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An ethanol solvate of Beclomethasone dipropionate

Philip J. Kuehl,[a]* Michael D. Carducci[b] and Paul B. Myrdal[a]

[a]College of Pharmacy, University of Arizona, 1703 E. Mabel St., Tucson, AZ 85721-0207, USA, and [b]University of Arizona, Department of Chemistry, 1306 E. University, Tucson, AZ 85721-0041, USA

Correspondence e-mail: kuehl@pharmacy.arizona.edu

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Key indicators

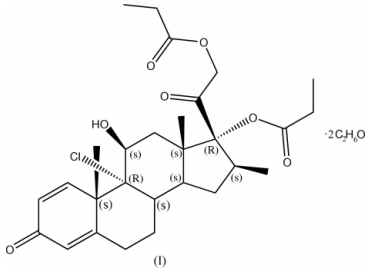
Single-crystal X-ray study
T = 170 K
Mean σ(C–C) = 0.005 Å
Some non-H atoms missing
Disorder in solvent or counterion
R factor = 0.067
wR factor = 0.118
Data-to-parameter ratio = 18.8

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Beclomethasone dipropionate (BDP) is a widely used corticosteroid formulated in metered dose inhalers (MDI) for the treatment of asthma. The crystal structure of a BDP ethanol solvate of apparent formula $C_{28}H_{37}ClO_7\cdot 2C_2H_6O$ has been determined at 170 K. The crystal investigated in this study was grown in a 3% (w/w) saturated solution of 200-proof ethanol (EtOH) at 203 K. Under these conditions, BDP crystallizes with a channel structure that allows for the inclusion of disordered ethanol molecules. The steroid molecules are held in place through intermolecular hydrogen bonding and chlorine–chlorine interactions.

Comment

While the molecular structure of a drug is responsible for its therapeutic activity, the solid-state chemistry is also a major concern. Solid-state chemistry affects the solubility, dissolution rate and, potentially, the bioavailability of the drug. Hence it is advantageous to understand and characterize potential solid-state forms of a drug. Beclomethasone dipropionate (BDP), a widely used corticosteroid for the treatment of chronic asthma, is currently formulated in metered dose inhalers (MDI). Previous research has shown that BDP forms a number of different crystal structures when crystallized under different conditions. Published BDP crystal structures include a monohydrate (Duax *et al.*, 1981), and an anhydrous form (Millard & Myrdal, 2002). Based on the knowledge that multiple crystal structures exist, an understanding of BDP's interactions with potential formulation excipients and polymorph formation should be completely characterized in order to avoid development problems. One of the best methods available to characterize different crystal structures is through the use of single-crystal X-ray diffractometry.



(I)

In this study, a BDP ethanol solvate was isolated from sub-ambient conditions, as described in the *Experimental* section. It was found that EtOH was included in the crystal structure; however, a stoichiometric relationship, if any, is not clear. The disolvate crystallizes in space group $P3_121$ and is calculated to have a density of 1.249 Mg m^{-3}.

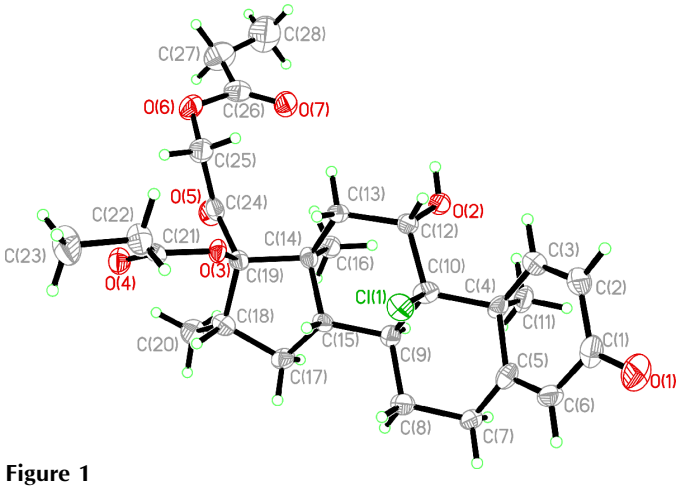


Figure 1
The structure of the BDP molecule with 50% probability displacement ellipsoids. H atoms are shown as spheres of arbitary radii.

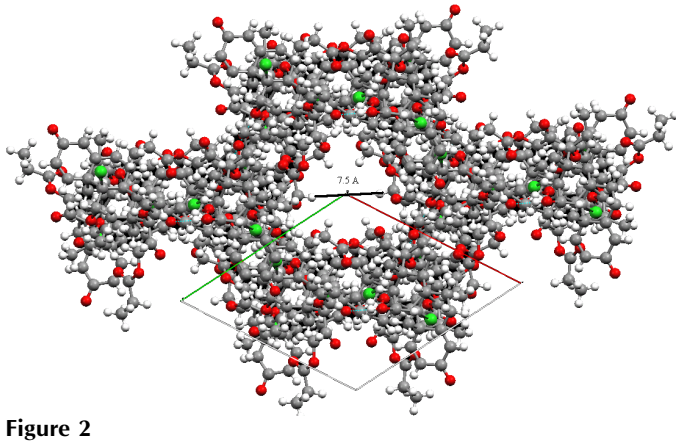


Figure 2
Packing diagram, viewed down the *c* axis, showing the channel occupied by disordered ethanol.

The steroid molecules in this solvate are in linear chains that form sheets perpendicular to the *c* axis. There is a hydrogen bond between O2 and O4 of adjacent steroid molecules, which helps to hold the linear chains together (see Fig. 1 for the numbering scheme). Also helping to hold the sheets in place are chlorine–chlorine interactions, with a distance of 3.501 (2) Å. This structure results in a solvent-accessible channel along the *c* axis. Interestingly, this arrangement of the steroid molecules orients the other carbonyl groups towards the inside of this channel, as shown in Fig. 2, for potential hydrogen bonding. However, these potential hydrogen-bond acceptors do not interact strongly with the ethanol solvent molecules. The weak hydrogen-bond interaction, coupled with the large channel void, makes the full characterization of the ethanol solvate difficult.

The monohydrate and anhydrous forms of BDP have different crystal structures, both in space group, $P2_12_12_1$, and their densities are 1.362 and 1.287 Mg m^{-3}, respectively, without any channels. The density of the ethanol disolvate (calculated as 1.249 Mg m^{-3}) is less than both of these. This lower density could be due to the absence of hydrogen bonding between the ethanol and the steroid molecules and/or the large solvent void in the crystal structure.

Interestingly, BDP forms a similar crystal structure to that of the ethanol disolvate when grown under different conditions. The crystal structure obtained from a mixture of 20% 200-proof ethanol and HFA-134a (Harris *et al.*, 2003) has a very similar solvent channel. The inclusion of HFA-134a or EtOH in this channel supports either the absence of binding or nonspecific binding of BDP to the solvent.

It is known that the ethanol solvate is not stable under ambient conditions. When removed from the growth conditions described in the *Experimental* section and dried, it readily collapses to either an amorphous solid or the monohydrate, depending on the relative humidity.

Experimental

BDP solvate crystals were grown in a 3% (*w*/*w*) supersaturated solution of 200-proof EtOH at 203 K. The solution was allowed to equilibrate for 3 h at room temperature before being placed in a freezer. Crystals were obtained from the solution by evaporation. A crystal was mounted on a glass fiber using paratone oil and placed in the cold stream of the diffractometer in about 1 min, in order to minimize the amount of ethanol that could escape from the channel.

Crystal data

$C_{28}H_{37}ClO_7\cdot 2C_2H_6O$
M_r = 613.16
Trigonal, $P3_121$
a = 13.4869 (10) Å
c = 31.046 (4) Å
V = 4890.6 (8) Å^3
Z = 6
D_x = 1.249 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 2588 reflections
θ = 2.2–17.8°
μ = 0.17 mm^{-1}
T = 170 (2) K
Block, colorless
0.21 × 0.17 × 0.11 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Bruker, 1997)
T_{min} = 0.870, T_{max} = 0.982
52 513 measured reflections
6110 independent reflections
4718 reflections with $I > 2\sigma(I)$
R_{int} = 0.133
θ_{max} = 25.6°
$h = -16 \rightarrow 16$
$k = -16 \rightarrow 16$
$l = -37 \rightarrow 37$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.067
$wR(F^2)$ = 0.118
S = 1.05
6110 reflections
325 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0511P)^2 + 0.134P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.42 e Å^{-3}
$\Delta\rho_{min}$ = −0.24 e Å^{-3}
Absolute structure: Flack (1983), 2466 Friedel pairs
Flack parameter = 0.04 (8)

Table 1
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O2—H2A···O4^{i}	0.84	2.16	2.978 (3)	164

Symmetry code: (i) $1-x, 1-x+y, \frac{1}{3}-z$.

As with any disordered solvent, refinement of the ethanol in this structure proved to be difficult. The disorder is due to the lack of strong hydrogen bonding between BDP and ethanol, which allows the solvent molecules to orient apparently at random. Initial refinement attempted an atomic model for the disordered EtOH, but no satisfactory model was found which maintained reasonable bond

distances and angles and accounted for all of the electron density.

The solvent void was analyzed using *PLATON* (Van Der Sluis & Spek, 1990) and showed a volume of 1382 Å^3 per unit cell, accounting for 27% of the total cell volume. By considering this volume as a cylinder, a calculated diameter of 7.53 Å is obtained. Measured distances across this channel give slightly smaller diameters of about 7.3 Å. A channel with this diameter would allow the inclusion of EtOH, which has a calculated diameter of 5.70 Å (assuming a spherical molecule), and possibly other solvent molecules.

Atoms in the channel were removed from the structure model and the solvent region was modeled as a diffuse contribution without specific atom positions, using the *PLATON* module SQUEEZE (Spek, 2003). This indicated approximately 276 electrons in the void, corresponding to a disolvate.

Further attempts to determine the number of EtOH molecules present in the channel employed thermogravimetric analysis (TGA), which showed a 1:1 molar ratio of BDP to EtOH, conflicting with the 1:2 ratio indicated crystallographically. TGA data showed weight loss as soon as the sample was placed on the instrument, before heating was initiated. This could be a result of facile ethanol loss because of the lack of hydrogen bonding between EtOH and BDP. Based on these data, a 2:1 ratio of EtOH to BDP has been tentatively assigned.

All H atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms, with C—H = 0.95–1.00 Å, O—H = 0.84 Å, and $U_{iso}(H) = xU_{eq}(C)$ [x = 1.5 for OH and methyl groups, and x = 1.2 for other H atoms].

Data collection: *SMART* (Bruker, 1997); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 1997); program(s) used to solve structure: *SHELXTL* (Bruker, 1997); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

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