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Beclomethasone dipropionate crystallized from HFA-134a and ethanol

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Key indicators

Single-crystal X-ray study
T = 170 K
Mean σ(C–C) = 0.003 Å
Some non-H atoms missing
R factor = 0.044
wR factor = 0.099
Data-to-parameter ratio = 21.5

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

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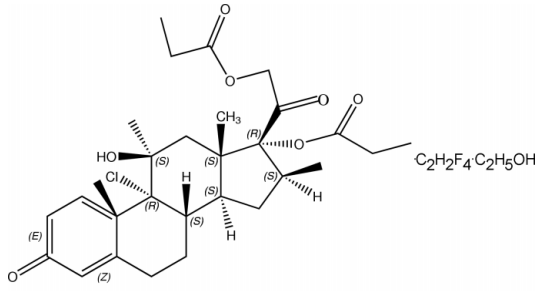
Beclomethasone dipropionate (BDP) is a long-acting inhaled corticosteroid, used for the treatment of asthma, and as an inhalation therapy with HFA-134a. The sample studied by X-ray crystallography was grown in a mixture of the aerosol propellant HFA-134a, $C_2H_2F_4$, and 200-proof ethanol. The formula of the crystalline material is $C_{28}H_{37}ClO_7\cdot 2C_2H_6O\cdot C_2H_2F_4$. In the crystal structure, disordered solvent occupies a channel which is perpendicular to the BDP molecules. The latter are are stacked together by hydrogen bonding.

Comment

Beclomethasone dipropionate (BDP) is an important corticosteroid that is used for the long-term treatment of asthma. Depending on the propellant system, BDP is formulated in both solution and suspension form, and delivered by pressurized metered-dose inhalers (MDIs). Since the crystalline structure can significantly affect formulation performance, it is important to determine at early stages of development the most stable crystal form in the presence of the propellant and other potential formulation ingredients. If a metastable form is used, the potential exists for the interconversion of BDP to other crystalline forms, thus affecting solubility and particle size.



(I)

In order to prevent future development problems, it is critical to characterize the crystal structure in formulation. The best way to determine structural change in BDP is to examine the single-crystal structure in controlled MDI conditions using diffractometry. The current study investigates the solid-state behavior of BDP in 20% ethanol/hydrofluoroalkane (HFA-134a). Initially, differential scanning calorimetry and hot-stage microscopy suggested the possibility of a solvated crystal form. In fact, desolvation seems to occur rapidly once the crystal is removed from the MDI formulation. Thus, it is uncertain if any of the propellant is incorporated within the crystal structure when grown in a mixture with 20%

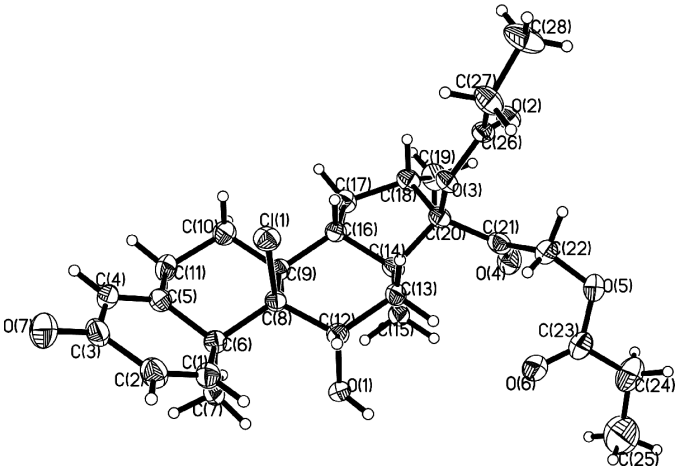


Figure 1
The molecular structure of beclomethasone dipropionate (BDP) in HFA-134a and 20% *w*/*w* absolute ethanol, showing 50% probability displacement ellipsoids and standard steroid atomic numbering scheme. The structure shown is BDP without disordered solvent, as calculated using SQUEEZE (Spek, 2003).

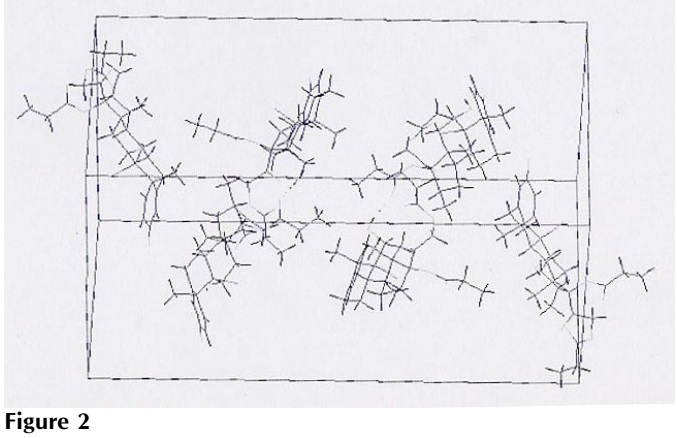


Figure 2
Packing diagram of one unit cell, viewed down the *c* axis. Hydrogen bonds are indicated by dashed lines. Note the herringbone stacking pattern among the six BDP molecules.

w/*w* absolute ethanol. Since HFA-134a has a low boiling point, 247 K, the rapid desolvation at ambient conditions may suggest the possibility of an HFA-134a solvate.

The resulting BDP crystal structure has a large channel where the solvent moves freely. The channel is perpendicular to the BDP crystal layers and lies along the *c* axis. Some hydrogen bonding may occur within the channel, but it is not likely to be sufficient to order the solvent. This was also found to be true in the case of BDP crystals grown in pure ethanol at low temperature, for which data were collected at low temperature (Kuehl *et al.* 2003). The hydrogen bonding that does exist does not appear to disrupt the threefold symmetry.

The BDP molecule has one hydroxyl group, which acts as a hydrogen donor. There are also four carbonyl groups, each of which is a potential acceptor. The carbonyl atom O2, on the shorter side-chain, accepts an intermolecular hydrogen bond from the hydroxyl group of a neighboring BDP molecule. The other carbonyl and ester O atoms of the side-chains protrude into the cavity channel for potential hydrogen bonding with the occluded solvent. Three BDP layers are stacked in a herring-bone pattern within the unit cell and the layers are related by a 120 degree rotation of the 3_1 axis.

Previous BDP research (Millard & Myrdal, 2002) has shown that the monohydrate (Duax *et al.*, 1981) and anhydrous crystalline forms both crystallize in space group $P2_12_12_1$, with similar structures and densities of 1.362 Mg m^{-3} and 1.287 Mg m^{-3}, respectively. These alternative crystal forms of BDP also differ in packing characteristics from the form reported in this paper. The density of the BDP framework with empty channels is lower, 1.063 Mg m^{-3}. Assuming a stoichiometric relationsip of 1 HFA-134a and 2 ethanol molecules, the inclusion of solvent in the channel would increase the density significantly (1.459 Mg m^{-3}). It is interesting to note that the BDP crystal channel reported in this paper is similar in structure to an isolated form that was grown in cold ethanol (Kuehl *et al.* 2003).

An interaction between BDP molecules and solvent molecules inside the MDI resulted in a conversion from the anhydrous form to a solvate/clathrate, which, surprisingly, is the most stable form. The knowledge gained from this exciting discovery will be helpful for future pharmaceutical work.

Experimental

The BDP crystals were obtained from a suspension of BDP in 20% *w*/*w* absolute ethanol and the propellant hydrofluoroalkane (HFA-134a) in a pressure-resistant vial and equilibrated. In order to isolate crystals for experimental use, dry ice was used to chill the formulation below the HFA boiling point, 247 K. The cap was removed and an amount of solution containing crystals was pipetted immediately on to a microscope slide with paratone oil. An oil-coated crystal was transferred within one minute to the 173 K cold stream on the goniometer.

Crystal data

$C_{28}H_{37}ClO_7\cdot 2C_2H_6O\cdot C_2H_2F_4$
M_r = 715.20
Trigonal, $P3_121$
a = 13.4642 (3) Å
c = 31.1187 (15) Å
V = 4885.5 (3) Å^3
Z = 6
D_x = 1.459 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 8036 reflections
θ = 2.2–21.6°
μ = 0.20 mm^{-1}
T = 170 (2) K
Hexagonal block, colorless
0.35 × 0.30 × 0.30 mm

Data collection

Bruker SMART 1000 CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Bruker, 1997)
T_{min} = 0.934, T_{max} = 0.943
59064 measured reflections
7130 independent reflections
6429 reflections with $I > 2\sigma(I)$
R_{int} = 0.058
θ_{max} = 27.0°
$h = -17 \rightarrow 17$
$k = -17 \rightarrow 17$
$l = -39 \rightarrow 39$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.044
$wR(F^2)$ = 0.099
S = 1.03
7130 reflections
331 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0537P)^2 + 0.7749P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.44 e Å^{-3}
$\Delta\rho_{min}$ = −0.23 e Å^{-3}
Absolute structure: Flack (1983), 2086 Friedel pairs
Flack parameter = 0.08 (5)

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

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1B···O2^{i}	0.84	2.11	2.9276 (18)	163

Symmetry code: (i) $1+y, x, -z$.

After completing the initial structure solution, it was found that 27% of the total cell volume was filled with disordered solvent, which could not be modeled as discrete molecules. This is common for a solvate due to the significant molecular mobility. Thus, it is difficult to know the exact location of each solvent molecule within the unit cell. Molecular-based models were attempted, but found to be unsatisfactory, because it was not possible to retain reasonable bond angles and distances of the solvent within the crystal channel while accounting for all observed density maxima. Analysis of the solvent void using *PLATON* (Spek, 2003) gave a volume of 1322.7 Å^3/cell, which is large enough for a number of HFA-134a and ethanol molecules to fit. From this point on, atoms in the region were removed and the solvent region was refined as a diffuse contribution without specific atom positions using the *PLATON* module SQUEEZE (Spek, 2003). The SQUEEZE program subtracts electron density from the void regions, by appropriately modifying the diffraction intensities of the overall structure. An electron count over the solvent region provides an estimate for the number of solvent molecules removed from the cell. The void volume can give the maximum number of solvent molecules remaining in the channel, but does not reveal an exact stoichiometric relationship. Given electron count and volume, it appears, on average, that the disordered solvent found within the BDP channel can be accounted for by 1 HFA-134a molecule and 2 ethanol molecules per formula unit. A dramatic improvement was observed in all refinement parameters and residuals when this procedure was applied. The H atoms were fixed by constrained refinement.

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

This structure was determined in the Molecular Structure Laboratory of the Department of Chemistry as part of the course Chem 517, University of Arizona, Tucson AZ 85721. The SMART1000 diffractometer was gratefully obtained with funds provided by NSF grant CHE9610374.

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