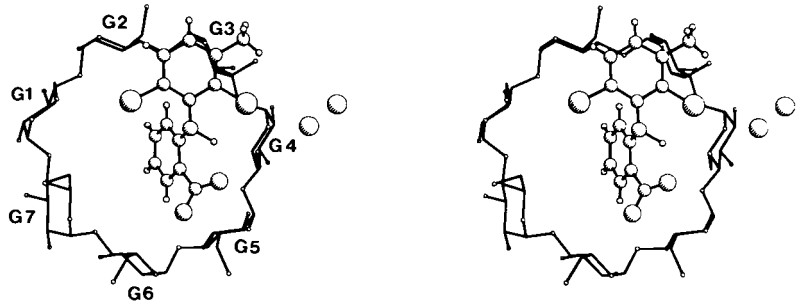

Figure 2. A stereodiagram of the meclofenamate sodium-β-cyclodextrin complex viewed down the host axis. The disordered Na^+ ion is shown as two open circles - Na(1A) (right) and Na(1B) (left).

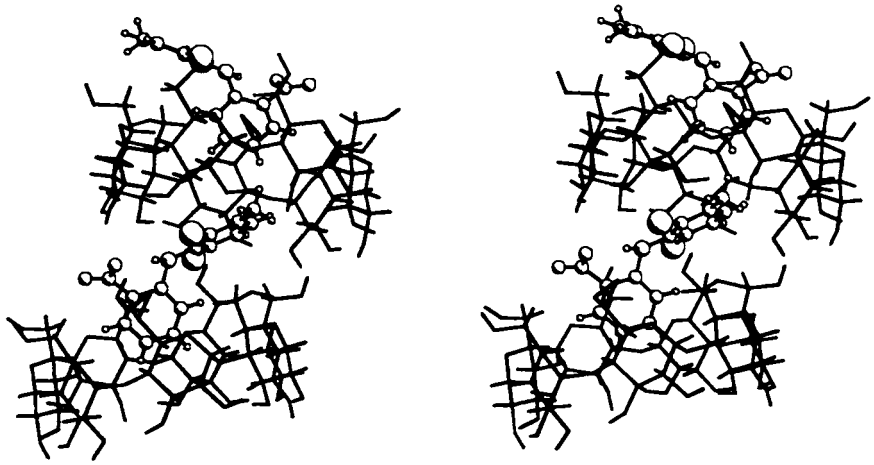

Figure 3. Two meclofenamate sodium-β-cyclodextrin complex units related by a twofold screw axis parallel to the *b*-axis.

mary hydroxyl side and the interaction is stabilised by the hydrogen bond between a carboxylate oxygen atom, O(19), and the major site of a primary hydroxyl group, (O64A), of the host molecule. Atom O(19) is also involved in an intramolecular N—H···O hydrogen bond which is observed in the isolated drug molecule. Analogous inclusion of the phenylacetate ring of diclofenac sodium occurs in complex **2**, but each carboxylate oxygen atom is separately involved in one of these hydrogen bonding interactions. The angle of inclusion (i.e. the angle between the plane of the included phenyl ring and the plane of the host O(4) heptagon) is 70.4° in **1** as opposed to 82.9° in **2**.

The bulky dichlorophenyl moiety protrudes from the host cavity in both **1** and **2**. This residue (with an additional methyl substituent in **1**) is included at the secondary hydroxyl side of a 2_1-related host molecule in **1** with an angle of inclusion of 28.6° (Figure 3). For complex **2**, the relevant cyclodextrin molecules are related instead by a 6_1-axis and the angle of inclusion is 26.6° (Figure 4). There

Table II. Crystal data, experimental and refinement parameters for the β-cyclodextrin complexes with meclofenamate sodium (**1**) and diclofenac sodium (**2**)

Complex	**1**	**2**
Molecular formula	$C_{42}H_{70}O_{35}\cdot C_{14}H_{10}Cl_2NO_2^-Na^+ \cdot 16H_2O$	$C_{42}H_{70}O_{35}\cdot C_{14}H_{10}Cl_2NO_2^-Na^+ \cdot 11H_2O$
M_r/g·mol^{-1}	1741.36	1651.29
Crystal system	Orthorhombic	Hexagonal
Space Group	$P2_12_12_1$	$P6_1$
Z	4	6
a (Å)	15.087(2)	15.956(8)
b (Å)	17.967(2)	
c (Å)	29.634(4)	50.95(1)
V (Å^3)	8033(2)	11 234(8)
D_m	1.44(1)	1.47(1)
D_x	1.440	1.451
Crystal dimensions (mm)	0.50 × 0.50 × 0.33	0.38 × 0.38 × 0.45
Temperature	294K	233K
Range scanned θ (°)	$1 \leq \theta \leq 25$	$1 \leq \theta \leq 25$
Scan type	ω	ω
Index range	h 0,17: k 0,21: l 0,35	h 0,19: k 0,19: l 0,60
Scan width (°)	0.8 + 0.35 tanθ	0.7 + 0.35 tanθ
Aperture width (mm)	1.12 + 1.05 tanθ	1.12 + 1.05 tanθ
No. of reflections collected	7766	7490
No. of unique reflections	7729	6167
R_{int}	0.00	0.034
No. of reflections with $I > 2\sigma(I)$	5349	5489
No. of L.S. parameters	1042	915
R ($I > 2\sigma(I)$)	0.076	0.056
Shift/e.s.d. max., average	1.136, 0.026	0.455, 0.001
$(\Delta\rho)_{max}$ final (e·Å^{-3})	0.63	0.57
$(\Delta\rho)_{min}$ final (e·Å^{-3})	−0.38	−0.36

are several weak interactions observed between the dichlorophenyl moiety and the secondary hydroxyl side of the screw-related host in **2** which are not present in **1**. These are shown schematically in Figure 5. Other close contacts between host and guest are also fewer in **1**. Comparison of space-filling diagrams of the two complexes reveals the much snugger fit of the diclofenac anion in the β-cyclodextrin cavity at the secondary hydroxyl side of the 6_1-related host molecule. In **1**, the dichloromethylphenyl moiety is shifted relative to what is observed for the

Table III. Geometrical data for β-cyclodextrin in **1** and **2**

(i) O(4)···O(4′)···O(4″) angle (°).

	1	**2**
O(4G7)···O(4G1)···O(4G2)	125.1	124.5
O(4G1)···O(4G2)···O(4G3)	132.3	127.4
O(4G2)···O(4G3)···O(4G4)	126.5	129.3
O(4G3)···O(4G4)···O(4G5)	128.8	131.8
O(4G4)···O(4G5)···O(4G6)	126.4	120.1
O(4G5)···O(4G6)···O(4G7)	131.4	130.3
O(4G6)···O(4G7)···O(4G1)	127.9	131.6
Average	128.3	127.9

(ii) O(4)···O(4′) distance (Å) and radius (Å) of the O(4) heptagon.

	1	**2**		**1**	**2**
O(4G1)···O(4G2)	4.41	4.36	G1	5.13	5.14
O(4G2)···O(4G3)	4.38	4.33	G2	4.89	5.09
O(4G3)···O(4G4)	4.34	4.50	G3	5.03	4.89
O(4G4)···O(4G5)	4.34	4.24	G4	5.05	4.90
O(4G5)···O(4G6)	4.32	4.32	G5	5.04	5.23
O(4G6)···O(4G7)	4.41	4.40	G6	4.88	4.86
O(4G7)···O(4G1)	4.28	4.31	G7	5.05	4.83
Average	4.35	4.35		5.01	4.99

(iii) Tilt angle (°) and deviation (Å) of each O(4) atom from the least-squares plane through the seven O(4) atoms

	1	**2**		**1**	**2**
G1	5.2	5.4	O(4G1)	0.167(4)	0.303(5)
G2	2.2	4.2	O(4G1)	0.055(4)	0.007(5)
G3	12.2	13.5	O(4G1)	0.226(4)	0.258(5)
G4	21.0	28.7	O(4G1)	0.058(4)	0.004(4)
G5	5.2	7.1	O(4G1)	0.228(4)	0.439(5)
G6	7.9	11.7	O(4G1)	0.211(4)	0.396(5)
G7	26.4	31.6	O(4G1)	0.070(4)	0.091(5)
Average	11.4	14.6			

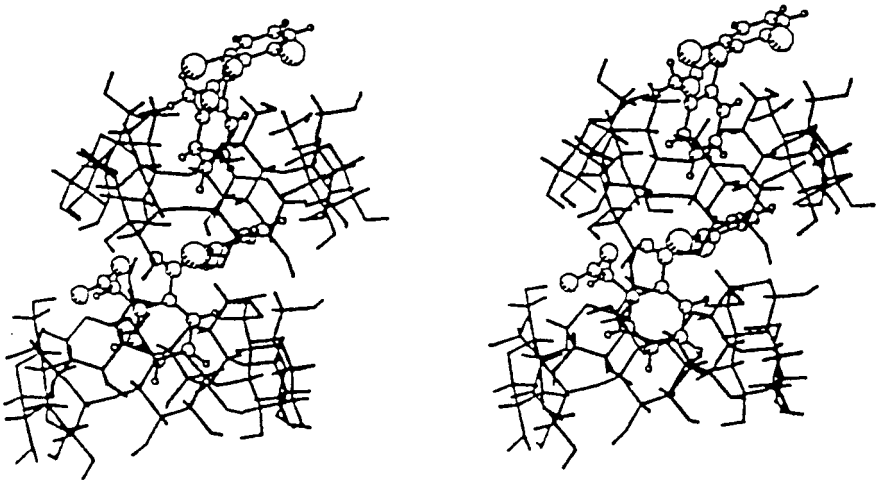

Figure 4. Two diclofenac sodium-β-cyclodextrin complex units related by a sixfold screw axis parallel to the *c*-axis.

dichlorophenyl moiety in **2** in order to accommodate the methyl group in the host cavity. Consequently, the chlorine substituents are shifted away from the middle of the cavity (i.e. the widest part) towards the side of the host where they can no longer fit into the cavity and therefore protrude slightly. This explains the lack of C—H···Cl hydrogen bonds between host and guest in **1**.

The Na^+ ion in **1** is disordered over two sites with site occupancies of 0.6 and 0.4 which are respectively octahedrally and tetrahedrally coordinated by water molecules and host hydroxyl oxygen atoms [14]. In contrast, the Na^+ ion in **2** is ordered and is octahedrally coordinated by oxygen atoms [10].

Figure 6 compares the conformations of the drug anions in the complexes. As indicated earlier, the drug anion in **1** has an intramolecular hydrogen bond which is also observed in two other crystal structures [19] containing the meclofenamate anion. The orientation of the two phenyl rings of the drug with respect to one another in the complex is described by the torsion angles $\tau 1$ and $\tau 2$, C(5)-C(4)-N(3)-C(10) and C(4)-N(3)-C(10)-C(11) (Fig.1), with values of $-126(1)$ and $-176.1(8)°$, respectively. The orientation of the carboxylate group with respect to its attached phenyl ring is described by the torsion angle $\tau 3$, C(10)-C(11)-C(17)-O(19), with a value of $-42(1)°$. Values for the corresponding angles in the crystallographically independent molecules of the other two crystal structures which contain the meclofenamate anion have been calculated using atomic coordinates retrieved from the CSD [13]. The two crystal structures are ethanolamine meclofenamate and choline meclofenamate [19]. The values obtained for the three torsion angles in these structures are 113, -175, 10° and 99, -175, 0° respectively for the two independent molecules in the former structure, and 111, -174, 0° and -109, 175, $-9°$ respectively for the two independent molecules in the latter. The conformations of the two independent molecules in the ethanolamine meclofenamate structure

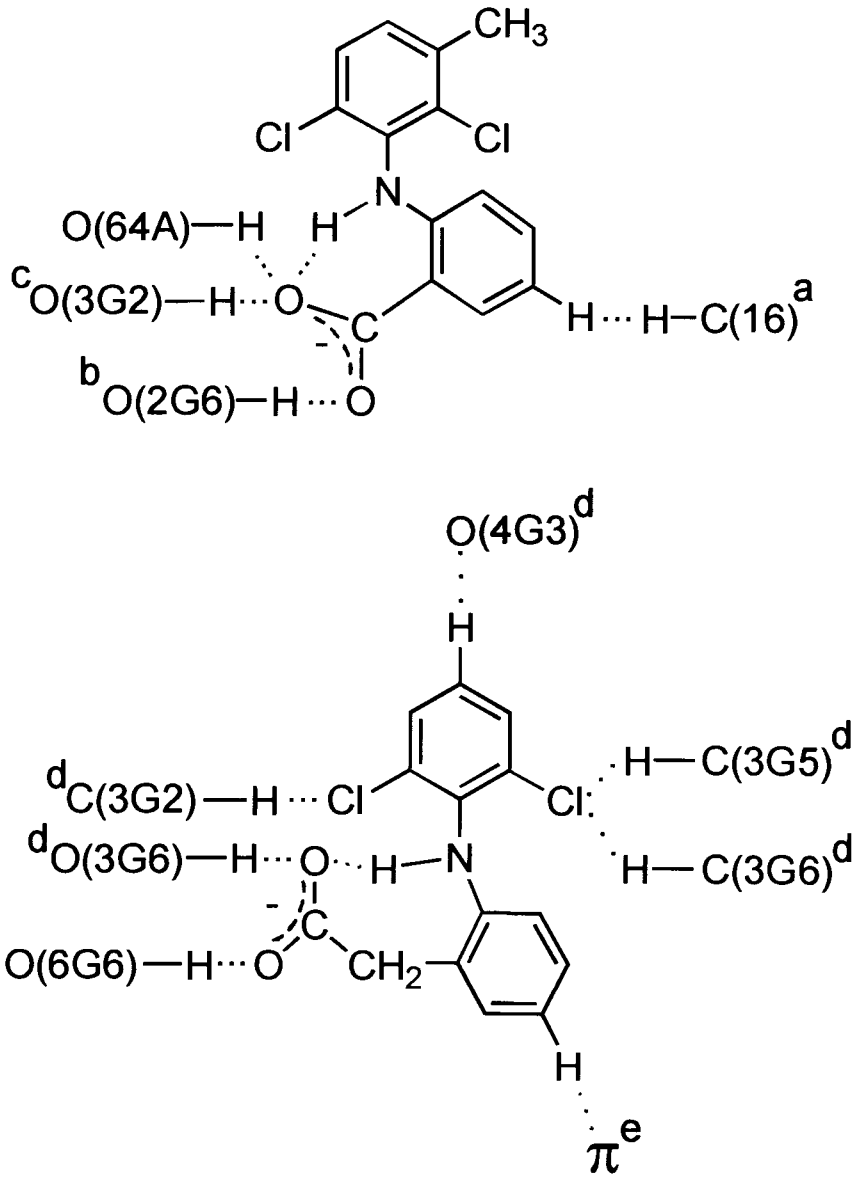

Figure 5. Schematic diagram showing host/guest–guest interactions in complex **1** (top) and complex **2** (bottom). Equivalent positions: (a) $-x$, $y-1/2$, $-z+1/2$; (b) $-x+1$, $y+1/2$, $-z+1/2$; (c) $-x$, $y+1/2$, $-z+1/2$; (d) y, $-x+y$, $z-1/6$; (e) $x-y$, x, $z+1/6$.

are very similar and, since the space group is centrosymmetric, the mirror images of the two molecules are also generated. Choline meclofenamate does not crystallise in a centrosymmetric space group, but the two independent molecules in this case are very nearly mirror images of one another. The conformation of the meclofenamate anion in **1** is most similar to that of the mirror image of the first molecule in ethanolamine meclofenamate, the largest difference lying in $\tau 3$. In the crystal structures of ethanolamine meclofenamate and choline meclofenamate, the carboxylate group is always coplanar or nearly coplanar with its attached phenyl ring. However, in **1** it is twisted out of the plane of the phenyl ring to maintain the drug intramolecular N—H···O hydrogen bond. An analogous guest intramolecular hydrogen bond occurs in **2**. Similar detailed examination of the four torsion angles which describe the conformation of the diclofenac anion in the crystal structures of both **2** and diclofenac sodium tetrahydrate [20] yields analogous results to those for **1**, thus emphasising not only the tendency of guests to maintain their preferred conformations (if possible) on complexation with cyclodextrins, but also the host's ability to discriminate between mirror image conformers of guest molecules [21].

In contrast to the situation in complex **2**, where the diclofenac anion is almost completely enveloped in an infinite helical host channel, host molecules in **1** related by the 2_1-axis parallel to *b* do not shield the guest completely from the intermolecular space since the axis of the host makes an angle of 9.4° with the *b*-axis, leaving the guest somewhat exposed on one side. Successive guest molecules in this direction also do not show the same weakly attractive C—H···π interaction (Figure 5) as in **2**, but there is nevertheless a close contact between a hydrogen atom of the phenylcarboxylate group and the methyl group of the dichloromethylphenyl moiety of the 2_1-related guest molecule.

Monomeric β-cyclodextrin complexes usually pack in a herring-bone arrangement [22], but two which pack in molecular layers roughly perpendicular to the axes of the host molecules have been reported, viz. those of the pyridine- [23] and 1,4-diazabicyclo[2.2.2]octane-β-cyclodextrin [17] complexes. The sulfathiazole-β-cyclodextrin complex [15], which is isomorphous with the latter, and the diclofenac sodium-β-cyclodextrin complex **2** [10] are also examples of monomeric β-cyclodextrin complexes with layered structures. Although the meclofenamate sodium-β-cyclodextrin complex **1** is monomeric and columns of complex units stack head-to-tail in screw-channel fashion along the *b*-axis as in the 1,4-diazabicyclo[2.2.2]octane-β-cyclodextrin complex, the sulfathiazole-β-cyclodextrin complex and the diclofenac sodium-β-cyclodextrin complex **2** (*c*-axis in this case), the crystal packing arrangement does not form molecular layers. The two additional twofold screw axes parallel to the *a*- and *c*-axes result in adjacent columns along *c* being antiparallel and shifted by approximately half a complex unit along *b* (Figure 7). This packing arrangement, although unique for a complex of unsubstituted β-cyclodextrin, is not unlike the arrangement seen in the majority of known complexes of heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin (TRIMEB), which also crystallise in the space group $P2_12_12_1$ [24–27]. The unit cell parameters for the

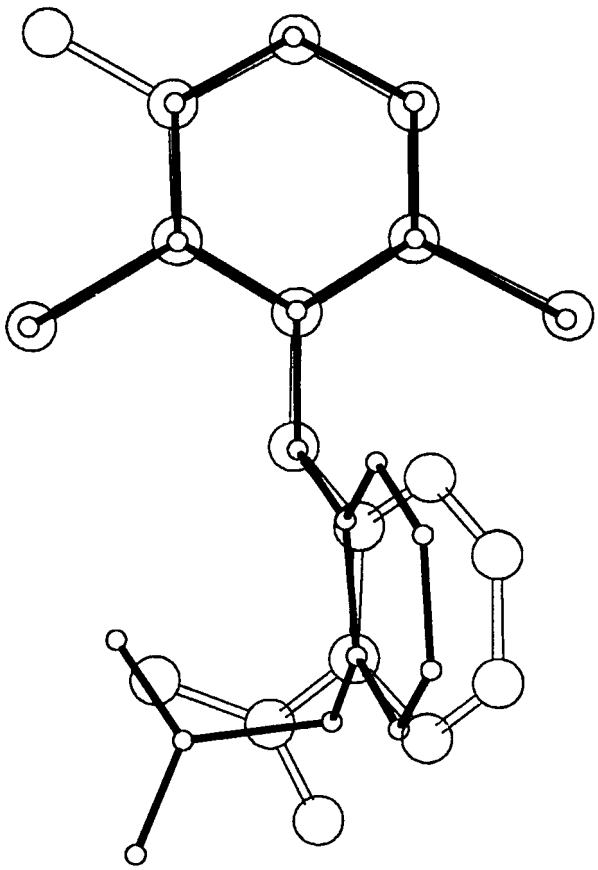

Figure 6. Superposition of the anionic guests in **1** (large open circles, unshaded bonds) and **2** (small circles, shaded bonds).

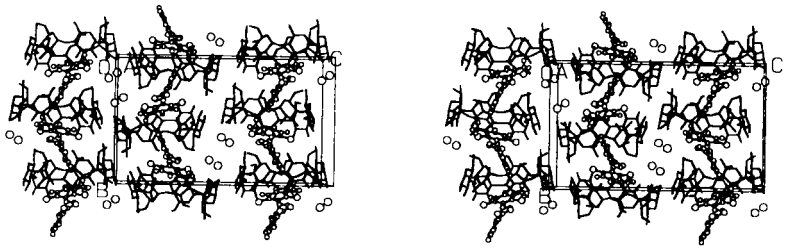

Figure 7. Stereo packing diagram of complex **1** viewed down the *a*-axis (the disordered Na^+ ion is represented by two large open circles and the water molecules have been omitted).

p-iodophenol-TRIMEB complex [23] (PIPTMB) are a = 14.997 Å, b = 21.368 Å and c = 28.205 Å. The b-axis in PIPTMB is longer by approximately 3.5 Å, as might be expected, on account of the additional methyl groups which increase the height of the host. In contrast, the c-axis is shorter by approximately 1.5 Å despite the fact that the much larger tilt angles in TRIMEB, together with the presence of the methyl groups, are expected to increase the diameter of the host, at least at the O(2), O(3) side of the molecule. On closer inspection, however, the reason for the apparent anomaly becomes clearer. Adjacent columns along the c-axis are not as closely packed in complex **1** because the Na^+ ions are accommodated between them (Figure 7). In addition, complex **1** also contains in its crystal structure many more water molecules than PIPTMB (sixteen as opposed to four), which fill the intermolecular spaces.

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References

1. *South African Medicines Formulary*, edited by C. J. Gibbon and C. R. Swanepoel, CTP Book Printers, Western Cape, South Africa (1995).
2. T. Loftsson, B. J. Olafsdottir, H. Frioriksdottir and S. Jonsdottir: *Eur. J. Pharm. Sci.* **1**, 95 (1993).
3. L. Santucci, S. Fiorucci, L. Patoia, F. Farroni, A. Sicilia, S. Chiucchiu, L. Bufalino and A. Morelli: *Drug Invest.* **2**(Suppl. 4), 56 (1990).
4. F. J. Otero-Espinar, S. Anguiano Igla, J. Blanco Mendez and J. L. Vilajato: *Int. J. Pharm.* **70**, 35 (1991).
5. C. M. Adeyeye and P. Li: *Analytical Profiles of Drug Substances*, Volume 19, Academic Press Inc., California, U.S.A. (1990).
6. *The Merck Index*, 11th edition, edited by S. Budavari, M. J. O'Neil, A. Smith and P. E. Heckelman, Merck and Co. Inc, New Jersey, U.S.A. (1989).
7. K. Ikeda, K. Uekama and M. Otagiri: *Chem. Pharm. Bull.* **23**, 201 (1975).
8. K. Ikeda, K. Uekama, M. Otagiri and M. Hatano: *J. Pharm. Sci.* **63**, 1168 (1974).
9. M. Oragiri, J. H. Perrin, K. Uekama, K. Ikeda and K. Takeo: *Pharm. Acta Helv.* **51**, 343 (1976).
10. M. R. Caira, V. J. Griffith, L. R. Nassimbeni and B. van Oudtshoorn: *J. Chem. Soc., Chem. Commun.* 1061 (1994).
11. M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, G. Polidori, R. Spagna and D. Viterbo: *J. Appl. Crystallogr.* **22**, 389 (1989).
12. G. M. Sheldrick, *J. Appl. Crystallogr.*, In prep.
13. *Cambridge Structural Database and Cambridge Structural Database System*, October 1995, Version 2.3.7, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Cambridge, England.
14. M. R. Caira, V. J. Griffith and L. R. Nassimbeni: *J. Therm. Anal.* **51**, 981 (1998).
15. M. R. Caira, V. J. Griffith, L. R. Nassimbeni and B. van Oudtshoorn: *J. Incl. Phenom.* **17**, 187 (1994).
16. W. Saenger: *Inclusion Compounds*, edited by J. L. Atwood, J. E. D. Davies and D. D. MacNicol, Academic Press, London, Volume 2, Chapter 8 (1984).

17. K. Harata: *Bull. Chem. Soc. Jpn.* **55**, 2315 (1982).
18. Lindner, K.; Saenger, W. *Angew. Chem. Int. Ed. Engl.* **17**, 694 (1978).
19. V. Dhanaraj and M. Vijayan: *Biochim. Biophys. Acta* **924**, 135 (1987).
20. G. Reck, G. Faust and G. Dietz: *Pharmazie* **43**, 771 (1988).
21. G. Tsoucaris, G. Le Bas, N. Rysanek and F. Villain: *J. Incl. Phenom.* **5**, 77 (1987).
22. D. Mentzafos, I. M. Mavridis, G. Le Bas and G. Tsoucaris: *Acta Crystallogr.* **B47**, 746 (1991).
23. C. de Rango, P. Charpin, J. Navaza, N. Keller, I. Nicolis, F. Villain and A. W. Coleman: *J. Am. Chem. Soc.* **114**, 5475 (1992).
24. K. Harata, K. Uekama, M. Otagiri and F. Hirayama: *Bull. Chem. Soc. Jpn.* **56**, 1732 (1983).
25. K. Harata, K. Uekama, T. Imai, F. Hirayama and M. Otagiri: *J. Incl. Phenom.* **6**, 443 (1988).
26. K. Harata, F. Hirayama, H. Arima, K. Uekama and T. Miyaji: *J. Chem. Soc., Perkin Trans. 2*, 1159 (1992).
27. D. Mentzafos, I. M. Mavridis and H. Schenk: *Carbohydr. Res.* **253**, 39 (1994).