Journal of Molecular Structure 1083 (2015) 187–193

Contents lists available at ScienceDirect

Journal of Molecular Structure

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

Halogen bonding in the antibacterial 1,2,4-triazole-3-thione derivative – Spectroscopic properties, crystal structure and conformational analysis

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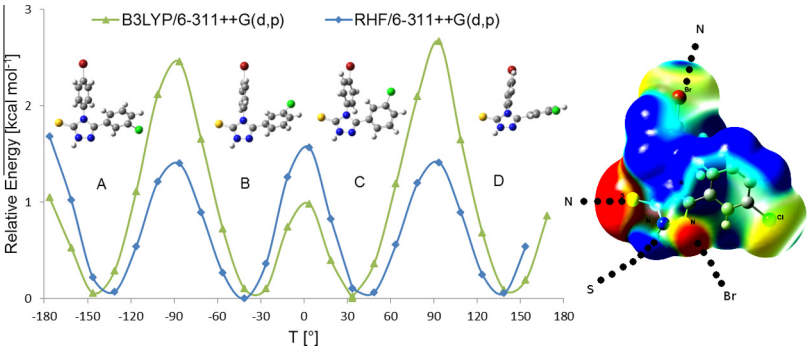
HIGHLIGHTS

- Conformational analysis of 1,2,4-triazole-3-thione halogen derivatives.
- Spectroscopic features of 1,2,4-triazole-3-thione derivative in the solid state.
- Halogen bonding in 1,2,4-triazole-3-thione derivatives.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 30 October 2014
Received in revised form 21 November 2014
Accepted 25 November 2014
Available online 2 December 2014

Keywords:
Conformational analysis
Rotational disorder
Molecular electrostatic potential
Mercaptotriazoles
Halogen bonding

ABSTRACT

The molecular structure of 4-(4-bromophenyl)-5-(3-chlorophenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (**TP-4**) has been determined by the X-ray diffraction experiment and compared to the geometry calculated in the ground state by using HF and DFT methods. The compound crystallizes in the triclinic *P*-1 space group. To explain the observed rotational disorder of *meta*-chloro-substituted aromatic ring the conformational analysis was performed for **TP-4** and the molecular energy profile has been obtained. The vibrational frequencies in the solid state were recorded and compared to the calculated in the ground state. The molecular electrostatic potential isosurfaces (MEPS) were calculated to confirm the role of halogen bonds in stabilizing the crystal structure.

Introduction

Our previous studies have demonstrated that 4-(4-bromophenyl)-5-(3-chlorophenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (**TP-4**) (Fig. 1) exerts multidirectional pharmacological activity. One of the significant activities of the title compound is the ability to inhibit the growth of Gram-positive bacteria, including *Staphylococcus aureus* strains – responsible for life-threatening infections. Moreover, it was observed that among the strains extremely susceptible to the activity of **TP-4** were *Bacillus subtilis* and *Bacillus cereus* [1]. The significance of this fact is due to the morphogenetic similarity of the latter strain to the *Bacillus anthracis* (causing anthrax) [2]. It is therefore highly probable that a compound exhibiting antibacterial activity against *B. cereus* will also constitute an efficient drug

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http://dx.doi.org/10.1016/j.molstruc.2014.11.060
0022-2860/

against anthrax. Further studies revealed the antiepileptic activity of **TP-4**, which was demonstrated in a maximum electroshock test [3]. The compound significantly elevated the threshold for electroconvulsions in mice and also enhanced the anticonvulsant activity of carbamazepine, phenobarbital and valproate. The observed synergism provides a basis for the development of novel pharmaceutical formulations, such as "**TP-4** + a classical antiepileptic drug" [4]. This would enable decreasing the doses required to obtain a therapeutic effect, which in turn would result in limiting adverse effects. The most recent pharmacological studies demonstrated that **TP-4** also exhibits analgesic activity at doses much lower than its toxicity threshold (unpublished results). Additionally, the compound may also be used as a precursor for other pain-relieving substances. The very promising biological activity of **TP-4** was an inspiration for studies aimed at determining the mechanisms of antibacterial, antiepileptic and analgesic activities. By using computational methods, it was proved that **TP-4** satisfies the requirements of so-called Unverferth's pharmacophore for potential antagonists of voltage-gated sodium channels [3,5]. It could not be also excluded that **TP-4**, as a 1,2,4-triazole derivative, might act through the GABA-ergic system (similarly to the drug loreclezole, a 1,2,4-triazole chlorinated derivative [6]). However, our recently obtained results permit us to conclude that despite the structural similarity of loreclezole and **TP-4**, their anticonvulsant activity is accomplished via completely different molecular mechanism [7]. The attempts to determine the mechanisms of antibacterial and analgesic activity are still in their early phases.

Among the studied derivatives of 1,2,4-triazole-3-thiones the derivatives with aryl rings substituted by Br or I atoms in *para* position showed the highest antimicrobial activity, especially against Gram-positive bacteria. They appeared to be even fourfold more effective against *B. cereus* ATCC 10876 than ampicillin [1].

We report here, the results of studies under the role of the interactions involving halogen atoms in the crystal structure of **TP-4**. The halogen bonding R–X···Y–R' (Y = Cl, Br, I) is a non-covalent bond between a halogen atom (X) (Lewis acid) and any electron donor moiety (Y). It is a semidirectional intermolecular interaction with weak to medium strength, and can compete or cooperate with hydrogen bonds [8]. There are numerous reports on enhancement of binding affinity by the presence of halogen atoms in the molecular structure of the ligand in natural systems for example in molecular recognition of thyroid hormones [9], as well as, in rational drug design [10–12]. The halogen derivatives are successfully used in medicine. Among approved drugs acting on $GABA_A$ receptors there are two well known: bromazepam – containing bromine atom and loreclezole – chloro-derivative of triazole [13] (Fig. 1).

In order to gain a better understanding of the mode in which **TP-4** binds to the receptors and/or enzymes constituting its molecular targets, the studies under the possible and energetically favorable conformations of the title compound have been undertaken. Additionally, on the basis of crystal structure and molecular electrostatic potential maps its preferential type of intermolecular interactions, including halogen bonds, has been determined.

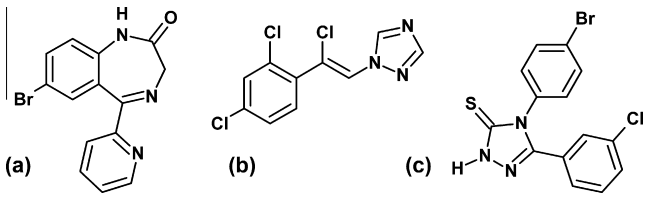

Fig. 1. Scheme of molecules of a) bromazepam, b) loreclezole and c) **TP-4**.

Materials and methods

Synthesis and IR spectrum

The title compound was synthesized as described previously [1]. The ATR-IR spectrum was recorded in the range 4000–400 cm^{-1} on a Nicolet 8700A spectrometer equipped with Smart Orbit TR diamond ATR accessory.

Crystallography

Intensity measurements were carried out at 295 K with Oxford Diffraction Xcalibur CCD diffractometer with the graphite-monochromatized Mo Kα radiation (λ = 0.71073 Å). Data sets were

Table 1
Crystallographic data for crystal of **TP-4**.

	TP-4
Empirical formula	$C_{14}H_9BrClN_3S$
Formula weight	366.66
Temp. (K)	295(2)
Crystal system	Triclinic
Space group	*P*-1
a (Å)	5.938(1)
b (Å)	11.258(1)
c (Å)	11.466(1)
α (°)	90.43(1)
β (°)	99.15(1)
γ (°)	94.42(1)
V (Å^3)	754.35(16)
Z	2
Crystal form/color	Block/colorless
Crystal size (mm)	0.38 × 0.35 × 0.30
D_{calc} (g cm^{-3})	1.614
μ (mm^{-1})	3.032
Absorption correction	Multiscan
θ range (°)	3.49–25.24
Reflns coll./unique (R_{int})	9256/2730 (0.042)
Data/parameters	2730/195
GooF on F^2	0.946
R_1, wR_2 [$I>2\sigma(I)$]	0.0544, 1366
R_1, wR_2 (all data)	0.0786, 0.146
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.906; −0.564

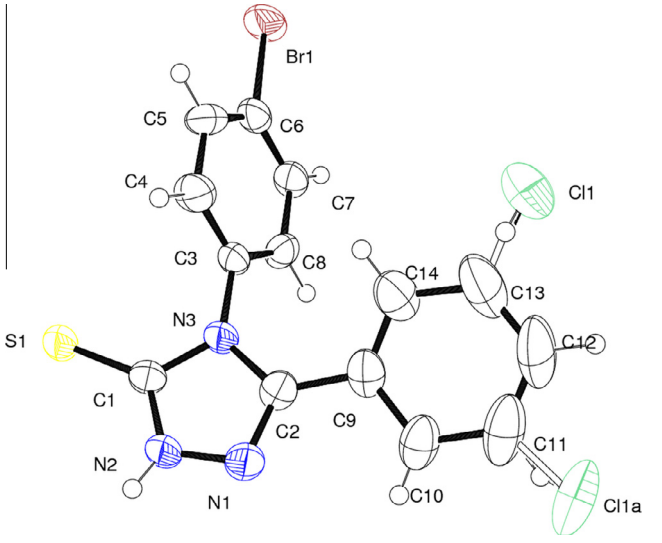

Fig. 2. Molecular structure of **TP-4** and atom numbering scheme for the title compound. Displacement ellipsoids were drawn at 50% probability level; the C–Cl and C–H bonds in the disordered part of the molecule for the minor ring orientation (*sof* = 0.400(5)) were marked by open lines.