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A new estra-1,3,5(10)-triene-3,17β-diol solvate: estradiol–methanol–water (3/2/1)

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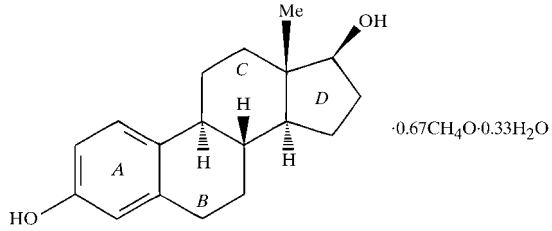
The title solvate of the steroid 17β-estradiol (E_2) with methanol and water, $C_{18}H_{24}O_2\cdot0.67CH_4O\cdot0.33H_2O$, is the first E_2 derivative to contain three crystallographically independent molecules in the asymmetric unit. The three steroid molecules, along with two methanol molecules and a water molecule, create a three-dimensional hydrogen-bonded system. Three-sided columns are formed, with the estradiol molecules aligned lengthwise parallel to (101), and joined by solvent molecules at both hydrophilic ends. The three estradiol molecules differ slightly in their ring-bowing angles, *i.e.* the angle between the mean plane of the *A* ring and that of the *BCD* ring; this angle ranges from 7.1 to 12.2°.

Comment

17β-Estradiol, E_2, is a member of the estrogen family of hormones. In recent years, interest in these molecules has focused primarily on understanding their biological role in initiating breast cancer. It is well known that their ability to form hydrogen bonds in the active site of the estrogen receptor (ER) influences biological activity. This ability to form hydrogen bonds has been clearly demonstrated in an array of crystal structures, especially in that of E_2, containing different solvent molecules or other hydrogen-bond acceptors.

When comparing these structures, the flexibility of the hydrophobic region of the molecule, more specifically the *B* ring, becomes very apparent. Several papers have already discussed the ring bowing of this molecule (Cooper *et al.*, 1969; Cody *et al.*, 1971; Busetta *et al.*, 1976; Duax *et al.*, 1979). Weise & Brooks (1994) took it a step further, performing molecular-modeling calculations on observed and novel confirmations. Ivanov and co-workers carried out a related study which included a larger body of compounds and more detailed analysis (Ivanov *et al.*, 1998). They concluded that there are two possible conformations very close in energy, which differ in the *B*-ring arrangement, although the chance of the strained-geometry binding is low, as one quarter of the binding energy (−11.9 kcal mol^{-1}; 1 kcal mol^{-1} = 4.184 kJ mol^{-1}) is predicted to be lost (Anstead *et al.*, 1997). The point initially postulated by Weise & Brooks remains, *i.e.* that the flexibility to allow bending or other conformational changes of the ligand in the receptor appears energetically achievable, and this could be an important property in determining their activity.

Molecular-dynamics studies on the ligand-binding domain (LBD) of the ER demonstrate that the motion of the LBD requires the *A* ring to remain fairly steady while the *CD* ring retains a higher degree of freedom. The range of motion found in that study (Maalouf *et al.*, 1998) agrees very well with the reported crystal structures. It is well known that the hydrogen bonding of the ligand in the LBD causes conformational changes in the receptor. This seemingly accommodating motion of the LBD and the ligand supports the idea postulated by Weise & Brooks that the flexibility of E_2, or of any other ligand which enters the LBD, could also effect the activity of the ligand. A more rigid or flexible ligand could change the natural motion of the ER complex, resulting in a change in activation factor (AF-2) activity, and therefore possibly effecting co-activator recruitment. This process is not well understood; the flexibility of the ligand is certainly only one of many physical factors associated in the activity of E_2. The structure of the title solvate, (I), continues the trend in observing the flexibility of this molecule from a structural and hydrogen-bonding point of view, while the molecule lies in the lowest energy conformation.



(I)

The crystal of (I) contains three crystallographically unique E_2 molecules (Fig. 1). The *B* rings of the E_2 molecules adopt the typical conformation of a distorted 7α,8β-half-chair, and this is responsible for most of the structural flexibility. Calculation of the ring-bowing angle, as defined by Duax & Norton (1975), reveals a range of 5.1° for the three molecules. Table 1 compares the ring-bowing angles of the currently

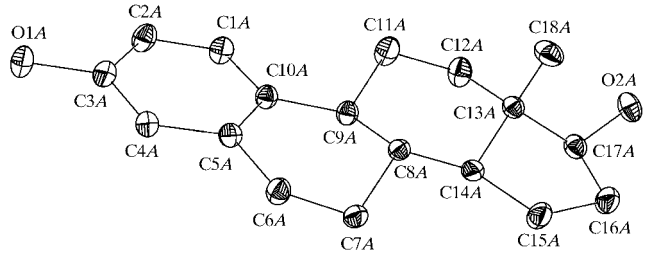


Figure 1
A view of molecule *A* of (I), with the atom-numbering scheme; the other two molecules are similarly labeled, with the corresponding suffix *B* or *C*. Displacement ellipsoids are plotted at the 50% probability level. The solvent molecules have been omitted for clarity.

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known E_2 crystal structures. The spread of over 12°, with angles found distributed over the entire range, indicate the shallowness of the potential associated with the bowing deformation. In a system as dynamic as the human body, the molecule would certainly have a wide range of conformations easily available.

The packing of (I) results in three-sided cylinders of estradiol molecules arranged parallel to (101), with the C18 methyl group pointing towards the center (Fig. 2). This, of course, aligns the large hydrophobic regions of the molecules, as well as the hydrophilic hydroxy groups. These cylinders then stack on top of each other, creating three-sided columns (Fig. 3) held together by hydrogen bonds involving the hydroxy groups and the three solvent molecules. A more detailed picture of the hydrogen bonding between the solvent and E_2 molecules can be seen in Fig. 4 and from the data in Table 3. There is also an intercolumnar hydrogen bond, which occurs between the water molecule and a 3-hydroxy group. This, along with the intercolumnar hydrogen-bonded solvent,

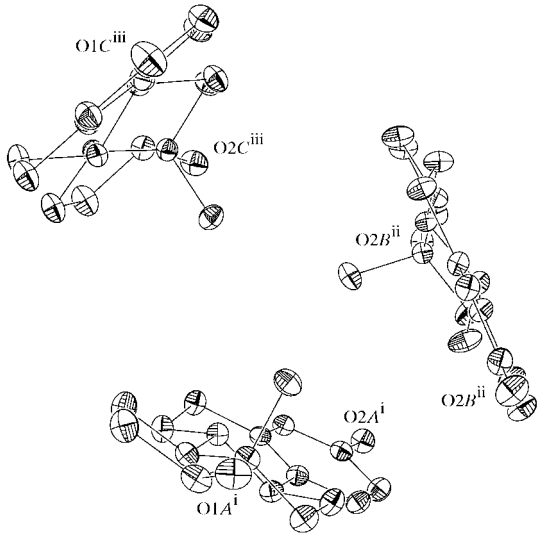

Figure 2
The molecular arrangement of (I), looking down the three-sided column. Displacement ellipsoids are plotted at the 50% probability level [symmetry codes: (i) x, y, z; (ii) $-2-x, y-\frac{1}{2}, -1-z$; (iii) $x-1, y, z$].

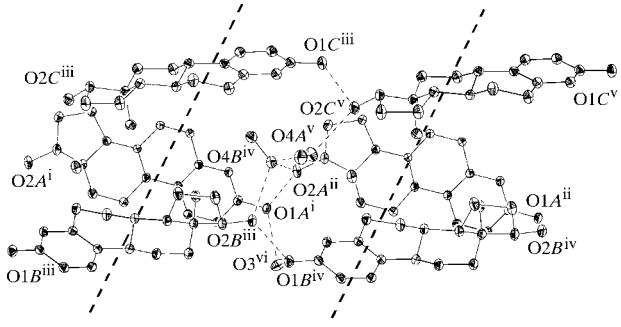

Figure 3
The packing of E_2 groups in (I), with the hydrogen-bonded solvent molecules, viewed perpendicular to the columns. Dotted lines indicate the region detailed in Fig. 4. Displacement ellipsoids are plotted at the 50% probability level [symmetry codes: (i) x, y, z; (ii) $1+x, y, 1+z$; (iii) $-2-x, y-\frac{1}{2}, -1-z$; (iv) $-1-x, y-\frac{1}{2}, -z$; (v) $x, y, 1+z$; (vi) $-x, y-\frac{1}{2}, -z$].

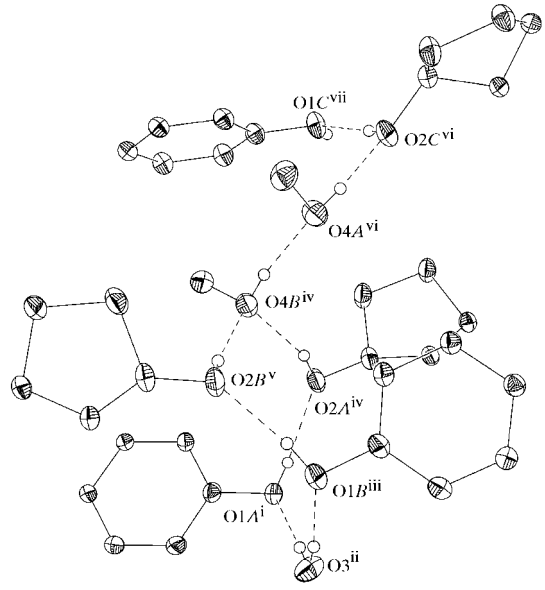

Figure 4
The hydrogen-bonded region of the column shown in Fig. 3, including the solvent molecules and only the *A* or *D* rings of E_2. Displacement ellipsoids are plotted at the 50% probability level [symmetry codes: (i) x, y, z; (ii) $-x, y-\frac{1}{2}, -z$; (iii) $-1-x, y-\frac{1}{2}, -z$; (iv) $1+x, y, 1+z$; (v) $-2-x, y-\frac{1}{2}, -1-z$; (vi) $x, y, 1+z$; (vii) $-1-x, y, z$].

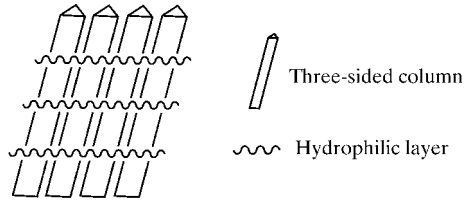

Figure 5
A schematic diagram of the packed columns in (I) and their relation to the hydrophilic layer containing the hydroxy groups and solvent molecules.

creates a hydrophilic layer which is approximately 30° from the perpendicular to the columns (Fig. 5). Structurally, all bond lengths and angles are in expected ranges (Table 2).

Experimental

Crystals were grown by slow evaporation from a methanol solution open to the air. It is presumed that the methanol was either wet prior to use in this experiment or absorbed atmospheric moisture. Crystals of (I) were grown over the course of 3 d and harvested when reaching the appropriate size.

Crystal data

$C_{18}H_{24}O_2\cdot0.67CH_4O\cdot0.33H_2O$
$M_r = 299.74$
Monoclinic, $P2_1$
$a = 11.7152\ (4)$ Å
$b = 19.6270\ (6)$ Å
$c = 12.1310\ (4)$ Å
$\beta = 117.978\ (1)°$
$V = 2463.34\ (14)$ Å^3
$Z = 6$
$D_x = 1.212$ Mg m^{-3}
Ag $K\alpha$ radiation
Cell parameters from 7309 reflections
$\theta = 2.3–27.9°$
$\mu = 0.05$ mm^{-1}
$T = 298\ (1)$ K
Cuboid, colorless
0.4 × 0.3 × 0.3 mm

Data collection

Siemens SMART Platform CCD area-detector diffractometer
ω scans
Absorption correction: empirical *via* multipole expansion (Blessing, 1995) using *SADABS* (Sheldrick, 1996)
T_{min} = 0.840, T_{max} = 0.985
44 195 measured reflections
21 122 independent reflections
15 597 reflections with $I > 2\sigma(I)$
R_{int} = 0.048
θ_{max} = 27.9°
$h = -18 \rightarrow 19$
$k = -32 \rightarrow 29$
$l = -20 \rightarrow 20$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.058
$wR(F^2)$ = 0.145
S = 0.99
21 122 reflections
698 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0812P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.41 e Å^{-3}
$\Delta\rho_{min}$ = −0.23 e Å^{-3}

Table 1
Comparison of ring-bowing angles (°) in reported E_2 crystal structres.

Compound	Molecule 1 angle	Molecule 2 angle	Molecule 3 angle
17β-estradiol–0.5H_2O†	15.6		
17β-estradiol–propanol†	12.9		
17β-estradiol–urea†	5.6		
17β-estradiol–0.5MeOH‡	10.4	3.4	
(I)§	12.2	11.9	7.1

† Wiese & Brooks (1994). ‡ Parrish & Pinkerton (1999). § This work.

Table 2
Selected bond lengths (Å).

O1*A*—C3*A*	1.3716 (18)	O2*A*—C17*A*	1.4354 (19)
O1*B*—C3*B*	1.3792 (17)	O2*B*—C17*B*	1.4305 (19)
O1*C*—C3*C*	1.3691 (18)	O2*C*—C17*C*	1.4400 (19)

Table 3
Hydrogen-bonding geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O1*A*—H1O*A*···O2*A*^{i}	0.74 (3)	1.89 (3)	2.6226 (17)	171 (3)
O1*B*—H1O*B*···O2*B*^{i}	0.85 (3)	1.83 (3)	2.6654 (18)	171 (3)
O1*C*—H1O*C*···O3	0.76 (3)	1.82 (3)	2.5767 (18)	170 (3)
O2*A*—H2O*A*···O4*B*	0.76 (3)	1.97 (3)	2.7017 (18)	162 (2)
O2*B*—H2O*B*···O4*B*^{ii}	0.73 (2)	2.06 (2)	2.7823 (19)	168 (2)
O2*C*—H2O*C*···O1*C*^{iii}	0.73 (2)	1.99 (3)	2.7169 (17)	175 (3)
O3—H3O*A*···O1*A*^{iv}	0.72 (4)	2.02 (4)	2.743 (2)	178 (4)
O3—H3O*B*···O1*B*^{v}	0.76 (3)	2.04 (3)	2.7926 (19)	173 (3)
O4*A*—H4O*A*···O2*C*	0.83 (3)	1.85 (3)	2.6809 (18)	174 (3)
O4*B*—H4O*B*···O4*A*^{vi}	0.78 (2)	1.88 (2)	2.6462 (17)	166 (2)

Symmetry codes: (i) $1+x, y, 1+z$; (ii) $-3-x, \frac{1}{2}+y, -2-z$; (iii) $x-1, y, z-1$; (iv) $-x, \frac{1}{2}+y, -z$; (v) $1+x, y, z$; (vi) $x-1, y, z$.

The absolute configuration of the E_2 molecules in (I) was known from the natural product starting material. The intensity data were corrected for decay and absorption using *SADABS* (Sheldrick, 1996). All H atoms of the solvent molecules and the hydroxy groups of the E_2 molecules were located in a difference map and refined with isotropic displacement parameters. The remaining H atoms were included with idealized geometries (C—H = 0.96–0.98 Å), and their isotropic displacement parameters were refined.

Data collection: *SMART* (Bruker, 1998); cell refinement: *SAINT* (Bruker, 1999); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL* (Siemens, 1994); software used to prepare material for publication: *SHELXTL*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SQ1003). Services for accessing these data are described at the back of the journal.

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