



HAL
open science

A network of weak hydrogen bonds in the crystal structure of Tetrzepam

H. Allouchi, R. Ceolin, A. Gueiffier, Ivo B. Rietveld

► **To cite this version:**

H. Allouchi, R. Ceolin, A. Gueiffier, Ivo B. Rietveld. A network of weak hydrogen bonds in the crystal structure of Tetrzepam. *Annales Pharmaceutiques Françaises*, 2019, 77 (2), pp.121-125. 10.1016/j.pharma.2018.11.002 . hal-02147887

HAL Id: hal-02147887

<https://hal-normandie-univ.archives-ouvertes.fr/hal-02147887>

Submitted on 22 Oct 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial| 4.0 International License

A Network of Weak Hydrogen Bonds in the Crystal Structure of Tétrazepam

Un Réseau de Liaisons Hydrogène Faibles dans la Structure Cristalline du Tétrazepam

Hassan Allouchi¹, René Ceolin², Alain Gueiffier¹, Ivo B. Rietveld^{3,4*}

¹ EA SIMBA: Synthèse et Isolement de Molécules BioActives, Laboratoire de Chimie Physique, Faculté de Pharmacie, 31, avenue Monge - 37200 Tours, France

² LETIAM, EA7357, IUT Orsay, université Paris Sud, rue Noetzlin, 91405 Orsay Cedex, France

³ Faculté de Pharmacie, Université Paris Descartes, USPC, 4 avenue de l'observatoire, 75006, Paris, France

⁴ Normandie Université, Laboratoire SMS - EA 3233, Université de Rouen, F 76821 Mont Saint Aignan, France

* corresponding author: ivo.rietveld@univ-rouen.fr

Abstract

The crystal structure of tetrazepam, a benzodiazepine derivative formerly used for its muscle relaxant properties, has been solved and found to be monoclinic, space group $P2_1/c$, with lattice parameters $a = 12.7386(7) \text{ \AA}$, $b = 11.3774(7) \text{ \AA}$, $c = 10.3084(7) \text{ \AA}$, $\beta = 103.175(5)^\circ$ and $V_{\text{unit-cell}} = 1454.69(16) \text{ \AA}^3$ at room temperature (293 K) with $Z = 4$ molecules in the unit-cell. A network of weak hydrogen bonds involving aliphatic hydrogen atoms plays an important role in the formation of this structure.

Résumé

La structure cristalline du tétrazépam, une benzodiazépine naguère utilisée pour ses propriétés de relaxation musculaire, a été résolue. Elle appartient au système monoclinique, groupe d'espace $P2_1/c$, et sa maille élémentaire possède les paramètres suivants : $a = 12.7386(7) \text{ \AA}$, $b = 11.3774(7) \text{ \AA}$, $c = 10.3084(7) \text{ \AA}$, $\beta = 103.175(5)^\circ$, $V_{\text{maille}} = 1454.69(16) \text{ \AA}^3$, et $Z = 4$ molécules par maille élémentaire à température ambiante (293 K). Un réseau de liaisons hydrogène faibles avec des hydrogènes aliphatiques joue un rôle important dans la formation de cette structure.

Keywords

Tetrazepam; crystal structure; weak hydrogen bonds

Mots-clés

Tétrazépam ; structure cristalline; liaisons hydrogène faibles

1 Introduction

Tetrazepam ($C_{16}H_{17}ClN_2O$, IUPAC name: 7-chloro-5-(cyclohex-1-enyl)-1,3-dihydro-1-methyl-2H-1,4-benzodiazepin-2-one, $M = 288.77 \text{ g mol}^{-1}$) is a benzodiazepine derivative formerly prescribed for its muscle relaxant properties and the management of anxiety disorders. However, due to side effects such as allergic hypersensitivity reactions, it has been suspended from the market in the European Union since 2013 [1].

Although it has been patented about fifty years ago [2], its structural details through X-ray diffractometry surprisingly have been found wanting. Therefore, the crystal structure of tetrazepam was solved using single-crystal X-ray diffractometry and the results are presented in the following.

2 Materials and methods

2.1 Crystal preparation

A sample of tetrazepam powder of medicinal grade was kindly supplied by Daiichi Sankyo France SAS and single crystals were obtained by slowly evaporating solutions in methanol at room temperature.

2.2 Single-crystal measurements, structure determination and refinement

Intensities were collected through ω scans at 293 K from a crystal mounted on a Bruker-Nonius κ -CCD diffractometer, equipped with a CCD camera as an area detector using a graphite-monochromator and Mo- $K\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$) from a fine-focus sealed tube. The unit cell determination, refinement, and data collection have been carried out using the Collect [3] and Dirax programs [4]. Data reduction was carried out with the EvalCCD program [5]. A semi-empirical absorption correction was carried out using the SADABS program [6]. The positions of non-hydrogen atoms have been determined and refined with the SHELXS program [7]. They were first refined isotropically and then anisotropically by a full-matrix least squares method based on F^2 using the SHELXe program [8]. The hydrogen atoms were introduced on positions determined by the geometrical model of the hybridized carbon atoms to which they are linked with isotropic atomic displacement parameters set proportional to those of the linked atoms by a factor of 1.2. Geometry and proportional constraints were kept constant (rigid group) reducing the refinement to that of the coordinates and atomic displacement parameters of the atoms to which the hydrogens are linked.

3 Results and discussion

Tetrazepam was found to crystallize at 293 K in the monoclinic system, space group $P2_1/c$, with lattice parameters $a = 12.7386(7) \text{ \AA}$, $b = 11.3774(7) \text{ \AA}$, $c = 10.3084(7) \text{ \AA}$, $\beta = 103.175(5)^\circ$, $V_{\text{cell}} = 1454.69(16) \text{ \AA}^3$, and $Z = 4$ molecules per unit-cell. Crystallographic information is compiled in Table 1 and the fractional atomic coordinates of the non-

hydrogen atoms are listed in Table 2. Other data (bond lengths, bond angles, anisotropic displacement parameters, hydrogen-atoms coordinates, torsion angles) can be found in Tables S1 to S4 of the Supplementary Information. The crystal structure in the form of a CIF has been submitted to the Cambridge Crystallographic Data Centre (CCDC) with the deposition number CCDC 1857121. The CIF contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the CCDC via www.ccdc.cam.ac.uk/data_request/cif.

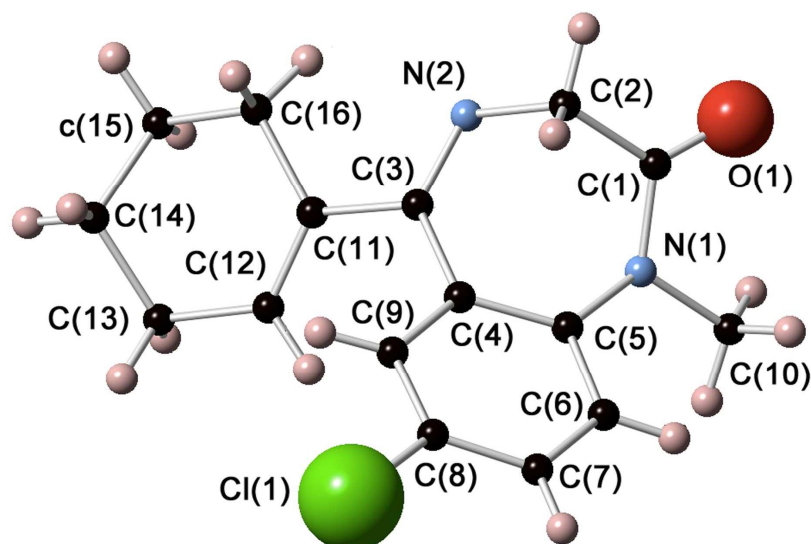


Figure 1. Tetrazepam molecule with labeled non-hydrogen atoms in the asymmetric unit. Pink = hydrogen atoms.

Molécule de tétrazépam avec la numérotation des atomes (à l'exception des atomes d'hydrogène) dans l'unité asymétrique. Rose = atomes d'hydrogène.

The molecular structure of tetrazepam with labels for the non-hydrogen atoms is presented in Figure 1. In the monoclinic packing of the tetrazepam crystals, the molecules are held together by a complicated network of weak C-H \cdots O and C-H \cdots Cl hydrogen bonds [9, 10, 11] whose distances and angles are listed in Table 3 and compared to values in the literature [12, 13]. Bonding analysis shows that intra- and intermolecular hydrogen bonds occur. One of the more important weak C-H \cdots O hydrogen bonds form centrosymmetric dimers shown in Figure 2.

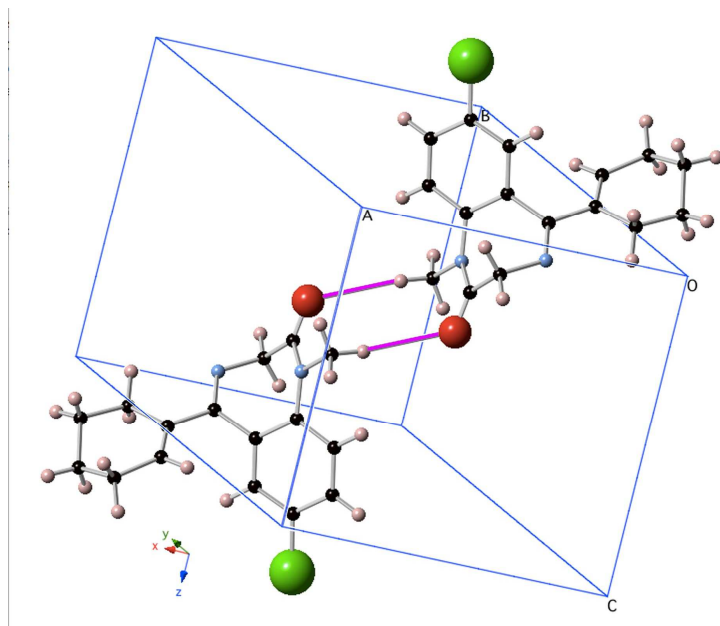


Figure 2. Hydrogen-bonded tetrazepam dimers. The dimers are formed by two weak C-H \cdots O hydrogen bonds, C(10)-H(10A) \cdots O(1), symbolized by the violet lines. The unit-cell is drawn in blue.

Dimère de tétrazépam formé par liaisons hydrogène. Les liaisons hydrogène C-H \cdots O faibles sont symbolisées par les segments violets. La maille élémentaire est représentée en bleu.

These dimers stack and form layers parallel to the **bc** plane, as shown in Figure 3.

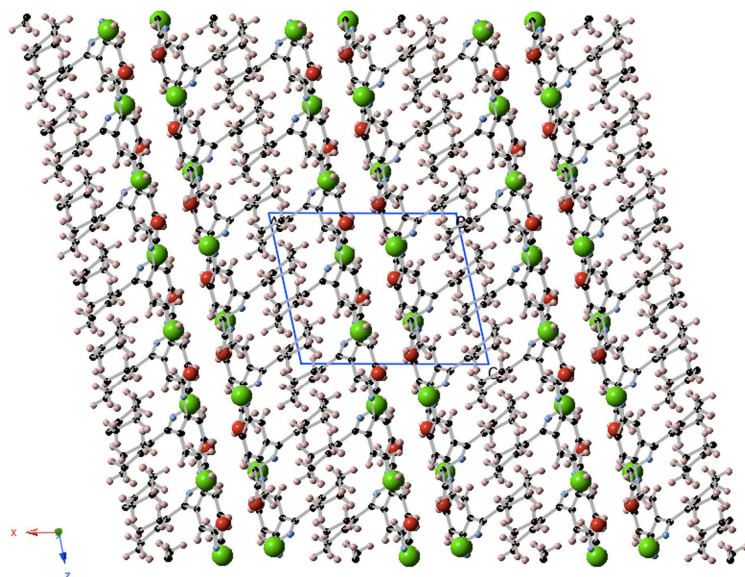


Figure 3. Monoclinic packing of the tetrazepam dimers parallel to the **bc** plane. View along cell axis **b**. The unit-cell is shown in blue.

*Empilement monoclinique des dimères de tétrazépam parallèlement au plan **bc**. Vue selon l'axe **b** de la maille élémentaire. Celle-ci est représentée en bleu.*

4 Concluding remarks

Although the European Community decided in 2006 through the REACH regulation [14] to “... *generate information on substances and their uses.*” and to demand that “*All available and relevant information on substances on their own, ... should be collected...*”, basic physicochemical properties such as crystal structures remain unknown for several older active pharmaceutical ingredients (API). In this context, the crystal structure of tetrazepam has been determined at room temperature and found to be monoclinic. Even if this API has been withdrawn from the European market, the present crystal structure can now be used for unambiguous characterization of the molecule in the solid state through X-ray powder diffraction.

Conflicts of interest

No conflicts of interest to declare.

References

- [1] B. Poy-Vega, N. Cano-Cuenca, C. Aguirre, J. Solís,-García del Pozo, J. Jordán. Requiem for tetrazepam. *Rev. Neurol.* 57(1), 2013, 1-2.
- [2] Patents **US3426014** (Clin-Byla ; 4. 2. 1969 ; F-prior. 9. 1. 1965, 9. 4. 1965), **US3551412** (Clin-Byla ; 29. 12. 1970 ; F-prior. 8. 8. 1967).
- [3] *COLLECT* program, Bruker AXS BV, 1997-2004.
- [4] Dirax/lsq program, Duisenberg & Schreurs, 1989-2000.
- [5] EvalCCD program, Bruker AXS BV, Duisenberg & Schreurs, 1990-2000.
- [6] G. M. Sheldrick. SADABS, “Empirical Absorption Correction Program,” University of Göttingen, Göttingen, 1997.
- [7] G.M. Sheldrick, A short history of SHELX. *Acta Crystallogr.* A64, 2008, 112-122.
- [8] C.B. Hübschle, G.M. Sheldrick, B. Dittrich. SHELXe. *J. Appl. Cryst.*, 44, 2011, 1281-1284.
- [9] G. R. Desiraju. The C-H...O Hydrogen Bond in Crystals: What Is It ? *Acc. Chem. Res.*, 24, 1991, 290-296.
- [10] T. Steiner, G. R. Desiraju. Distinction between the weak hydrogen bond and the van der Waals interaction. *Chem. Commun.*, 1998, 891-892.
- [11] T. Steiner. C-H...O hydrogen bonding in crystals. *Crystallography Reviews.* 9(2-3), 2003, 177-228.
- [12] G. A. Jeffrey, L. Lewis.

Cooperative aspects of hydrogen bonding in carbohydrates.
Carbohydrate Research. 60, 1978, 179-182.

[13] R. Taylor, O. Kennard.

Comparison of X-ray and Neutron Diffraction Results for the N-H...O=C Hydrogen Bond.
Acta Crystallogr. B39, 1983, 133-138.

[14] Regulation (EC) N° 1907/2006 of the European Parliament and of the Council of 18 December 2006, concerning the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH).

Tables

Table 1. Crystal data and structure refinement for tetrazepam at 293 K

Table 1. Données cristallines et affinement de la structure du tétrazepam à 293 K

Empirical formula	C ₁₆ H ₁₇ ClN ₂ O
Formula weight	288.76 g/mol
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P 2 ₁ /c
Unit-cell dimensions	a = 12.7386(7) Å
	b = 11.3774(7) Å
	c = 10.3084(7) Å
	α = 90°
	β = 103.175(5)°
	γ = 90°
Unit-cell volume	1454.69(16) Å ³
Z	4
Density (calculated)	1.319 mg/m ³
Absorption coefficient	0.260 mm ⁻¹
F(000)	608
Crystal size	0.40 x 0.25 x 0.18 mm ³
Theta range for data collection	2.706 - 26.366°.
Index ranges	-15 ≤ h ≤ 14, -13 ≤ k ≤ 14, -10 ≤ l ≤ 12
Reflections collected	13165
Independent reflections	2960 [R(int) = 0.067]

Completeness to theta = 25.242°	99.5 %
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	2960 / 0 / 183
Goodness-of-fit on F ²	1.137
Final R indices [I>2sigma(I)]	R1 = 0.0693, wR2 = 0.1768
R indices (all data)	R1 = 0.0868, wR2 = 0.1975
Extinction coefficient	0.169(15)
Largest diff. peak and hole	0.566 and -0.467 e.Å ⁻³

Table 2. Fractional atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for the non-hydrogen atoms of Tetrazepam^a

Table 2. Coordonnées atomiques réduites ($\times 10^4$) et paramètres d'agitation thermique isotrope ($\text{\AA}^2 \times 10^3$) des atomes du Tetrazepam^a

	x	y	z	U(eq) ^b
Cl(1)	1464(1)	-929(1)	7813(1)	57(1)
O(1)	963(2)	1738(2)	689(2)	60(1)
N(1)	1607(2)	424(2)	2312(2)	39(1)
N(2)	2441(2)	2617(2)	3686(2)	39(1)
C(1)	1274(2)	1526(2)	1873(3)	40(1)
C(2)	1335(2)	2447(2)	2931(3)	39(1)
C(3)	2838(2)	1819(2)	4535(2)	33(1)
C(4)	2230(2)	736(2)	4737(2)	30(1)
C(5)	1658(2)	80(2)	3654(2)	32(1)
C(6)	1111(2)	-926(2)	3888(3)	40(1)
C(7)	1070(2)	-1258(2)	5161(3)	42(1)
C(8)	1592(2)	-577(2)	6215(3)	36(1)
C(9)	2188(2)	397(2)	6025(2)	32(1)
C(10)	1541(3)	-482(3)	1288(3)	57(1)
C(11)	3933(2)	2015(2)	5382(2)	38(1)
C(12)	4536(2)	1144(2)	6010(3)	45(1)
C(13)	5625(2)	1305(3)	6922(4)	66(1)
C(14)	5833(4)	2599(4)	7287(5)	105(2)
C(15)	5480(3)	3402(3)	6234(5)	94(2)
C(16)	4317(3)	3273(3)	5503(4)	65(1)

^a e.s.d.'s in parentheses

^b U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 3. Hydrogen bonds of the monoclinic tetrazepam packing at 293 K (distances d in Å and angles in °)

Liaisons hydrogène de l'empilement monoclinique du tetrazepam à 293 K (distances d en Å et

angles en °)

Bond D-H...A	d(D-H) This work	d(H...A) This work	d(H...A) literature ^a	d(D...A) This work	Angle (D-H...A) This work	Angle (D-H...A) literature ^a
Intramolecular interactions						
C(10)-H(10C)...O(1)	0.960(4)	2.471(2)	2.472	2.663(4)	90.81(22)	88.03
C(16)-H(16A)...N(2)	0.970(4)	2.523(2)	2.516	2.781(4)	95.01(21)	92.52
Intermolecular interactions						
C(2)-H(2B)...O(1)#1	0.970(3)	2.507(2)	2.451	3.128(4)	121.77(16)	119.59
C(9)-H(9)...N(2)#1	0.930(2)	2.697(2)	2.573	3.513(3)	146.85(15)	144.02
C(7)-H(7)...O(1)#2	0.930(3)	2.614(2)	2.493	3.412(2)	144.22(17)	142.20
C(10)-H(10C)...Cl(1)#3	0.960(4)	2.907(1)	2.832	3.597(3)	129.70(18)	127.84
C(10)-H(10A)...O(1)#4	0.960(3)	2.750(2)	2.638	3.660(4)	158.62(21)	157.674

Symmetry transformations used to generate equivalent atoms (*opérateurs de symétrie utilisés pour engendrer les atomes équivalents*):

#1: x,-y+1/2, z+1/2. #2: -x, y-1/2,-z+1/2. #3: x, y, z-1. #4:-x,-y,-z.

^a from references [12] and [13].