(100 K), which correspond to twice the cone angle subtended at the cage center by the O—D bond length. Thus, it is inferred that the C→Cl vectors are not pointing toward the oxygen vertices, but rather are 'precessing' around these directions coupled to deuteron disorder in molecules $(D_2O)e$ and $(D_2O)g$ by weak attractive interactions.

We are grateful to Mr Joseph Henriques for technical assistance, to Dr Christopher Ashton for use of his computer programs in illustrating spherical harmonics functions, and to Dr Enrique Abola for his help with other computer-graphics displays.

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Crystal and Molecular Structures of the Inclusion Compounds of Cholic Acid with Methanol, Ethanol and 1-Propanol

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Abstract

The 1:1 inclusion compounds of cholic acid with methanol ($C_{24}H_{40}O_5.CH_4O$), ethanol ($C_{24}H_{40}O_5.C_2H_6O$) and 1-propanol ($C_{24}H_{40}O_5.C_3H_8O$) crystallize in the $P2_12_12_1$ space group with unit-cell dimensions at 293 K: $a = 15{\cdot}198$ (6), $b = 11{\cdot}625$ (7), $c = 14{\cdot}560$ (9) Å; $a = 14{\cdot}653$ (7), $b = 11{\cdot}739$ (4), $c = 15{\cdot}045$ (2) Å; and $a = 15{\cdot}026$ (2), $b = 11{\cdot}864$ (9), $c = 14{\cdot}951$ (4) Å; $Z = 4$. The structures were solved using direct methods. Full-matrix least-squares refinement reduced the conventional R factor to values of 0·109, 0·066 and 0·071, respectively. The alcohol molecules are contained in cavities created by the cholic acid molecules and are involved in the hydrogen-bonding scheme consisting of five unique hydrogen bonds. Statistical disorder is observed for the ethanol and 1-propanol molecules.

Introduction

The bile acids are derivatives of the steroid 5β-cholan-24-oic acid. *In vivo*, the bile acids are conjugated with the amino acids glycine and taurine and exist as salts of sodium or potassium in the bile.

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These salts are responsible for many physiological functions, including the promotion of lipid diffusion through intestinal mucosa, the resorption of drugs, vitamins and hormones, the activation/inhibition of various enzymatic reactions and the excretion of cholesterol (Admirand & Small, 1968; Sobotka, 1934). The mechanisms of these functions are not entirely understood although it is likely that the bile salts form micelles in solution to entrap a variety of molecules (Admirand & Small, 1968; Small, 1971).

A great deal of structural work has been carried out on deoxycholic acid ($3\alpha,12\alpha$-dihydroxy-5β-cholan-24-oic acid, DCA) inclusion compounds (choleic acids) in an attempt to understand the physiological roles of bile salts by the examination of the nature of the association between DCA and the included guest molecules (Giglio, 1984, and references therein). This information is also necessary for the use of these compounds in applications such as polymerization (Audisio & Silvani, 1976; Giglio, Mazza & Scaramuzza, 1985; Miyata, Noma, Tsuzuki & Takemoto, 1987), drug transport (Jones, Schwarzbaum & Lessinger, 1982) and regio/stereospecific interactions (Padmanabhan, Ramamurthy & Venkatesan, 1987; Popovitz-Biro, Tang, Chang, Lahav & Leiserowitz, 1985).

However, very little structural work has been undertaken on the naturally abundant cholic acid ($3\alpha,7\alpha,12\alpha$-trihydroxy-5β-cholan-24-oic acid). In solution, cholic acid has been reported complexed with azo dyes (Angelescu & Nicolau, 1965; Cilento, 1951, 1952), stearic and oleic acids (Fernández, López & Aenlle, 1964), and lauric and palmitic acids and *n*-hexanol and *n*-octanol (Angelescu & Nicolau, 1965). Some crystalline compounds have been synthesized including cholic acid with some alcohols, mercaptans (Mylius, 1887) and iodine (Barger & Field, 1912). Only two structural reports of cholic acid inclusion compounds with water (Lessinger, 1982) and ethanol (Johnson & Schaefer, 1972) guest molecules have been reported. These structures belong to the monoclinic and orthorhombic space groups $P2_1$ and $P2_12_12_1$, respectively. In the $P2_1$ space group, the water molecules are included in the hydrophilic region of the bilayer, structurally similar to the tetragonal class of DCA inclusion compounds. The structure of the $P2_12_12_1$ structure will be described in more detail later in this paper.

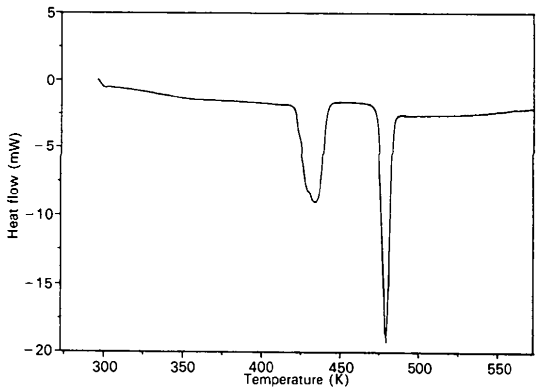

Fig. 1. DSC curve for ECHO. Heating rate 10 K min^{-1} for sample of 8·7 mg.

It was decided to extend the work of Mylius (1887) in which he reported crystalline complexes of cholic acid with various alcohols. Thus, we describe the structures of cholic acid with methanol (MECHO), ethanol (ECHO) and 1-propanol (PRONCH). The inclusion compound with ethanol has been described previously (Johnson & Schaefer, 1972), but has been re-solved by the present authors with modelling of the disorder of the ethanol molecule and an improved *R* value.

Experimental

Transparent tabular crystals were obtained by the slow evaporation of alcoholic solutions (methanol, ethanol, 1-propanol, Merck) of cholic acid (Sigma). Crystals of MECHO are unstable in air. Host–guest ratios were established by density measurements and thermogravimetric analyses (TGA). ECHO and PRONCH gave host–guest ratios of 1:1 while MECHO gave a host–guest ratio which varied from 1:1·4 to 1:3. Combined TGA and differential scanning calorimetry (DSC) experiments yielded the enthalpy change, ΔH_R, as measured for the release of one guest molecule: 45·3 kJ mol^{-1} (PRONCH), 31·7 kJ mol^{-1}(ECHO) and 15·9 kJ mol^{-1} (MECHO). A typical thermogram is shown in Fig. 1.

Density measurements were made by flotation of crystals in a water/saturated KI solution. DSC and TGA analyses were performed on a 951 Du Pont thermogravimetric analyser and 910 Du Pont differential scanning calorimeter at a heating rate of 10 K min^{-1}. Single crystals with dimensions given in Table 1 were mounted on glass fibres for the data collection except in the case of MECHO in which the crystal was mounted in a Lindemann capillary surrounded by its mother liquor.

Data collection

24 reflections in the range $15 \leq \theta \leq 17°$ were used to determine lattice parameters. Intensity data in the range $1 \leq \theta \leq 25°$ were collected on an Enraf–Nonius CAD-4 diffractometer with graphite-monchromated Mo $K\alpha$ radiation at 293 K. The data were recorded in the ω-2θ scan mode with a scan width of $(1{\cdot}0 + 0{\cdot}35\tan\theta)°$ and maximum recording time of 40 s reflection^{-1}. Three standard reflections were monitored for instability during the course of

Table 1. *Additional crystal and final refinement data*

	MECHO	ECHO	PRONCH
M_r	440·63	454·66	468·70
V (Å^3)	2572 (2)	2588 (2)	2665 (2)
D_m (g cm^{-3})	1·175	1·166	1·160
D_x (for $Z = 4$) (g cm^{-3})	1·138	1·167	1·168
μ(Mo $K\alpha$) (cm^{-1})	0·46	0·47	0·46
F(000)	968	1000	1032
Crystal dimensions (mm)	0·30 × 0·35 × 0·38	0·50 × 0·40 × 0·20	0·50 × 0·44 × 0·56
Absorption correction			
Maximum transmission	—	99·98	99·97
Minimum transmission	—	97·50	97·02
Range h	0–17	0–17	0–17
k	0–13	0–13	0–14
l	0–18	0–17	0–17
Standard reflections	3	3	3
Intensity variation (%)	14·6	1·1	2·7
Reflections collected	2574	2599	2671
Observed reflections [$F > 4\sigma(F)$]	1442	1722	2017
Parameters refined	210	243	248
R	0·109	0·066	0·071
wR	0·117	0·070	0·080
$g \times 10^5$*	445	59	63
Maximum Δ/σ	0·001	0·024	0·001
Maximum $\Delta\rho$ (e Å^{-3})	0·74	0·35	0·32
Minimum $\Delta\rho$ (e Å^{-3})	−0·49	−0·26	−0·27

* $w = [\sigma^2(F) + gF^2]^{-1}$.

the data collection. Empirical absorption (North, Phillips & Mathews, 1968), Lorentz and polarization corrections were applied to the data of ECHO and PRONCH. No absorption correction was applied to the data of MECHO owing to the instability of the standard reflections, which had an average intensity variation of 14·6%. Further details of the data collection are given in Table 1.

Structure solution and refinement

The structures were solved by direct methods using *SHELXS*86 (Sheldrick, 1985). All the non-H cholic acid atoms were revealed in the initial E map. The positional and thermal parameters of the host atoms were then refined by full-matrix least squares, minimizing $\sum w(|F_o| - |F_c|)^2$ using the *SHELX*76 program (Sheldrick, 1978). A subsequent three-dimensional difference electron density map was calculated; peaks for the ECHO and PRONCH structures could only be interpreted by invoking statistical disorder of the guest ethanol and 1-propanol molecules. Atomic numbering of the disordered molecules, bond lengths and bond angles are shown in Fig. 2. Although no disorder was observed for methanol, the electron density remaining in the region of the guest cavity was high, consistent with the presence of more methanol molecules as determined by other physical methods.

In the case of the host molecule, the C atoms of the side chain and all the O atoms were modelled anisotropically. All the H atoms of cholic acid were geometrically positioned with a common temperature factor. The guest molecules were treated differently in the three structures. In MECHO, the C and O atoms were refined isotropically and the methyl H atoms were fixed geometrically. In ECHO, the C and O atoms were refined anisotropically and the H atoms fixed geometrically. The bond lengths C(G2)—C(G3) and O(G)—C(G3) were constrained to chemically reasonable distances consistent with the electron density distribution. The refinement of the 1-propanol molecules in PRONCH proved more difficult and the final model adopted a mixture of isotropic and anisotropic atoms for the two disordered moieties. All the bond lengths between non-H guest atoms were constrained. No H atoms were invoked for this guest. All five hydroxyl H atoms, four from the host and one from the guest,

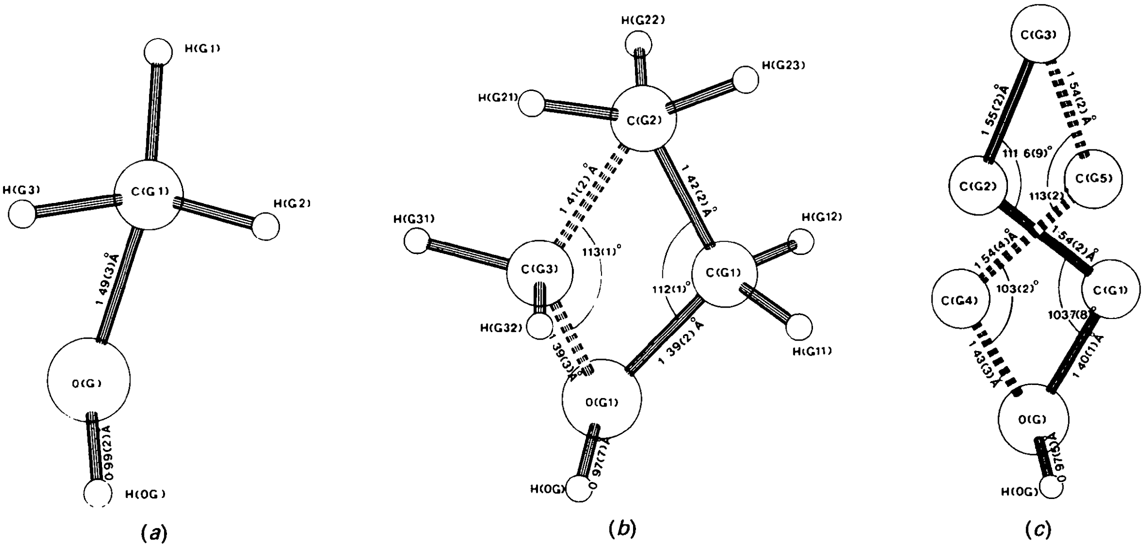

Fig. 2. Atomic numbering, bond lengths and angles for the guest molecules: (*a*) methanol, (*b*) ethanol and (*c*) propanol. The disordered forms are shown with solid and dashed bonds.

were successfully located in the electron density maps. These were refined independently with a common temperature factor.

The atomic scattering factors used for the non-H atoms were from Cromer & Mann (1968) and for the H atoms from Stewart, Davidson & Simpson (1965). Molecular parameters were calculated with *PARST* (Nardelli, 1983*a*), drawings were made with *PLUTO* (Motherwell, 1974) and volume calculations were performed with *OPEC* (Gavezzotti, 1983). Computations were performed on a Sperry 1100/81 computer.

Discussion

The atomic numbering of cholic acid is shown in Fig. 3. The final atomic coordinates and $U_{\rm iso}/U_{\rm eq}$ values are given in Tables 2–4.*

The bond lengths and angles are typical of those observed in steroids (Duax & Norton, 1975) and the C—O bond lengths of the carbonyl and hydroxyl O atoms are distinctly different. Higher $U_{\rm iso}/U_{\rm eq}$ values and e.s.d.'s for the bond lengths and angles are observed for guest relative to host molecules. This difference is common for most inclusion compounds in which the anchorage and hence thermal stability of the guest molecules is lower than that of the host molecules. $U_{\rm iso}/U_{\rm eq}$ values and e.s.d.'s are significantly higher in MECHO than ECHO or PRONCH. The instability of the crystals of MECHO and consequent high thermal motion especially, but not exclusively, in the region of the guest molecules is responsible for this difference.

The symmetry of rings, *A*, *B* and *C* is described by the chair conformation by analysis of asymmetry (Duax, Weeks & Rohrer, 1976) and displacement asymmetry (Nardelli, 1983*b*) parameters derived from the torsion angles. The range of pseudorotation, Δ, and maximum angle of torsion, ψ_m, values (Altona, Geise & Romers, 1968) for ring *D* are 17·5–23·1° and 46·3–46·9°, respectively. This corresponds to a conformation between a half-chair and a β-envelope ($\Delta = 0$ and 36°, respectively). The true energy minimum is around $\Delta = 15°$ and indicates the lack of strain imposed on this ring as a result of crystal packing.

Table 2. *Fractional atomic coordinates* (× 10⁴) *and thermal parameters* (Å² × 10³) *with e.s.d.'s in parentheses for MECHO*

	x	y	z	$U_{\rm iso}/U_{\rm eq}$*
C(1)	2043 (8)	−71 (12)	−2150 (8)	59 (3)
C(2)	1389 (9)	230 (11)	−2938 (9)	61 (3)
C(3)	1517 (8)	1452 (11)	−3211 (9)	58 (3)
C(4)	1356 (8)	2259 (11)	−2398 (8)	52 (3)
C(5)	1976 (7)	1987 (9)	−1577 (7)	45 (3)
C(6)	1820 (8)	2789 (10)	−774 (8)	52 (3)
C(7)	1002 (7)	2549 (9)	−218 (7)	41 (3)
C(8)	913 (7)	1277 (9)	49 (7)	40 (3)
C(9)	1059 (6)	452 (8)	−801 (7)	35 (2)
C(10)	1940 (7)	704 (9)	−1287 (7)	43 (3)
C(11)	946 (7)	−806 (9)	−506 (7)	45 (3)
C(12)	93 (6)	−1074 (9)	38 (7)	38 (2)
C(13)	−26 (6)	−259 (8)	845 (6)	35 (2)
C(14)	46 (6)	979 (8)	499 (6)	36 (2)
C(15)	−247 (7)	1710 (10)	1333 (8)	50 (3)
C(16)	−933 (8)	934 (10)	1801 (8)	50 (3)
C(17)	−941 (7)	−223 (9)	1321 (7)	38 (3)
C(18)	686 (7)	−553 (10)	1565 (8)	50 (4)*
C(19)	2719 (8)	428 (11)	−642 (10)	65 (5)*
C(20)	−1232 (7)	−1220 (10)	1949 (8)	47 (3)*
C(21)	−1147 (9)	−2415 (11)	1513 (9)	62 (5)*
C(22)	−2158 (8)	−1007 (13)	2311 (10)	75 (5)*
C(23)	−2439 (9)	−1696 (14)	3044 (10)	77 (6)*
C(24)	−3353 (9)	−1610 (14)	3362 (11)	72 (5)*
O(3)	942 (9)	1680 (8)	−3953 (6)	92 (4)*
O(7)	212 (5)	2901 (6)	−718 (6)	52 (3)*
O(12)	−673 (5)	−1085 (6)	−571 (5)	51 (3)*
O(24)	−3844 (8)	−741 (12)	3194 (10)	118 (6)*
O(25)	−3620 (6)	−2478 (9)	3854 (10)	103 (5)*
O(*G*)	313 (9)	5216 (14)	−507 (12)	156 (6)
C(*G*1)†	966 (19)	5578 (21)	198 (17)	150
H(O3)	811 (101)	2474 (42)	−3805 (99)	103 (23)
H(O7)	209 (96)	3594 (78)	−346 (92)	103 (23)
H(O12)	−740 (100)	−294 (40)	−741 (105)	103 (23)
H(O25)	−4271 (31)	−2336 (142)	4021 (102)	103 (23)
H(O*G*)‡	−185	5690	−719	103 (23)

* $U_{\rm eq}$ is defined as one third of the trace of the diagonalized U_{ij} matrix.
† Atom fixed with respect to $U_{\rm iso}$.
‡ Atom fixed with respect to its atomic coordinates.

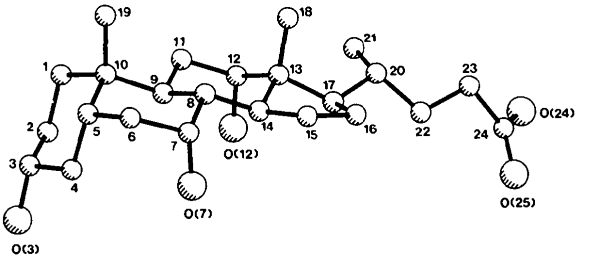

Fig. 3. Perspective view of cholic acid with atomic numbering. O(24) and O(25) refer to carbonyl and hydroxyl O atoms, respectively.

Selected torsion angles of ring *D* and the side chain, and Δ and ψ_m values are given in Table 5. Intramolecular van der Waals energy calculations on the torsion angles, C(13)—C(17)—C(20)—C(21), C(17)—C(20)—C(22)—C(23) and C(20)—C(22)—C(23)—C(24) (ψ_1, ψ_2 and ψ_3, respectively) produce five minima for the section at $\psi_1 = -60°$ (Giglio & Quagliata, 1975). The structures described here have conformations close to the minimum at $\psi_2 = -170°$ and $\psi_3 = 165°$. This minimum includes the side chain of DCA in the hexagonal inclusion compound with ethanol and water (Candeloro de Sanctis, Coiro, Giglio, Pagliuca, Pavel & Quagliata, 1978), chenodeoxycholic acid (Lindley, Mahmoud, Watson & Jones, 1980), deoxycholic acid *p*-bromoanilide (Schaefer & Reed, 1972) and sodium cholate in an

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* Lists of structure factors, anisotropic thermal parameters, bond lengths, bond angles, torsion angles, and H-atom positional and thermal parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52586 (54 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 3. *Fractional atomic coordinates* ($\times 10^4$) *and thermal parameters* ($Å^2 \times 10^3$) *with e.s.d.'s in parentheses for ECHO*

	x	*y*	*z*	$U_{\rm iso}/U_{\rm eq}$*
C(1)	2006 (4)	-39 (5)	-2207 (4)	53 (2)
C(2)	1307 (5)	275 (5)	-2925 (4)	54 (2)
C(3)	1429 (5)	1502 (5)	-3179 (5)	58 (2)
C(4)	1325 (4)	2269 (5)	-2377 (4)	50 (2)
C(5)	1994 (4)	1978 (5)	-1644 (4)	47 (2)
C(6)	1894 (4)	2758 (5)	-834 (4)	51 (2)
C(7)	1069 (4)	2523 (5)	-257 (4)	45 (2)
C(8)	975 (4)	1272 (5)	-5 (4)	39 (1)
C(9)	1072 (4)	485 (5)	-828 (3)	37 (1)
C(10)	1961 (4)	694 (5)	-1350 (4)	42 (1)
C(11)	944 (4)	-768 (5)	-554 (4)	43 (1)
C(12)	97 (4)	-1024 (5)	4 (4)	40 (1)
C(13)	19 (4)	-231 (4)	807 (3)	37 (1)
C(14)	100 (4)	998 (4)	484 (3)	37 (1)
C(15)	-156 (4)	1718 (5)	1285 (4)	51 (2)
C(16)	-853 (4)	966 (5)	1784 (4)	50 (2)
C(17)	-908 (4)	-171 (5)	1301 (4)	38 (1)
C(18)	785 (4)	-554 (5)	1469 (4)	49 (2)*
C(19)	2807 (4)	399 (6)	-811 (4)	59 (2)*
C(20)	-1189 (4)	-1168 (5)	1909 (4)	49 (2)*
C(21)	-1173 (6)	-2324 (6)	1448 (5)	73 (3)*
C(22)	-2150 (5)	-932 (6)	2302 (4)	60 (2)*
C(23)	-2415 (5)	-1730 (7)	3013 (5)	72 (3)*
C(24)	-3344 (5)	-1611 (6)	3377 (5)	64 (3)*
O(3)	767 (4)	1761 (4)	-3858 (3)	82 (2)*
O(7)	250 (3)	2912 (3)	-680 (3)	54 (2)*
O(12)	-712 (3)	-1015 (3)	-534 (3)	52 (2)*
O(24)	-3832 (4)	-776 (5)	3269 (4)	91 (2)*
O(25)	-3588 (3)	-2500 (4)	3845 (4)	83 (2)*
O(*G*)	408 (6)	5196 (5)	-457 (6)	129 (4)*
C(*G*1)†	665 (9)	5549 (8)	386 (9)	86 (5)*
C(*G*2)	1572 (9)	5975 (11)	403 (9)	128 (6)*
C(*G*3)‡	1131 (16)	5966 (22)	-429 (13)	73 (13)*
H(O3)	762 (56)	2545 (24)	-4061 (53)	107 (12)
H(O7)	235 (56)	3744 (11)	-635 (56)	107 (12)
H(O12)	-833 (59)	-286 (33)	-794 (49)	107 (12)
H(O25)	-4210 (27)	-2367 (69)	4134 (51)	107 (12)
H(O*G*)	60 (48)	5769 (50)	-774 (48)	107 (12)

* $U_{\rm eq}$ is defined as one third of the trace of the diagonalized U_{ij} matrix.
† Site-occupancy factor = 0·77.
‡ Site-occupancy factor = 0·23.

Table 4. *Fractional atomic coordinates* ($\times 10^4$) *and thermal parameters* ($Å^2 \times 10^3$) *with e.s.d.'s in parentheses for PRONCH*

	x	*y*	*z*	$U_{\rm iso}/U_{\rm eq}$*
C(1)	2022 (4)	-67 (5)	-2164 (4)	56 (2)
C(2)	1367 (4)	212 (5)	-2917 (4)	53 (1)
C(3)	1469 (4)	1427 (5)	-3184 (4)	59 (2)
C(4)	1330 (4)	2194 (5)	-2393 (3)	51 (1)
C(5)	1967 (4)	1934 (5)	-1622 (4)	51 (1)
C(6)	1830 (4)	2727 (5)	-826 (4)	52 (1)
C(7)	1009 (4)	2492 (5)	-274 (4)	47 (1)
C(8)	935 (3)	1239 (4)	-8 (3)	41 (1)
C(9)	1054 (3)	457 (4)	-813 (3)	40 (1)
C(10)	1940 (4)	679 (5)	-1326 (4)	45 (1)
C(11)	959 (4)	-797 (4)	-524 (4)	46 (1)
C(12)	109 (3)	-1046 (4)	15 (3)	42 (1)
C(13)	1 (3)	-255 (4)	816 (3)	40 (1)
C(14)	67 (3)	969 (4)	463 (3)	41 (1)
C(15)	-212 (4)	1694 (5)	1250 (4)	54 (2)
C(16)	-919 (4)	955 (5)	1741 (4)	54 (1)
C(17)	-923 (3)	-214 (4)	1280 (3)	42 (1)
C(18)	732 (4)	-523 (5)	1504 (4)	53 (2)*
C(19)	2752 (4)	397 (6)	-750 (5)	63 (2)*
C(20)	-1194 (4)	-1177 (5)	1909 (4)	50 (2)*
C(21)	-1133 (5)	-2339 (5)	1477 (5)	70 (2)*
C(22)	-2141 (4)	-957 (5)	2266 (4)	57 (2)*
C(23)	-2393 (4)	-1725 (6)	3041 (5)	65 (2)*
C(24)	-3310 (4)	-1557 (5)	3377 (4)	61 (2)*
O(3)	862 (4)	1665 (4)	-3890 (3)	81 (2)*
O(7)	220 (2)	2836 (3)	-728 (3)	53 (1)*
O(12)	-658 (3)	-1085 (3)	-553 (3)	52 (1)*
O(24)	-3761 (4)	-719 (4)	3304 (4)	92 (2)*
O(25)	-3578 (3)	-2440 (4)	3832 (4)	93 (2)*
O(*G*)	109 (5)	5024 (4)	-329 (6)	138 (4)*
C(*G*1)†	550 (7)	5468 (8)	416 (6)	83 (5)*
C(*G*2)†	1429 (8)	5924 (12)	26 (9)	130 (8)*
C(*G*3)	2016 (6)	6470 (8)	756 (7)	117 (4)*
C(*G*4)‡	910 (16)	5640 (32)	-375 (17)	119 (16)
C(*G*5)‡	1151 (13)	5797 (23)	620 (17)	80 (10)
H(O3)	973 (50)	2443 (21)	-4049 (51)	96 (11)
H(O7)	148 (45)	3639 (18)	-588 (51)	96 (11)
H(O12)	-714 (52)	-399 (35)	-886 (44)	96 (11)
H(O25)	-4066 (36)	-2017 (56)	4166 (45)	96 (11)
H(O*G*)	-267 (40)	5668 (40)	-451 (50)	96 (11)

* $U_{\rm eq}$ is defined as one third of the trace of the diagonalized U_{ij} matrix.
† Site-occupancy factor = 0·70.
‡ Site-occupancy factor = 0·33.

Table 5. *Torsion angles* (°)

Torsion angles are given as defined by the convention of Klyne & Prelog (1960).

	MECHO	ECHO	PRONCH
Side-chain conformation			
C(13)—C(17)—C(20)—C(22)	-178·3 (10)	-178·2 (5)	-178·7 (5)
C(17)—C(20)—C(22)—C(23)	-166·2 (12)	-169·9 (6)	-167·8 (5)
C(20)—C(22)—C(23)—C(24)	-174·0 (12)	-175·9 (6)	-178·1 (6)
C(13)—C(17)—C(20)—C(21)	-51·5 (14)	-54·5 (7)	-54·5 (7)
C(16)—C(17)—C(20)—C(21)	-173·5 (10)	-175·5 (5)	-175·8 (5)
C(21)—C(20)—C(22)—C(23)	65·5 (15)	64·4 (8)	66·5 (7)
C(22)—C(23)—C(24)—O(24)	-20·0 (23)	-15·5 (11)	-23·4 (10)
C(22)—C(23)—C(24)—O(25)	161·8 (14)	165·2 (6)	160·5 (6)
Ring *D* conformation			
C(17)—C(13)—C(14)—C(15)	45·7 (9)	45·5 (5)	46·4 (5)
C(13)—C(14)—C(15)—C(16)	-32·5 (10)	-31·2 (5)	-33·0 (6)
C(14)—C(15)—C(16)—C(17)	6·5 (11)	4·6 (6)	6·9 (6)
C(15)—C(16)—C(17)—C(13)	21·3 (11)	23·1 (6)	21·4 (6)
C(14)—C(13)—C(17)—C(16)	-40·8 (9)	-41·3 (5)	-40·5 (5)
Δ	18·7	23·1	17·5
ψ_m	46·3	46·4	46·9

inclusion compound with water (Cobbledick & Einstein, 1980). The higher van der Waals energy of the extended side chain in these compounds is counterbalanced by the energy gained from the formation of hydrogen bonds.

Molecular packing

No bilayers are observed and the host molecules are packed in a three-dimensional array with hydrogen bonds involving the guest molecules stabilizing the crystal lattice. The guest molecules are contained within cavities interconnected by narrow channels. It was found by volume analysis of the cavities that the dimensions of 1-propanol approximate those of the cavity. Methanol on the other hand occupies only about 50% of the cavity and therefore allows the inclusion of further methanol molecules without hydrogen bonding. Loss of these molecules through the interconnecting channels is easier than for the larger alcohol molecules, and accounts for the instability of this structure. The alcohols are attached to the host molecules by the hydrogen bonds of the O(*G*) atom. Further stabilization by favourable contacts exists between the host lattice and the hydrocarbon moiety of the alcohol and increases in the series MECHO < ECHO < PRONCH. This relates to the enthalpies observed. A stereodiagram of the molecular packing viewed along *a* is shown in Fig. 4.

Intermolecular hydrogen bonds of PRONCH involving three host and two guest molecules (translated in the *b* axis) viewed along **b** are shown in Fig. 5. Roman numerals refer to the symmetry operations described in Table 6. The O···O distances for the three structures are shown in Table 6.

The size of the guest cavity precludes the inclusion of nonbranched alcohols larger than 1-propanol in an isomorphous structure. 1-Butanol and 2-propanol have been found to form inclusion compounds with cholic acid in the space group $P6_522$ (Jones & Nassimbeni, 1990).

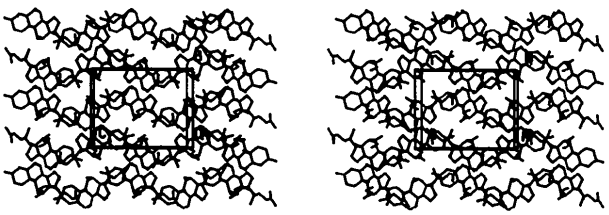

Fig. 4. Packing diagram for PRONCH viewed along [100].

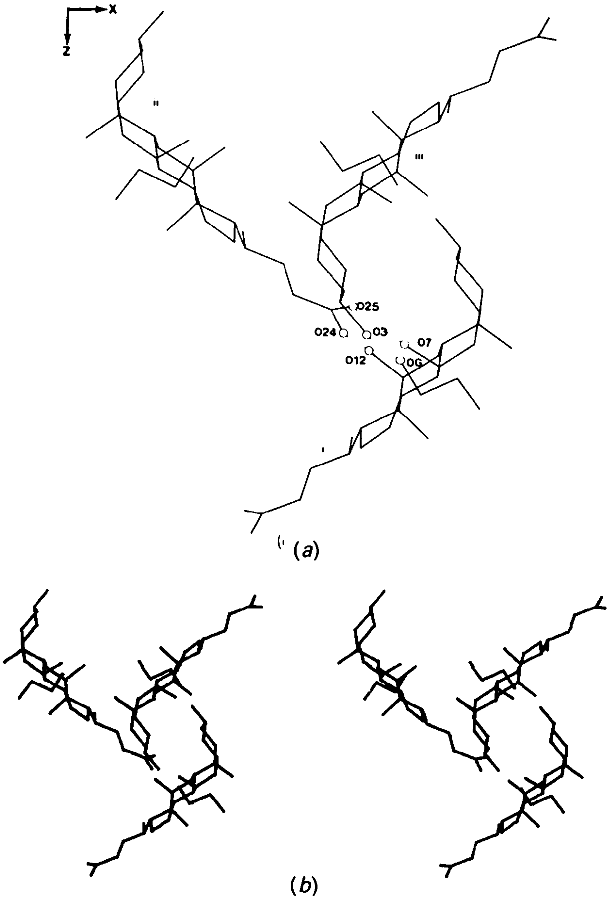

Fig. 5. (*a*) Intermolecular hydrogen bonding of PRONCH involving three host molecules and two guest molecules, viewed along [010]. (*b*) Stereoview of PRONCH viewed along [010].

Table 6. *Hydrogen-bond distances* (Å)

	MECHO	ECHO	PRONCH
O(7')···O(25'')	2·55 (1)	2·584 (6)	2·596 (7)
O(9')···O(7')	2·71 (2)	2·714 (7)	2·669 (7)
O(3''')···O(9^{iv})	2·68 (2)	2·720 (9)	2·700 (8)
O(12')···O(3''')	2·72 (1)	2·765 (6)	2·813 (6)
O(24'')···O(12')	2·88 (2)	2·847 (7)	2·876 (7)

Symmetry code: (i) x, y, z; (ii) $-x-0·5, -y, z-0·5$; (iii) $-x, y-0·5, -z-0·5$; (iv) $x, y-1, z$.

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Molecular Structure of Opiate Alkaloids. III.* Crystal Structure of Two 7-(1-Cyclohexylethyl)oripavine Analogues

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Abstract

An X-ray crystallographic analysis and a conformational study of two oripavine opiate narcotic analgesics are reported. These compounds are C7-substituted analogues of 16-methyl- and 16-ethyl-6,14-*endo*-ethenotetrahydrooripavines, respectively. Crystals of both molecules are orthorhombic, space group $P2_12_12_1$, $Z = 4$, $T = 293$ K: compound (I), 7-(1-cyclohexyl-1-hydroxyethyl)-16-methyl-6,14-*endo*-etheno-6,7,8,14-tetrahydro-3-oripavinyl methyl ether, $a = 11{\cdot}441$ (2), $b = 21{\cdot}479$ (2), $c = 10{\cdot}570$ (2) Å; compound (II), 7-(1-cyclohexyl-1-hydroxyethyl)-16-ethyl-6,14-*endo*-6,7,8,14-tetrahydro-3-oripavinyl methyl ether, $a = 11{\cdot}364$ (2), $b = 21{\cdot}643$ (4), $c = 10{\cdot}946$ (2) Å. Both structures were solved by direct methods and refined by full-matrix least-squares procedures to $R = 0{\cdot}06$ and $0{\cdot}05$ for 1572 and 2666 reflections with $I \geq 2\sigma(I)$, respectively. The molecular structures are almost identical; the 16-alkyl substitutions do not modify the structure of the multi-ring system and, in particular, do not alter the orientation of the N atom. Both molecules have an intramolecular hydrogen bond between the C19—OH and C6—O—CH_3 groups. This feature is correlated to the differences in pharmacological activity between diastereoisomers at C19 and is used to build a general molecular model in the search for the biologically active conformation of opiate narcotics.

Introduction

In the last decade, considerable effort was made to elaborate a three-dimensional description for the opioid receptor. Beckett & Casy (1954) proposed a model based on the assumption that the association of a drug on the receptor site involved three specific subsites: an anionic center to interact with the N atom, a hydrophobic site where the aromatic ring lies and a 'hole' to accommodate C15 and C16. In a recent article (Michel, Evrard, Norberg & Milchert, 1988) we reported the conformational properties of two 16-alkyl analogues of thebaine and oripavine: compounds (III) and (IV) (Fig. 1). More recently, the discovery of three major receptor types (μ, K, δ) renewed the interest in the development of a better model for the opioid receptor which would account for the distinction between the three receptor types. This question was addressed in a previous study (DiMaio, Bayly, Villeneuve & Michel, 1986) where we demonstrated that the opiate alkaloid PEO (VI) was a good semirigid template on which analogs of enkephaline peptides (VII) could be fitted. Unfortunately, our attempts to obtain suitable crystals of PEO where unsuccessful and we decided to investigate the series of ethenotetrahydrothebaine and -oripavine analogues (I)–(V). Although different from the PEO template, these molecules allowed us to build a reasonable molecular model for PEO and also address pertinent conformational questions in relation to the description of the opiate receptor. Particularly, the presence of the 6–14 etheno bridge in conjunction with an intramolecular hydrogen bond will be correlated with the stereoselectivity observed at C19 and the high agonist potency (as much as 1000 times higher than morphine). The model of PEO based on the crystal structure determination will be shown to fit very well with cyclic analogs of enkephaline (VII) and will constitute an excellent template for further molecular modeling studies of the opiate receptor and particularly to distinguish between μ and δ receptors.

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