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The Crystal Structure of the Inclusion Complex of the Sodium Salt of Piroxicam with β-cyclodextrin

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The structural characterization by X-ray diffraction analysis of the title compound is reported. Crystallographic details are: $C_{42}H_{70}O_{35}\cdot C_{15}H_{12}N_3O_4SNa\cdot 8D_2O$, triclinic, space group P1, $a = 14.767(3)$, $b = 12.237(2)$, $c = 11.537(2)$ Å, $\alpha = 79.49(1)$, $\beta = 110.91$-(1), $c = 104.61(1)°$, $d_{calc} = 1.460$ g/cm^3, $Z = 1$, $R = 0.045$ for 6635 observed reflections. The crystal structure consists of head-to-tail β-cyclodextrin molecules (β-CD) linked together by piroxicam anions in infinite polymeric chains running along the *c* axis. In a chain each β-CD molecule takes up simultaneously two guest molecules including on the secondary hydroxyl end the benzene ring and on the primary hydroxyl end the pyridine ring of two adjacent piroxicam anions. The piroxicam anion is located with its central hydrophilic moiety at the interface between two adjacent β-CD molecules, forming with them hydrogen bonds through the enolate and amide oxygen atoms. Conformation of piroxicam is different from those observed for its neutral and zwitterionic forms. It assumes the *ZZE* conformation expected for the enolate. The six-coordinated sodium cation acts as a bridge between adjacent polymeric chains linking them along the *b* axis. This results in the formation of hydrophilic channels filled by deuterium oxide molecules.

Keywords: β-cyclodextrin, piroxicam, drug, solid state structure, inclusion

INTRODUCTION

The cyclodextrins (CD) are widely used for formulations of drugs and cosmetics because of their ability to form inclusion complexes. The guest molecule, surrounded or incapsulated by CD, shows advantageous changes in its physical and chemical properties such as stability, solubility and bioavailability [1].

Piroxicam, a non-steroidal antiinflammatory and analgesic drug, is an intrinsically interesting chemical compound by virtue of its tautomeric switches [2–5] and of possessing a variety of possible donor sites. Its donor ability toward metal centres has been recently investigated [6, 7].

The interactions between piroxicam and β-CD in aqueous solution were investigated by circular dichroism, UV spectroscopy and phase solubility curves [8a]. Evidence that both aromatic ends of piroxicam are alternately included in the cavity of β-CD was obtained from ^{1}H-NMR spectra carried out in aqueous solution on

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the sodium salt of piroxican complexed with β-CD [8b]. However a conclusive indication on the topology of the inclusion compound and the nature of the host–guest interactions could not be obtained.

The present X-ray crystal structure determination was undertaken in order to examine the binding of piroxicam in the cavity of β-CD and to elucidate the role played by the sodium cation in assembling the molecules. The structural investigation is important in order to analyse both the ligating ability of the drug and the effects of inclusion on its conformation. The results could be significant in the studies of the biopharmaceutic of piroxicam as well as in the application of cyclodextrins as drug carriers.

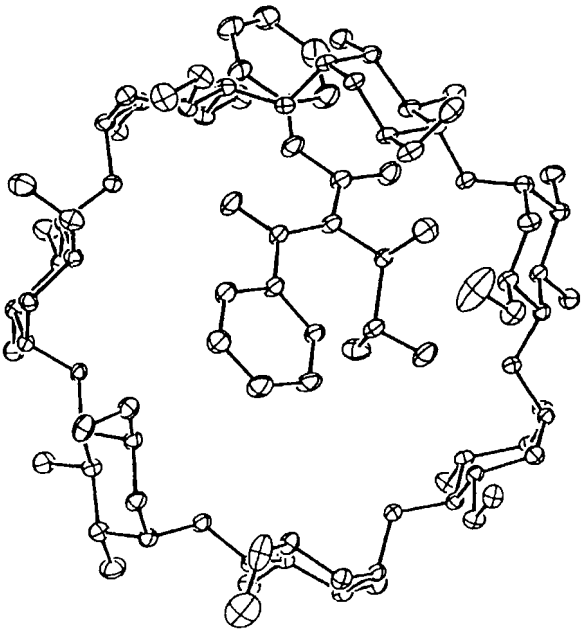


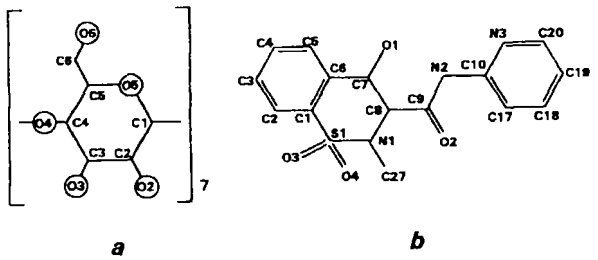
FIGURE S1 An ORTEP drawing of a β-CD-piroxicam unit (30% probability ellipsoids).

RESULTS AND DISCUSSION

Host–Guest Interaction

In the triclinic unit cell there are a β-cyclodextrin molecule (β-CD), a piroxicam anion, a sodium cation and eight deuterium oxide (water-d_2) molecules of crystallization. The numbering scheme adopted for cyclodextrin uses a two-digit code as follows: the first digit represents the individual glucose residue and the second digit represents atoms within the glucose residue (Scheme 1a). The arbitrary numbering scheme adopted for piroxicam is given in the Scheme 1b.

The inclusion complex consists of an infinite channel of head-to-tail β-CD molecules filled by piroxicam anions and running along the *c* axis. The β-CD molecular axis (defined as the normal to the best mean plane through the secondary hydroxyl oxygen atoms) is tilted by 28.4(1)° with respect to the *c* axis resulting in a zig-zag chain of β-CD molecules. Figure 1 shows a perspective view of a polymeric chain.



SCHEME 1 Arbitrary labeling scheme adopted (a) for β-CD, (b) for piroxicam.

Each β-CD molecule includes the aromatic ends of two adjacent piroxicam enolates. Piroxicam enters the cavity of two adjacent head-to-tail β-CD molecules pointing the benzene ring towards the secondary hydroxyl end (tail) and the pyridine ring towards the primary hydroxyl end (head) respectively (Fig. 1). The encapsulation of the benzene ring inside the cavity gives rise to CH...O van der Waals contacts involving the C2, C3, C4 ring atoms and the secondary (O43) and glycosidic (O54, O64) oxygen atoms respectively as shown in Figure 2a. The pyridine ring points the hydrogen atom bonded to C19 towards the glycosidic $O14^{i}$ oxygen atom (Fig. 2b). The geometries of the C—H...O contacts are quoted in Table IA. These findings confirm the model of interactions between piroxicam

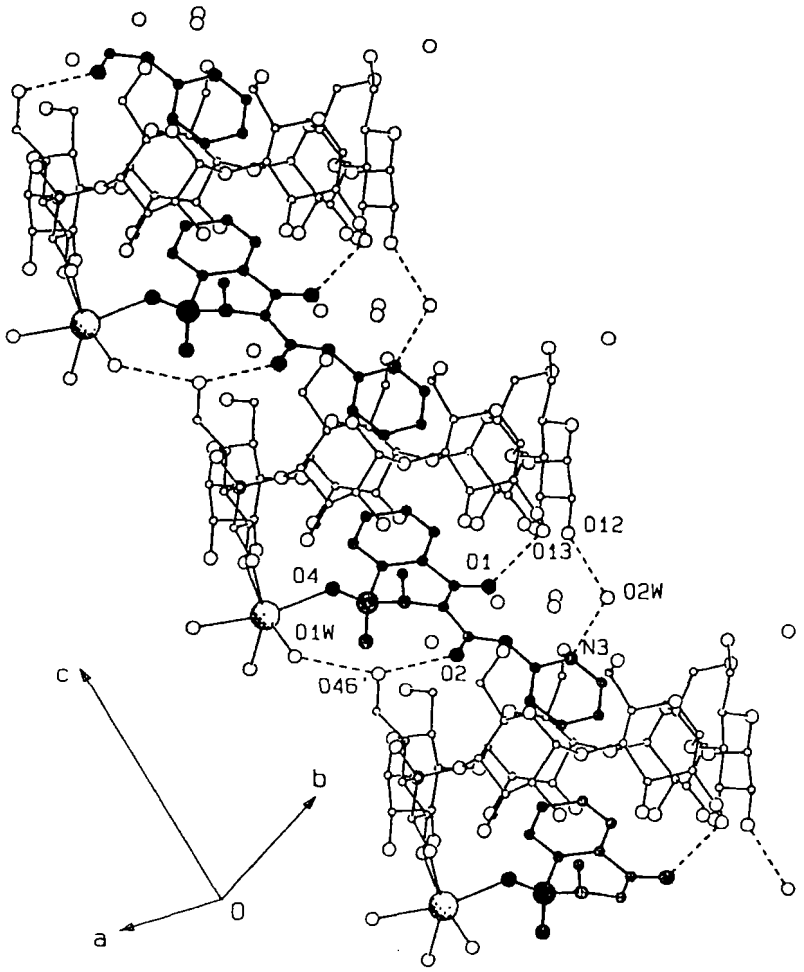


FIGURE 1 A SCHAKAL perspective view of a polymeric chain.

and β-CD in solution based on NOE measurements [8b].

As shown in Figure 1 the central hydrophilic moiety of piroxicam lies within the interface between two β-CD molecules forming hydrogen bonds between the O1 enolate oxygen and the O13 secondary hydroxyl and between the O2 amide oxygen and the $O46^{i}$ primary hydroxyl (Tab. IB). The O2W water-d_2 molecule contributes to the stabilization of the inclusion compound by bridging host and guest through hydrogen bonds involving the O12 secondary hydroxyl oxygen and the N3 pyridine nitrogen (Tab. IB). In the chain the distance between the mean planes through primary and secondary oxygen atoms of adjacent β-CD molecules is 4.454(16) Å. Piroxicam is oriented in adjacent cavities with the C3...C19 axis tilted by 48.8(4)° with respect to the β-CD molecular axis and by 20.6(1)° with respect to the *c* axis.

Sodium Cation Environment and D_2O Molecules

The sodium cation is anchored to the inclusion complex through the O4 sulphonic oxygen of piroxicam and the O42 and O43 secondary oxygens of β-CD (Tab. IIA). It behaves as a bridge between adjacent polymer chains along the *b* axis being bonded to the $O25^{ii}$ and $O26^{ii}$

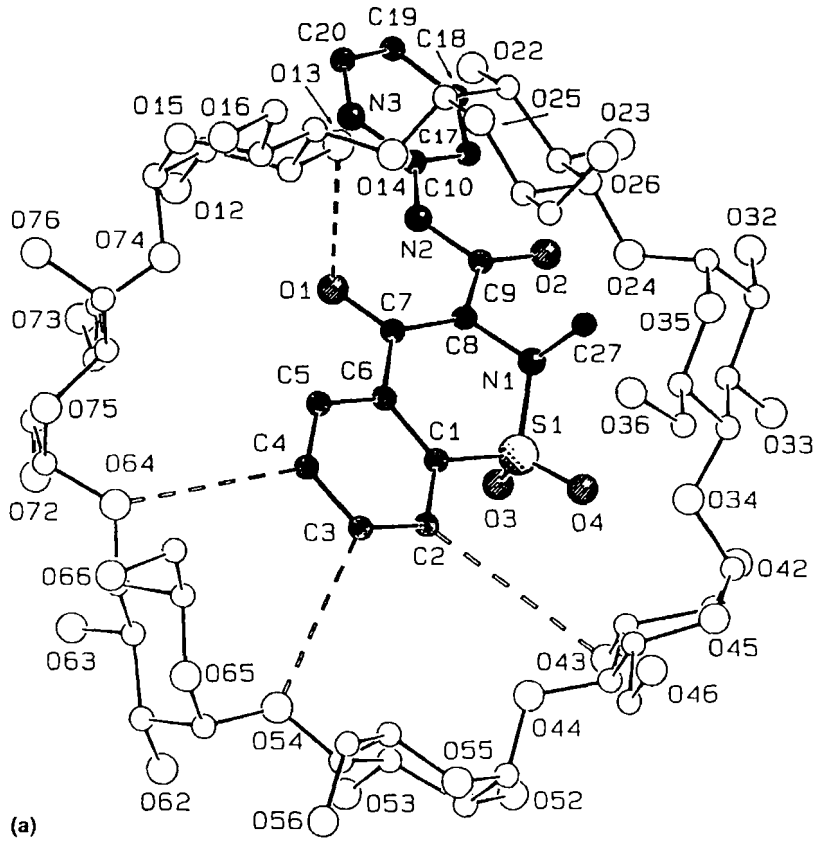


FIGURE 2 A SCHAKAL drawing showing host–guest interactions: (a) between piroxicam and β-CD. (b) between piroxicam and β-CD translated by $x, y, z-1$.

oxygen atoms (Fig. 3). The six-coordination is achieved through the O1W water-d_2 molecule (Tab. II) which is also engaged in a hydrogen bond with the $O46^{i}$ primary hydroxyl (Tab. ID). Along the *b* direction the cohesion is also ensured by a hydrogen bond between the O53 and $O16^{ii}$ hydroxyl groups (O53...$O16^{ii}$, 2.702 Å; O53—H53...$O16^{ii}$ 161°; $ii = x, -1+y, z$). This arrangement of the polymeric chains produces hydrophilic channels filled with water-d_2 molecules (Fig. 3).

β-CD Geometry and Conformation

Bond distances, bond angles and torsion angles within the β-CD molecule are unexceptional. β-CD assumes the usual torus conformation with an approximately circular section stabilized by intramolecular hydrogen bonds between secondary hydroxyl groups of adjacent glucose moieties. The glucose units 1, 3, 5 act as H-donors, the glucose units 2, 4, 6 act as H-acceptors, while the glucose units 7 acts both as H-donor and -acceptor, as it can be seen from the data given in Table IC based on the direct localization of H atoms. H-bonds lie in the usual range with the exception of the O62...O53 distance [3.183(5) Å] which suggests a slightly weaker hydrogen bond.

The primary hydroxyl groups of the glucose units 2, 5, 6, 7 assume *gauche*$^+$–*gauche*$^-$ orientations (Tab. IIIA) and point outside the macrocycle cavity. The primary hydroxyl groups of the glucose units 1, 3, 4 point inward the cavity, the

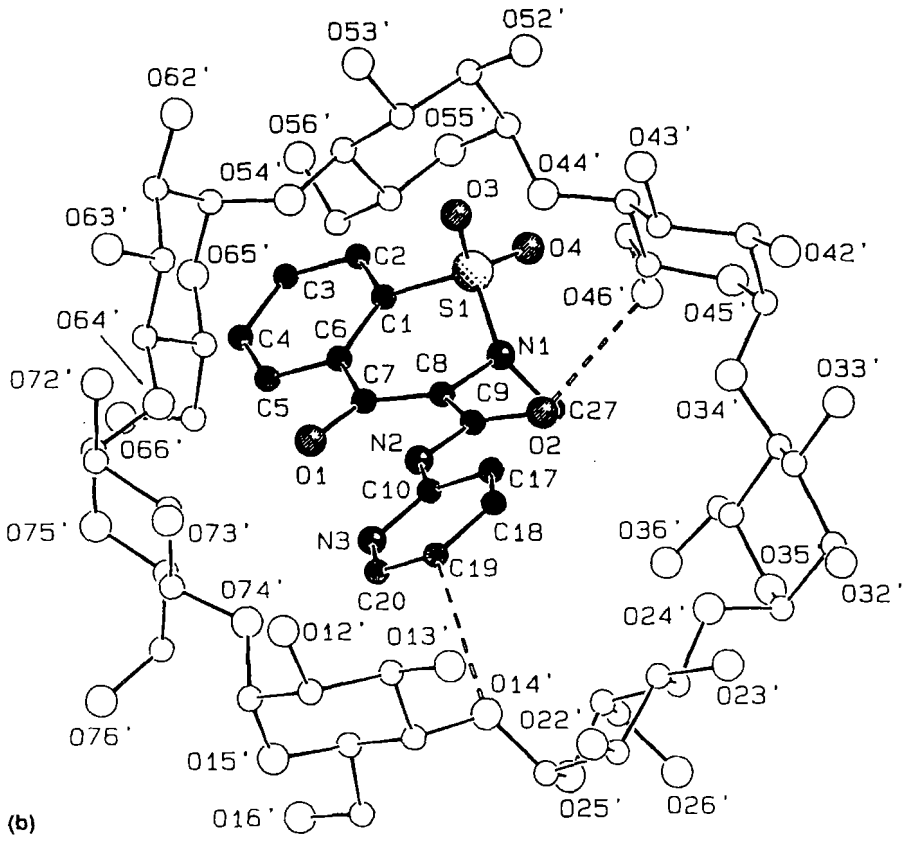


FIGURE 2 (Continued).

C6 —O6 bond being *trans* to the C4 —C5 bond and *gauche*$^+$ to the O5 —C5 bond. Except for O46, H-bonded to piroxicam, the primary hydroxyl ends are hydrogen-bonded to water-d_2 molecules (Tab. ID). The simultaneous insertion of the planar benzene and pyridine rings inside the cavity does not severely affect the cross section of β-CD as indicated by the values of the $O4_n \cdots O4_{n+1}$ distances (average value 4.37(2) Å) and of the C4-O4$\cdots$C1′ angles (average value 118.2(4)°) which are in good agreement with those reported in the literature for β-CD. The average value of 128.4(13)° for the $O4_n \cdots O4_{n+1} \cdots O4_{n+2}$ angles is consistent with the value expected for an ideal heptagon. The glucose units are in the usual $^4C_1$ chair conformation as indicated by the Cremer and Pople puckering parameters listed in Table IIIB.

Piroxicam Geometry and Conformation

Bond distances and angles within piroxicam (Tab. IIB) are in a very good agreement with those found in the free enolate [5], confirming that the deprotonation occurs at the enol oxygen site, as evidenced by the X-ray analysis. Piroxicam shows a *ZZE* conformation stabilized by a strong intramolecular hydrogen bond [N2...O1, 2.635(7) Å, N2 —H1...O1, 143°]. This conformation is similar to that found for the free anion and differs from those found for the free zwitterion (ZZZ) [2], for the free neutral molecule (*EZE*) [3], and for the complexed anion (ZZZ) [6]. The chain C8, C9, O2, N2 is not coplanar with the pyridyl ring, the dihedral angle being 18.5(2)°. The thiazine ring exhibits a half chair conformation, S1 and N1 being

TABLE I Selected interatomic distances (Å) and angles (°)

A. β-CD – piroxicam C —H...O contacts less than 3.9 Å			
C2...O43	3.873 (6)	C2 —H2...O43	171
C3...O54	3.690 (7)	C3 —H3...O54	162
C4...O64	3.583 (7)	C4 —H4...O64	160
C19...O14^{i}	3.741 (6)	C19 —H19...O14^{i}	151
B. β-CD – piroxicam hydrogen bonds			
O1...O13	2.935 (5)	O1...H13O —O13	169
O2...O46^{i}	2.790 (5)	O2...H46O^{i} — O46^{i}	144
N3...O2W	2.960 (8)	N3...H22W —O2W	177
O12...O2W	2.752 (6)	O12 —H12O...O2W	173
C. Intramolecular hydrogen bonds within β-CD			
O22...O13	2.779 (4)	O22 —H22O...O13	143
O23...O32	2.898 (4)	O23 —H23O...O32	175
O42...O33	2.680 (4)	O42 —H42O...O33	166
O43...O52	2.823 (4)	O43 —H43O...O52	162
O62...O53	3.183 (5)	O62 —H62O...O53	162
O63...O72	2.726 (4)	O63 —H63O...O72	160
O73...O12	2.788 (5)	O73 —H73O...O12	163
D. β-CD – D_2O interactions			
O16...O5W	2.841(10)	O16 —H16O...O5W	170
O26...O7W	2.864(11)	O26 —H26O...O7W	168
O36...O4W	2.958(12)	O36...H41W —O4W	163
O56...O6W	2.79 (2)	O56 —H56O...O6W	151
O66...O3W	2.746 (5)	O66 —H66O...O3W	175
O52...O4W^{ii}	2.774 (6)	O52 —H52O...O4W^{ii}	177
O1W...O46^{i}	2.844 (5)	O1W —H12W...O46^{i}	157
O1W...O63^{iii}	2.831 (6)	O1W —H11W...O63^{iii}	166
O2W...O53^{v}	2.886 (5)	O2W —H21W...O53^{v}	168
O22...O4W^{i}	2.844 (7)		
O23...O8W	2.910(14)		
O73...O3W^{i}	2.921 (8)		
O76...O5W	2.832 (7)		
E. β-CD – β-CD and D_2O – D_2O interactions			
O53...O16^{ii}	2.702 (5)	O53 —H53O...O16^{ii}	161
O32...O75^{iii}	2.807 (5)	O32 —H32O...O75^{iii}	149
O33...O66^{iii}	2.642 (4)	O33 —H33O...O66^{iii}	169
O72...O45^{iv}	2.768 (3)	O72 —H72O...045^{iv}	169
O5W...O6W^{v}	2.847 (19)	O5W —H52W...O6W^{v}	145
O3W...O6W	2.941 (14)		
O8W...O7W^{i}	3.03 (3)		

i = *x*, *y*, *z*−1; *ii* = *x*, *y*−1, *z*; *iii* = *x*+1, *y*, *z*; *iv* = *x*−1, *y*, *z*−1; *v* = *x*, *y*+1, *z*−1.

displaced by 0.316(1) and −0.435(4) Å, respectively, from the plane defined by C1, C6, C7, C8.

CONCLUSIONS

The present work unambiguously shows that β-CD is able to take up simultaneously two aromatic rings. The main driving forces for the complexation are provided (i) by C —H...O interactions between the aromatic ends of the guest and the O4 glycosidic oxygens at the inner surface of β-CD, and (ii) by hydrogen bonds involving the hydrophilic moiety of the guest and the primary and secondary ends of adjacent β-CD molecules. The β-CD molecules and piroxicam are mutually oriented to lead to the best fit for complexation favoured by the *ZZE* conformation of piroxicam. Piroxicam is confirmed to be a very interesting chemical compound: it interacts with the alkali cation through the O4 sulphonic oxygen, the N and O donor

TABLE II Selected bond distances (Å) and angles (°)

A. Within the sodium coordination sphere			
Na1–O25^{ii}	2.389 (3)	Na1–O43	2.365 (4)
Na1–O26^{ii}	2.404 (4)	Na1–O4	2.393 (4)
Na1–O42	2.291 (3)	Na1–O1W	2.256 (5)
O4–Na1–O1W	85.2 (1)	O26^{ii} –NA1–O4	166.5 (1)
O43–Na1–O1W	168.2 (2)	O26^{ii} –NA1–O43	82.2 (1)
O43–Na1–O4	84.8 (1)	O25^{ii} –NA1–O42	156.5 (1)
O26^{ii} –Na1–O1W	107.5 (2)		
B. Within the piroxicam anion			
S1–O3	1.431 (4)	N2–C9	1.367 (5)
S1–O4	1.426 (3)	N2–C10	1.387 (7)
S1–N1	1.614 (3)	N3–C10	1.332 (6)
S1–C1	1.758 (5)	N3–C20	1.345 (7)
O1–C7	1.285 (5)	C6–C7	1.487 (7)
O2–C9	1.240 (6)	C7–C8	1.390 (7)
N1–C8	1.444 (5)	C8–C9	1.458 (7)
N1–C27	1.477 (5)		
S1–N1–C27	118.3 (3)	O1–C7–C8	124.0 (4)
S1–N1–C8	114.1 (3)	N1–C8–C7	121.5 (4)
C8–N1–C27	117.1 (3)	C7–C8–C9	125.5 (4)
C9–N2–C10	128.7 (5)	N1–C8–C9	113.0 (4)
C10–N3–C20	116.5 (5)	N2–C9–C8	114.9 (4)
O1–C7–C6	117.3 (4)	O2–C9–C8	122.4 (4)
C6–C7–C8	118.8 (4)	O2–C9–N2	122.7 (4)

$ii = x, y-1, z$.

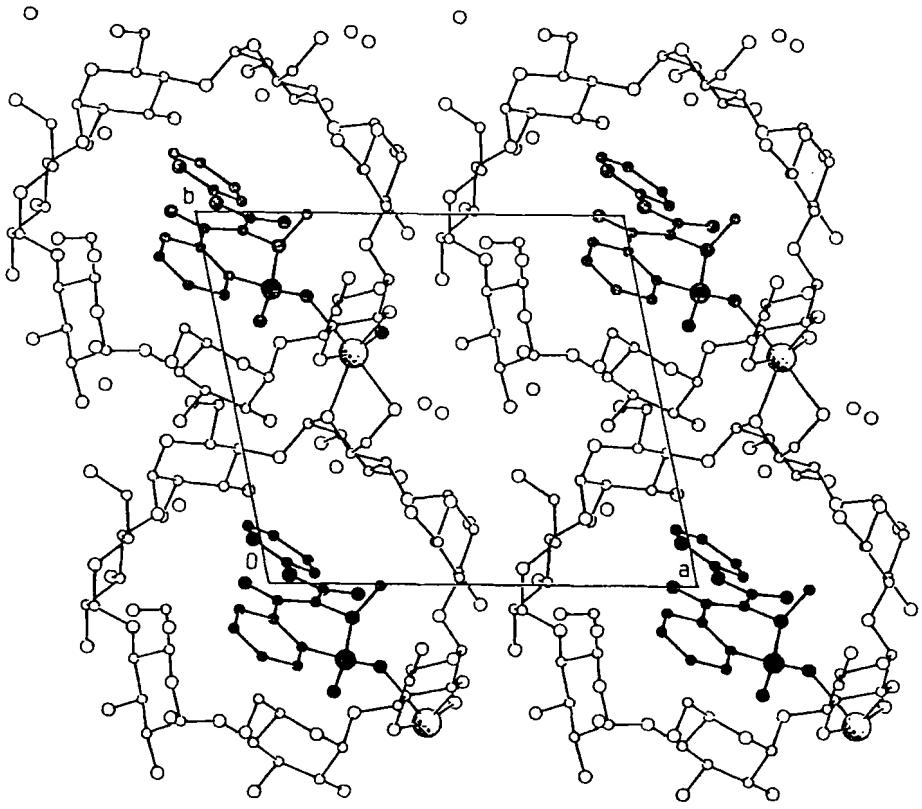


FIGURE 3 A SCHAKAL projection of the structure onto the (001) plane.

TABLE III (A) Selected torsion angles (°) describing the linkage between the glucose residues and the orientation of the primary hydroxyls; (B) puckering parameters of glucose units

	G1	G2	G3	G4	G5	G6	G7
A							
C(3) n–C(4)n–O(4)n–C(1)n+1	136.9 (4)	129.1 (4)	108.2 (3)	136.3 (3)	145.2 (3)	113.9 (3)	119.0 (3)
C(5) n–C(4)n–O(4)n– C(1)n+1	−104.3 (4)	−111.7 (4)	−134.1 (3)	−103.0 (4)	−94.2 (4)	−128.4 (3)	−121.3 (3)
O(5) n–C(1)n–O(4)n – 1–C(4)n – 1	107.0 (4)	124.7 (4)	107.7 (4)	111.6 (3)	122.1 (3)	107.4 (4)	106.3 (3)
C(2) n–C(1)n–O(4)n – 1–C(4)n – 1	−132.9 (3)	−113.8 (4)	−132.8 (4)	−127.6 (3)	−116.9 (3)	−130.9 (4)	−132.6 (3)
C(4) n–C(5)n–C(6)n–O(6)n	−179.5 (4)	53.8 (5)	−170.7 (5)	179.7 (3)	55.2 (7)	66.3 (5)	53.6 (5)
O(5) n–C(5)n–C(6)n–O(6)n	58.9 (5)	−65.8 (5)	67.2 (6)	59.6 (4)	−65.0 (6)	−53.4 (5)	−68.1 (5)
B							
Q (Å)	0.579 (4)	0.568 (4)	0.576 (4)	0.589 (3)	0.559 (4)	0.591 (5)	0.564 (4)
θ (°)	3.1 (4)	5.1 (4)	2.3 (5)	7.8 (3)	4.2 (4)	3.8 (5)	1.3 (4)

atoms involved in piroxicam–metal complexes being here engaged in complexation with β-CD molecules. Most of the D_2O molecules are space fillers except two of them (O1W and O2W) which contribute to complexation.

MATERIALS AND METHODS

Materials

β-cyclodextrin (water content 11%) (Roquette Company, Lestrem, France), piroxicam (Secifarma, Milano, Italy) were used as received.

Preparation

Piroxicam (330 mg, 1.0 mmol) was dissolved in a warm 1.0 M solution of NaOH in D_2O (1 ml). β-Cyclodextrin (1.26 g, corresponding to 1.0 mmol of anhydrous product) and D_2O (1 ml) were added and the mixture warmed until a clear yellow solution was obtained. After standing at room temperature overnight, a gel containing suspended crystals of β-CD was formed; the β-CD crystals were eliminated by filtration after the mass was fluidified by gentle warming. The resulting solution was heated to 90°C, maintained at this temperature in an open flask until almost dryness and then left at room temperature for two days. From the heterogeneous solid mixture obtained, yellow crystalline agglomerates were isolated and recrystallized from D_2O to give pale yellow crystals suitable for X-ray analysis.

X-Ray Diffraction Analysis

A pale yellow prismatic crystal of dimensions $0.18 \times 0.26 \times 0.54$ mm was glued on a glass fiber and mounted on a Siemens AED single crystal diffractometer equipped with graphite-monochromated Cu Kα radiation ($\lambda = 1.54178$ Å). The reduced cells were obtained with use of TRACER [8]. Crystal data and details associated with data collection are given in Table IV. A total of 6904 data were collected at 295 K with a $\theta/2\theta$ scan mode up to 140° in 2θ. For intensities and background the individual reflection profiles were analyzed [9]. The structure amplitudes were obtained after the usual Lorentz and polarization corrections [10] and the absolute scale was established by the Wilson method [11]. The intensities of three standard reflections measured every 100 data collected showed no appreciable crystal decay. No correction for absorption was deemed necessary because of the low value of the linear absorption coefficient and the small dimensions of the crystal used. Anomalous scattering corrections were included in all structure factor calculations [12b]. Scattering factors for neutral atoms were taken from Ref. [12a] for nonhydrogen atoms and from Ref. [13] for H. Structure solution and refinement were based on the 6862 unique reflections having $F^2 > 0$.

TABLE IV Crystal data and Experimental Details

Crystal color and habit	pale yellow prisms
Crystal size (mm^3)	$0.18 \times 0.26 \times 0.54$
Molecular formula	$C_{42}H_{70}O_{35} \cdot C_{15}H_{12}N_3O_4SNa \cdot 8D_2O$
Molecular mass	1648.5
Space group	$P\bar{1}$
Unit cell:	
a (Å)	14.767 (3)
b (Å)	12.237 (2)
c (Å)	11.537 (2)
α (°)	79.49 (1)
β (°)	110.91 (1)
γ (°)	104.61 (1)
Volume (Å^3)	1874.6 (6)
Z	1
D_{calc}(g cm^{-3})	1.460
μ (cm^{-1})	13.93
2θ range (°)	6–140
Unique obs data $[I > 2\,\sigma(I)]$	6635
Transmission factors	0.840–1.000
R[b]	0.045 [0.046][a]
$wR2$[c]	0.127 [0.132]
GOF	1.021
Largest shift/esd, final cycle	0.001
Largest peak, e/Å^3	0.50

[a] values in square brackets refer to the "inverted" structure.
[b] $R = \Sigma||\Delta F|/\Sigma|F_o|$ calculated for the unique observed data.
[c] $wR2 = [\sum w|\Delta F^2|^2/\sum w|F_o^2|^2]^{1/2}$ calculated for the unique reflections having $I > 0$; $GOF = [\Sigma w|\Delta F^2|^2/(NO - NV)]^{1/2}$.

The structure was solved by direct methods using SIR-92 [14]. Refinement was carried out first isotropically then anisotropically for all non-H atoms by full matrix least-squares minimizing the function $\Sigma w(\Delta F^2)^2$ using a weighting scheme based on counting statistics $\{w = 1/[\sigma^2(F_0^2) + (aP)^2];\ P = (F_0^2 + 2F_c^2)/3;\ a = 0.0978$ at convergence$\}$ [15]. All the hydrogen atoms of piroxicam and β-CD, but those associated to the O36 and O76 hydroxyl groups, were located from difference Fourier maps, as well as the deuterium atoms of O1W, O2W, O5W and one of those bonded to O4W. Attempts to localize the missing hydrogen atoms on the basis of the hydrogen bonding scheme failed. The hydrogen atoms were introduced in the final refinement as fixed atom contributions with isotropic U's fixed at 0.08 Å^2.

The final difference map showed no unusual feature, the maximum and minimum residual peaks being 0.50 and -0.31 eÅ^{-3} respectively. Since the space group is polar, the crystal chirality was tested by inverting all the coordinates ($x, y, z \rightarrow -x, -y, -z$) and refining to convergence again. The resulting R values ($R = 0.046$, $wR2 = 0.132$) indicated the original choice should be considered the correct one.

Final atomic coordinates for non-H atoms, atomic coordinates for H-atoms, bond lengths, bond angles and anisotropic thermal parameters have been deposited with the Cambridge Crystallographic Data Bank as Supplementary Material.

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