Journal of Molecular Structure 1123 (2016) 271–275

Contents lists available at ScienceDirect

Journal of Molecular Structure

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

Structural characterization and Hirshfeld surface analysis of racemic baclofen

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ARTICLE INFO

Article history:
Received 25 February 2016
Received in revised form
13 June 2016
Accepted 14 June 2016
Available online 16 June 2016

Keywords:
Baclofen
Structure characterization
Hirshfeld surfaces
Hydrogen bonding
GABA derivative

ABSTRACT

The crystal structure of baclofen, (R,S) [4-amino-3-(4-chlorophenyl)butanoic acid], ($C_{10}H_{12}ClNO_2$, M_r = 213.66) has been determined by single crystal X-ray diffraction analysis. The title compound crystallizes in the orthorhombic space group *Pbca* (No. 61) with a = 9.2704(5), b = 7.0397(4), c = 30.4015(15) Å, V = 1984.0(2) Å^3 and Z = 8. The molecules exist as zwitterions, adopting a *gauche* conformation with respect to the C_α–C_β bond, and held in a cross-linked chain arrangement by strong N–H···O hydrogen bonds and C–Cl···π interactions. The electrostatic molecular potential as well as the intermolecular interactions of the title compound were analyzed by the Hirshfeld surfaces. The FT-IR spectrum is also reported. The DTA, TG and DTG results indicate that baclofen is stable up to 205 °C.

1. Introduction

The spasticity is very common potentially disabling and bothersome complications affecting individuals with spinal cord lesion [1]. It may be defined as a motor disorder characterized by an overactivity of stretch reflexes [2]. Clinically, this can cause for instance weakness of voluntary movement, increased muscle tone, and increased tendon reflexes. Curtis (et al.) has postulated that γ-aminobutyric acid (GABA), which is the hyperpolarizing inhibitory transmitter responsible for the prolonged postsynaptic inhibition of spinal motoneurons can be used in the treatment of spasticity [3]. However, attempts to use GABA in such a therapy appeared ineffective. For this reason a number of GABA derivatives were synthesized with lipophilic substituents and subsequently tested; of these, baclofen, γ-aminobutyric acid ($GABA_B$) receptor agonist, was found to be the most active one and now is regarded as a drug of choice in the treatment of spasticity and trigeminal neuralgia [4–7]. It is thus somewhat surprising that, despite the fact of using the title compound as a drug by more than 30 years no crystal structure of pure baclofen or any its solvate has yet been reported. On the basis of a literature review we have only found reports on crystal structures of (R,S)- or R-baclofen hydrochloride salts [8], baclofen cocrystal with ferulic acid [9] and very recently multi-component co-crystals formed between baclofen and selected monocarboxylic and dicarboxylic acids [10]. It was also confirmed by various analytical techniques, that baclofen can exist in two crystalline forms, the anhydrate and monohydrate. Since, there are distinct differences in the powder diffraction patterns of the anhydrate and monohydrate, indicating that these two solid forms have unique crystal structures [11]. We report here the crystal and molecular structure of racemic baclofen as part of our ongoing study of the structural characterization and properties of drug molecules.

2. Experimental

The baclofen was obtained by neutralization of baclofen hydrochloride using $NH_3\cdots H_2O$. For this purpose, methanol solution of the baclofen hydrochloride was heated to 60 °C and 12% $NH_3\cdots H_2O$ was dropped carefully to the reaction mixture to pH 6.9–7.0 and then the reaction mixture was intensively stirred for 2 h. Crystallization was conducted from methanol. Very thin needle crystals were filtered and washed with cold water. The product was dried at 60 °C. Yield of synthesis was 41%. Despite repeated attempts it appeared very difficult to obtain really good quality crystals for X-ray diffraction analysis.

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http://dx.doi.org/10.1016/j.molstruc.2016.06.041
0022-2860/

Table 1
Crystal and structure refinement data.

Formula	$C_{10}H_{12}ClNO_2$
CCDC no.	1455243
Formula weigh	213.66
Temperature, K	100
Wavelength, Å	CuK_α
Crystal system	Orthorhombic
Space group	*Pbca*
Unit cell dimensions, Å	9.2704(5)
	7.0397(4)
	30.4015(15)
Volume, Å^3	1984.0(2)
Z	8
Calculated density, g cm^3	1.431
Absorption coefficient mm^{-1}	3.197
θ range for data collection	5.6–66.0
Limiting indices (*h*, *k*, *l*)	−10/10, −7/7, −35/36
Reflections collected/unique	13172/1558
Data/restraints/parameters	1558/0/139
R_{int}	0.053
Goodness-of-fit on F^2	1.146
R[$F^2 > 2\sigma(F^2)$]	0.0858
R (all data)	0.0888
w*R*[$F^2 > 2\sigma(F^2)$]	0.240
w*R*(F^2)	0.241
Largest diff. peak and hole, e Å^{-3}	1.03, −0.45

$w = 1/[\sigma^2(Fo^2) + (0.0803P)^2 + 14.7802P]$ where $P = (Fo^2 + 2Fc^2)/3$.

2.1. Fourier transform infrared (FT-IR) spectroscopy

The FT-IR spectrum was obtained by using a Thermo Nicolet 6700 spectrometer (Thermo Scientific, USA) with MCT detector (photoconductive detector HgCdTe). Sample was scanned by transmission through KBr pellet. FT-IR spectrum was recorded at room temperature in the range of 4000–500 cm^{-1}. Infrared spectrum exhibited characteristic bands at 3050-2950 cm^{-1} (C–H stretch), 1680 cm^{-1} (C=O, stretch), 1585 cm^{-1} (N–H, bending), 860 cm^{-1} (C–Cl, stretch). The FT-IR spectrum is illustrated in Fig. 1S enclosed in Supporting Information.

2.2. Thermal analysis

The thermal properties of baclofen were studied by DTA-TG-DTG techniques in the range of temperature from 25 up to 700 °C and at a heating rate of 10 °C min^{-1}. The SETSYS-16/18 (Setaram) apparatus was used. The sample (9.91 mg) was studied in flow of air atmosphere using aluminum crucibles. The DTA-TG-DTG methods were used to describe of thermal properties of baclofen in air atmosphere. The DTA-TG-DTG curves are illustrated in Fig. 2S enclosed in Supporting Information. At about 205 °C, a sharp mass loss starts due to the degradation of the compound and there is no mass loss observed up to this temperature, hence the crystal might not have any solvent in it.

Table 2
Selected bond lengths (Å) and angles (°).

Cl1–C8	1.759(7)	O2–C1–C2	118.1(4)
O1–C1	1.273(6)	O1–C1–O2	123.3(5)
O2–C1	1.250(6)	O1–C1–C2	118.7(4)
N1–C4	1.485(8)	C1–C2–C3	115.5(4)
C1–C2	1.523(8)	C2–C3–C4	108.4(4)
C2–C3	1.538(8)	C2–C3–C5	111.1(4)
C3–C4	1.527(8)	C4–C3–C5	111.3(5)
C3–C5	1.528(8)	C3–C4–N1	112.9(4)
C5–C10	1.391(8)	C6–C5–C10	118.6(5)
C5–C6	1.388(8)	C3–C5–C6	120.8(5)
C6–C7	1.381(8)	C3–C5–C10	120.5(5)
C7–C8	1.370(9)	C5–C6–C7	121.2(5)
C8–C9	1.376(9)	C6–C7–C8	118.3(5)
C9–C10	1.386(9)	C7–C8–Cl1	119.0(5)
		C9–C8–Cl1	118.1(5)
		C7–C8–C9	122.9(6)
		C8–C9–C10	117.9(5)
		C5–C10–C9	121.1(5)

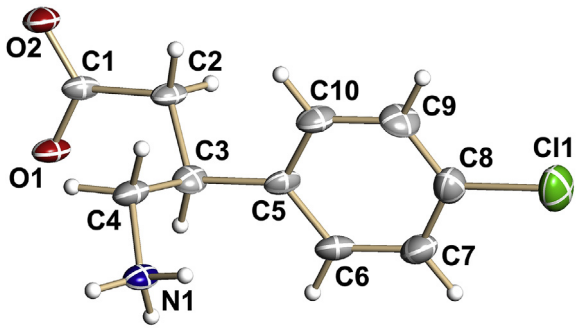

Fig. 1. A perspective view of the baclofen with atom labeling scheme. Thermal ellipsoids are drawn at the 50% probability level.

2.3. X-ray crystallography

X-ray diffraction data were collected at 100 K by the ω-scan technique using a Bruker AXS Smart APEX-II CCD diffractometer with MonoCap capillary and 30 W Incoatec Microfocus Source IμS with Montel optics and Cu-Kα radiation (λ = 1.54178 Å). Data collection, cell refinement, data reduction, analysis and absorption correction were carried out with the SMART and SAINTPLUS [12]. The structure was solved by direct methods with SHELXS [13] and refined by a full-matrix least-squares technique on F^2 using SHELXL-2014 [14] with anisotropic thermal parameters for the non-H atoms. All H-atoms were located using difference Fourier techniques and refined with isotropic temperature factors. Molecular graphics used: program Mercury [15]. Additional details of the data collection and refinement are listed in Table 1. Selected bond lengths and angles are given in Table 2.

2.4. Hirshfeld surface analysis

The electrostatic molecular potential for baclofen was mapped on Hirshfeld surfaces (HS) over the range −0.05 au (red), through 0 (white), to 0.05 au (blue). Ab initio wavefunctions were obtained using Tonto program [16]. A 6-311++G (3df, 2pd) basis set at the Hartree–Fock level and molecular geometries directly from the relevant crystal structure was employed. The HS divide the crystal space into smooth non-overlapping molecular volumes and give a unique information about each molecule in a crystal. This enables a convenient analysis of intermolecular interactions in a crystal. The Hirshfeld surfaces [17] and the related 2D-fingerprint plots [18] were calculated using CrystalExplorer (Ver. 3.1) [19]. Before

Table 3
Hydrogen bonding (Å,°).

D–H···A	D–H	H···A	D···A	D–H···A
N1–H11···O1^{i}	0.94(8)	1.85(8)	2.777(6)	171(7)
N1–H12···O2^{ii}	0.97(5)	1.83(5)	2.742(6)	156(5)
N1–H13···O1^{iii}	0.97(8)	1.84(8)	2.801(6)	170(7)

Symmetry code: (i) 1/2−x, ½+y, z; (ii) 1−x,1−y,−z; (iii) x,1+y,z.