Journal of Molecular Structure 891 (2008) 437–442

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstruc

The structure of betaxolol from single crystal X-ray diffraction and natural bond orbital analysis

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ARTICLE INFO

Article history:
Received 28 February 2008
Received in revised form 11 April 2008
Accepted 14 April 2008
Available online 24 April 2008

Keywords:
Betaxolol
Molecular structure
X-ray diffraction
Density functional theory
NBO analysis
Molecular flexibility conformers

ABSTRACT

The structure of betaxolol obtained from ethanol:water solution was studied by X-ray diffraction. The geometrical parameters needed to define the structure are tabulated. The X-ray data show the existence of two conformers in the unit cell differing only in the conformation of the cyclopropylmethoxy fragment. Differences in the bond lengths angles and dihedral between both conformations are observed. The cyclopropyl groups lie in approximately perpendicular planes.

The two molecular geometries identified by single crystal X-ray diffraction were optimized at the B3LYP/6-31G(d,p) level of theory. Both isolated molecules are retained as distinct conformers upon geometry optimization, despite some dihedral relaxation.

The electronic structure of the most important molecular fragments was described in terms of Natural Bond Orbitals. The energetic and spatial features of the occupied and vacant orbitals were studied.

The different structures observed in the solid state were explained by the specific interactions involving the oxygen lone pairs in cyclopropylmethoxy. It was observed some orbital and geometry distortion in cyclopropyl caused by the crystal packing.

1. Introduction

The knowledge of the structure of a compound in multiple phases used as a medicine is a prerequisite to interpret its chemical and biological activity and to explore further applications [1]. Nowadays, it is common knowledge that minute structural details play an important role in the biological activity or in the properties required by formulation and the chemical and thermal stability of the drug. Hence the interest dedicated to the solid state research by the pharmaceutical industry.

This paper deals with the structure of the betaxolol, 1-[4-[2-(cyclopropylmethoxy)ethyl]phenoxy]-3-(1-methylethylamino) propan-2-ol, a common drug used for hypertension and glaucoma treatment. It belongs to the beta blocker class drugs, with which it shares part of its molecular structure. It is specifically a β_1 selective agent [2].

The crystalline structure of betaxolol is characterized experimentally in this work by means of single crystal X-ray diffraction. The electronic structure of the single crystal molecular conformation was studied by Density Functional Theory, using the B3LYP functional with the 6-31(d,p) basis set. This included Natural Bond Orbital (NBO) analysis of the most important orbital interactions, in order to clarify general structural features of β-blockers and others specific of betaxolol.

2. Experimental

2.1. Preparation and characterization of the crystals

(*R*,*S*)-betaxolol (BT) was prepared from its hydrochloride salt kindly provided by Capsifar Ltd. The compound was certified as 99.68%. A purity test by HPLC analysis did not show any extraneous peak in the chromatogram.

The compound was obtained by solvent extraction from an alkaline aqueous solution of betaxolol hydrochloride (BTH) with methylene chloride. The organic phase was dried at 25 °C in a rotary vacuum evaporator. Crystalline betaxolol was then recrystallized from methanol:water (20:80, v/v). Bidistilled water and spectroscopic grade methanol (99.9% GC) were used. The crystallization was performed by slow evaporation of the solvent.

The microscopic examination of the solid under polarized light shows the presence of birefringent acicular crystals (Fig. 1). The solid was also characterized by Differential Scanning Calorimetry

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doi:10.1016/j.molstruc.2008.04.029

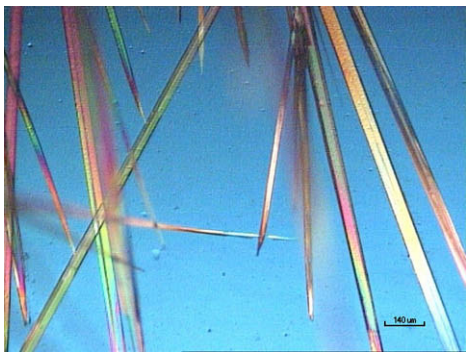

Fig. 1. Photomicrography of (*R*,*S*)-betaxolol crystals observed under polarized light 50×.

(DSC) with a Pyris 1 Perkin Elmer, following routine calibration procedure. No additional peaks were observed on heating from 25 °C to fusion (Fig. 2). This phase transition takes place at T_{onset} = (67.49 ± 0.26) °C (n = 5) and is followed by an enthalpy variation, ΔH_{fus} = (45.9 ± 0.2) kJ mol^{-1} (n = 7).

2.2. X-ray data collection and structure determination

X-ray diffraction measurements were carried out by Mo Kα radiation on a CAD-4 diffractometer equipped with a conventional detector. Data reduction was performed with HELENA [3]. Lorenz and polarization corrections were applied. The structure was solved with direct methods using SHELXS-97 [4], and refined on F^2's by full-matrix least-squares with SHELXL-97 [4]. The anisotropic displacement parameters for non-hydrogen atoms were applied with exception of those that are disordered over two positions. Hydrogen atoms were placed at calculated positions and refined with isotropic parameters as riding atoms.

3. Results and discussion

3.1. Discussion of the X-ray data

The X-ray diffraction crystal data and details concerning data collection and structure refinement are given in Table 1. The ORTEPII [5] diagram for (*R*,*S*)-betaxolol using probability ellipsoids are shown in Fig. 3. Atomic coordinates have been deposited at the Cambridge Crystallographic Data Centre and allocated under deposition number CCDC 648386.

The (*R*,*S*)-betaxolol crystallizes in a centrosymmetric space group P$\bar{1}$. The molecule consists of a central planar phenoxy group, a methylethylamino head and a cyclopropylmethoxy tail (Fig. 3). C13 also shares the least-squares phenoxy plane with a deviation

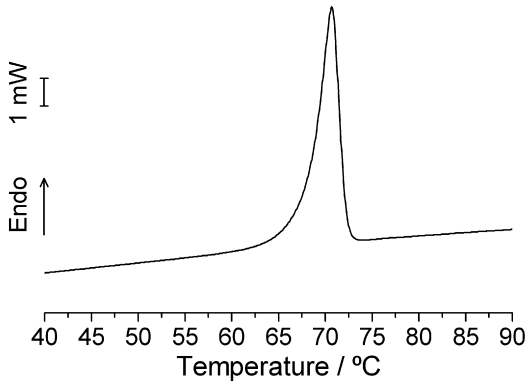

Fig. 2. DSC fusion curve of BT run at 10 °C min^{-1} scanning rate.

Table 1
Crystal data and structure refinement parameters for (*R*,*S*)-betaxolol

Empirical formula	$C_{18}H_{29}NO_3$
Formula weight	307.42
Temperature (K)	293(2)
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	$P\bar{1}$
a (Å)	4.9799(11)
b (Å)	10.010(2)
c (Å)	19.123(3)
α (°)	103.022(17)
β (°)	91.29(3)
γ (°)	102.079(16)
Volume (Å^3)	905.8(3)
Z	2
Calculated density/g cm^{-3}	1.1272(4)
Absorption coefficient (mm^{-1})	0.076
F(000)	336
Crystal size/mm	0.43 × 0.16 × 0.12
θ Range for data collection (°)	3.29–22.46
Index ranges	$-5 < h < 5, -10 < k < 10, -20 < l < 20$
Reflections collected/unique	3925/2348 [R(int) = 0.0475]
Completeness to θ_{max} (%)	99.7
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2348/0/235
Goodness-of-fit on F^2	1.023
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0540 $wR2$ = 0.1455
R indices (all data)	$R1$ = 0.1119 $wR2$ = 0.1709
Largest diff. peak and hole/e Å^{-3}	0.224 and −0.150

of −0.007(4) Å. In this molecule N1–C3–C2–C1 also shares a plane that makes an angle of 68.0(2)° with the phenoxy plane. When viewed along the C2–C3 bond, shows a staggered conformation with C1 *trans* relative to N1 and O2 *gauche* to N1, the O2–C2–C3–N1 torsion angle is −62.1(4)°.

The cyclopropylmethoxy group has two alternative configurations, differing one from another just from O3 onwards. The structures A and B are detailed in Fig. 4, and can be characterized by geometrical parameters presented in Table 3.

The A and B alternate structures can interconvert by two distinct paths: by rotation of the O3–C15 and C15–C16 bonds or by inversion centered in C16.

The relative occupation is 59% for A and 41% for B. The uncertainty of the cyclopropyl atoms is higher than in the remaining structure. The two planes defined by each of the alternate cyclopropyl positions form an 82° angle.

The mean value found by experimental techniques for C–C length in cyclopropane and derivatives is 1.509 Å with the standard deviations of 0.002 Å [6]. As shown in Table 3, both cyclopropyl groups of betaxolol present significant deviations from this values and deviation between themselves.

The individual molecules are assembled in the crystal in such a fashion that the mutually inverted neighbors face each other head to head and tail to tail. This allows the formation of H-bonds between the hydroxy and amino groups (Fig. 5 and Table 2). Attending to the geometrical parameters the hydrogen bond, when O2–H2 acts as a donor is much stronger then when it acts as acceptor. The π electron cloud of the aromatic phenyl ring also acts as an acceptor in this structure joining the molecules along the *a*-axis. The donor (C1)-ring centroid distance is 4.044 Å, with a bond angle of 149.4° and with the shared hydrogen deviating 16.8° from the ring plane normal. A weak intramolecular bond could also be formed with a hydrogen being shared between C3 and O1 based only in the relatively large H3′...O1 distance (2.57 Å), as the C3–H3′...O1 angle is not favorable (101°). However, as can been seen in NBO analysis, no evidence of this interaction was found.

The intermolecular H-bonds join the molecules in ribbons along the *a*-axis as seen in Fig. 5. Each O2–H2...N1^{i} (i) and N1–H1...O2^{ii} (ii) delineate 10-membered rings.