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Structural study of polymorphism in methylprednisolone aceponate

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ABSTRACT

The crystal structures of methylprednisolone aceponate were determined by X-ray diffraction analysis at temperatures 90 K and 150 K: space group $P2_12_12_1$, $a = 14.8592(2)$, $b = 19.6844(5)$, $c = 26.1626(4)$ Å, $Z = 12$; $R = 0.0598$ (T = 90 K); space group $P2_12_12_1$, $a = 6.57348(14)$, $b = 14.8295(3)$, $c = 26.2214(5)$ Å, $Z = 4$; $R = 0.0518$ (T = 150 K). Features of structural changes in the phase transition were revealed. The abrupt change in the unit cell parameters in the phase transition was shown by low-temperature X-ray powder. The methods of degree of invariance of crystal electron density and molecular Voronoi–Dirichlet polyhedra were used for the analysis of polymorphism in methylprednisolone aceponate. The atomic structure at 90 K have a translational pseudosymmetry of electron density $\eta = 0.329(1)$. The decrease of number of intermolecular contacts in the high-temperature modification due to rupture of intermolecular non-valence contacts C/O was observed.

1. Introduction

Methylprednisolone aceponate (CAS: 86401-95-8) is a new potent topical corticosteroid. The introduction of two ester groups results in a molecule with increased lipophilicity and enhanced penetration into skin [1]. It is rapidly metabolised and then conjugated so that although potent, it does not appear to cause serious local or systemic side effects [2]. Methylprednisolone aceponate has anti-inflammatory and vasoconstrictive actions. It is bioavailable from various formulations, such us ointment, cream and lotion. When applied topically the concentration of methylprednisolone aceponate is highest in the outer layer of the epidermis and decreases in the deeper strata.

This work is a continuation of systematic studies of steroid hormones. Earlier in the articles [3–5], we have investigated the thermodynamic properties of hydrocortisone acetate, methylprednisolone and methylprednisolone aceponate.

We found a reversible phase transition at 131 K in the study of the temperature dependence of the heat capacity of methylprednisolone aceponate [5]. However, it was not clear the reason of the phase transition. It should be noted that the structural investigations in the field of phase transition in steroid hormones were not carried out previously. The goals of this work include X-ray study of the modifications of the methylprednisolone aceponate with the purpose of understanding of the possible reasons of polymorphism in steroid hormones.

2. Experimental

Methylprednisolone aceponate (MPA) was purchased from Fluka. Synthesis of single crystals of methylprednisolone aceponate was carried out by isothermal crystallization from an acetone solution at 280 K.

All single crystal X-ray diffraction experiments were carried out using XtaLAB Pro MM003 diffractometer (MoKα, λ = 0.71073 Å, ω-scans) with Cobra Oxford Cryosystems cooler. Data collection and reduction were carried out using CrysAlis Pro [6] software. The crystallographic parameters and the X-ray-data-collection and structure-refinement statistics are given in Table 1. We have denoted **I** - structure of MPA at T = 150 K and **II** - structure of MPA at T = 90 K. The initial structural fragment of **I** and **II** structures were solved by direct methods. The positions of the missing non-hydrogen atoms were found in difference-electron-density maps and refined with anisotropic displacement parameters. The coordinates of some hydrogen atoms were found in difference-electron-density maps and refined independently with isotropic displacement parameters. Others hydrogen atoms were placed in calculated positions and refined in the “riding-model”. X-ray diffraction study were deposited in the Cambridge Crystallographic

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Table 1
Crystallographic parameters and the X-ray-data-collection and structure-refinement statistics.

Formula	$C_{27}H_{36}O_7$	
CCDC	1509285	1509283
T, K	150(2)	90(2)
M	472.56	
Symmetry, Z	Orthorhombic $P2_12_12_1$, 4	Orthorhombic $P2_12_12_1$, 12
a, Å	6.57348(14)	14.8592(2)
b, Å	14.8295(3)	19.6844(5)
c, Å	26.2214(5)	26.1626(4)
V, Å^3	2556.11(9)	7652.4(2)
ρ, g•cm^{-3}	1.228	1.231
μ, mm^{-1}	0.088	0.088
F(000)	1016	3048
Size, мм	0.973 × 0.298 × 0.248	
Diffractometer/	XtaLAB Pro MM003/	
Radiation/	MoKα, λ = 0.71073 Å/	
Scan	ω-scans	
Range of θ, deg.	3.467–26.369	3.319–26.371
Range of indices	$-8 \le h \le 8$	$-18 \le h \le 18$
	$-18 \le k \le 18$	$-24 \le k \le 24$
	$-32 \le l \le 32$	$-32 \le l \le 32$
Measured reflections, all/independent/with $I > 2\sigma(I)$/R_{int}	44287/5225/4583/0.0634	133064/15622/12647/0.0663
Parameters/restraints	401/15	943/3
GOOF	1.063	1.022
R[$F^2 > 2\sigma(F^2)$]	R = 0.0426	R = 0.0417
	w*R* = 0.0858	w*R* = 0.0913
R [all]	R = 0.0518	R = 0.0598
	w*R* = 0.0889	w*R* = 0.0986
Δρ(min/max), e/A^3	−0.193/0.175	−0.207/0.451
Software	CrysAlis Pro [6], SHELX-2014 [7], WinGX [8], Mercury [9]	

Data Centre (CCDC **I** – 1509285 and **II** – 1509283).

The low-temperature X-ray powder diffraction was carried out on X-ray diffractometer XRD-6000 (Shimadzu) in the 2θ range from 5° to 60° using Attachment TTK-450 (Anton Paar) in the temperature interval from 120 K to 325 K.

The method of degree of invariance of crystal electron density was used for the quantification of pseudosymmetry atomic structures of crystals [10–12]. The method of molecular Voronoi–Dirichlet polyhedra was used for the analysis of the polymorphic system of methylprednisolone aceponate [13,14].

3. Results and discussion

Both modifications I and II were shown to be orthorhombic with space group $P2_12_12_1$, but with considerably different cell dimensions (for modification II: a = 14.8592(2), b = 19.6844(5), c = 26.1626(4) Å, Z = 12; for modification I: a = 6.57348(14), b = 14.8295(3), c = 26.2214(5) Å, Z = 4), indicating a different packing of MPA molecules. The basis of the structure of MPA molecule is a steroid core, which consists of 17 carbon atoms, bonded in four rings connected by edges: three cyclohexane rings and one cyclopentane ring (Fig. 1). The functional groups (methyl, aceponate, hydroxyl) were attached to steroid core. MPA molecules form a typical molecular crystal whose molecules are linked together by van der Waals forces and hydrogen bonds. Parameters of hydrogen bonding at various temperatures are shown in Table 2.

There are three molecules of MPA for one unit cell period along the crystallographic direction [010] in the low-temperature phase (T = 90 K) (Fig. 2). In general, the spatial orientation of these molecules is almost identical, but the methyl groups are C54, C27 and C81 are disordered. If conditionally orientation of the methyl groups indicated by arrow up (↑) and down (↓), then schematically orientation distribution methyl groups in modification II along the direction [010] can be written as … [C_{54}↓ C_{27}↑ C_{81}↓] [C_{54}↓ C_{27}↑ C_{81}↓] …where the square brackets denote limits of one unit cell.

The degree of invariance of crystal electron density ρ(**r**) with respect to operation $\hat{q}$ is determined by the functional $\eta_{\hat{q}}[\rho(\mathbf{r})] = K^{-1}\int_V \rho(\mathbf{r})\rho(\hat{q}\mathbf{r})dV$, where *K* is normalization factor, $\hat{q}$ is a coordinate transformation operator. The value of the functional characterizes the fraction of crystal electron density that is

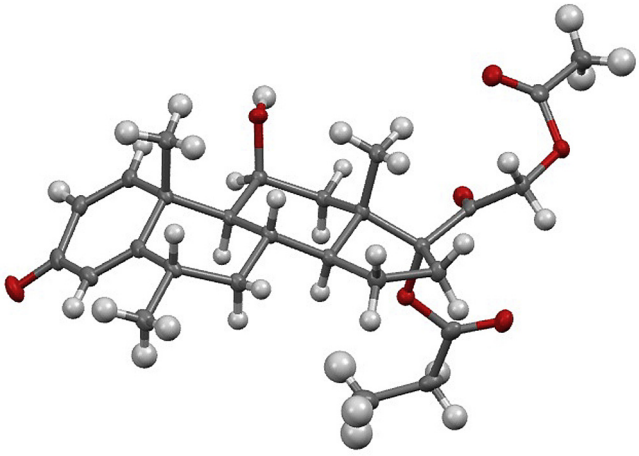

Fig. 1. The structure of the molecule of methylprednisolone aceponate.

Table 2
Hydrogen-bond geometry.

D–H…A	D–H, Å	H…A, Å	D…A, Å	D–H…A, °
I				
O2–H2*A*…O1^{ii}	0.85(1)	1.91(1)	2.753(3)	174(3)
O9–H9*A*…O15^{iii}	0.85(1)	1.95(1)	2.787(3)	171(3)
O16–H16···O8	0.85(1)	1.91(1)	2.750(3)	169(3)
II				
O2–H2A…O1^{i}	0.82	2.05	2.753(3)	143

Symmetry code: (i) x−1/2, −y+1/2, −z; (ii) x+1/2, −y+1/2, −z; (iii) x−1, y, z.