Packing of Two Independent Molecules: 3-Amino-2-benzyl-6-bromo-1,2,4-triazin-5(2H)-one

Long-Chih HWANG,^{*,†} Chung-Lin CHUANG,^{*} Chun-Wei SU,^{*} and Gene-Hsiang LEE^{**}

^{*}Department of Medicinal and Applied Chemistry, College of Life Sciences, Kaohsiung Medical University, Kaohsiung City 80708, Taiwan, ROC

^{**}Instrumentation Center, College of Science, National Taiwan University, Taipei City 106, Taiwan, ROC

The two independent molecules in a single crystal of the title compound, 3-amino-2-benzyl-6-bromo-1,2,4-triazin-5(2H)-one (C₁₀H₉BrN₄O), was determined by X-ray crystallography. The compound was grown from a protic polar solvent, EtOH, and crystallized in an orthorhombic system. It was characterized as follows: *Pbca*, *a* = 23.6829(13) Å, *b* = 7.5558(4) Å, *c* = 24.1777(13) Å, *V* = 4326.4(4) Å³ and *Z* = 16, resulting in a density, *D*_{calc}, of 1.726 g/cm³. The hydrogen-bonding systems assemble with N-H...O [graph set C₁¹(6)], N-H...N [graph set R₂²(8)], and N-H...N combine with N-H...O [graph set R₄⁴(12)].

(Received March 21, 2016; Accepted May 20, 2016; Published on web July 10, 2016)

1,2,4-Triazine is an aza analogue of pyrimidine and 3-amino-1,2,4-triazine is known to have several promising biological activities.¹ The C-5 oxide of 3-amino-1,2,4-triazine, 3-amino-1,2,4-triazin-5(2H)-one (6-azaisocytosine), is an isosteric isomer of isocytosine. We investigated the Kekulé structure, which gave a higher contribution to the ground state of 3-amino-1,2,4-triazine, and studied the most contributed prototropic tautomerism of 3-amino-1,2,4-triazin-5(2H)-one by X-ray crystallographic analysis.^{2,3} The title compound (Fig. 1), an isosteric isomer of 2-benzyl-1,2,4-triazin-3,5(2H,4H)-dione (1-benzyl-6-azauracil), exhibits anticoccidial activity,⁴ and has the property of an aldose reductase inhibitor.⁵ We previously reported on the X-ray structure of the title compound; it was crystallized in an aprotic polar solvent, DMSO, and a monoclinic system with space group *P2₁/n* was afforded; this molecule administered codenamed **I**.⁶ In this paper, we report and discuss here two independent molecules (**Ia** and **Ib**) in a single crystal, which crystallized in a protic polar solvent, EtOH, giving an orthorhombic system with the space group *Pbca*.

The title compound was prepared according to a method described by Hwang.⁷ A plate colorless crystal having dimensions of 0.28 × 0.28 × 0.02 mm³ was obtained by recrystallization from an ethanol. The crystal and experimental data are listed in Table 1. The X-ray data were collected by

graphite-monochromatized Mo K_α radiation (λ = 0.71073 Å) at 295(2)K. An absorption correction was applied by multi-scan from equivalents. The crystal structure was solved by direct methods using SHELXS-97, and refined by full-matrix least-squares methods on *F*² using SHELXL-97. All of the non-hydrogen atoms were refined anisotropically. All hydrogen atom positions were calculated and included in the calculation using the riding atom model. The final positional parameters for all non-hydrogen atoms are given in CIF file (see Supporting Information). The interesting feature of the structure in a comparison of the bond lengths between **Ia**, **Ib** and **I** reveals that the structure **Ib** is almost identical to the molecule **I**. Meanwhile, the bond angles of structure **Ib** are also similar to **I** (a comparison of selected bond lengths and angles for **I**, **Ia** and

Fig. 1 Chemical structure of the title compound and IUPAC atom-numbering scheme.

Table 1 Crystal and experimental data

Formula: C ₁₀ H ₉ BrN ₄ O	
Formula weight = 281.12	
Crystal system: orthorhombic	Space group: <i>Pbca</i>
<i>a</i> = 23.6829(13) Å	
<i>b</i> = 7.5558(4) Å	
<i>c</i> = 24.1777(13) Å	
<i>V</i> = 4326.4(4) Å ³	<i>Z</i> = 16
<i>D</i> _{calc} = 1.726 g/cm ³	
Radiation: Mo K _α (λ = 0.71073 Å)	
μ(Mo K _α) = 3.784 mm ⁻¹	<i>F</i> (0 0 0) = 2240
No. of reflections collected = 23631	
No. of independent reflections = 4959 (<i>R</i> _{int} = 0.0982)	
θ range for data collection: 1.68 to 27.50°	
Data/Restraints/Parameters = 4959/0/289	
Goodness-of-fit on <i>F</i> ² = 1.060	
<i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)] : <i>R</i> 1 = 0.0527, <i>wR</i> 2 = 0.1161	
<i>R</i> indices (all data): <i>R</i> 1 = 0.1003, <i>wR</i> 2 = 0.1348	
(Δ/σ) _{max} = 0.005	
(Δρ) _{max} = 0.545 eÅ ⁻³	(Δρ) _{min} = -0.431 eÅ ⁻³
Measurement: Bruker SMART APEXCCD	
Program system: Bruker SAINT	
Structure determination: direct methods (SHELXS-97)	
Refinement: full-matrix least-squares (SHELXL-97)	
CCDC deposition number: CCDC 1465495	

[†] To whom correspondence should be addressed.
E-mail: lncchw@kmu.edu.tw

Fig. 2 Two independent molecules in the title compound, showing the atom-labeling scheme in (**Ia**) the type I molecule and (**Ib**) the type II molecule. Displacement ellipsoids are drawn at the 50% probability level.

Table 2 Hydrogen-bond geometry (Å, °) of **Ia** and **Ib**

Notation	D–H···A	D–H	H···A	D···A	D–H···A
a	N4–H4B···O2 ⁱ	0.86	2.238	2.887(5)	132.2
b	N8–H8B ⁱⁱ ···O1	0.86	2.117	2.890(5)	149.3
c	N8–H8A ⁱⁱⁱ ···N3	0.86	2.116	2.964(5)	168.8
d	N4–H4A···N7 ⁱⁱⁱ	0.86	2.348	3.086(5)	144.2
e	N4–H4B ^{iv} ···O2	0.86	2.238	2.887(5)	132.2
f	N8–H8B···O1 ^v	0.86	2.117	2.890(5)	149.3
g	N8–H8A···N3 ^{vi}	0.86	2.116	2.964(5)	168.8
h	N4–H4A ^{vi} ···N7	0.86	2.348	3.086(5)	144.2

Symmetry codes: (i) 1.5–x, 1–y, –0.5+z; (ii) 2–x, –0.5+y, 0.5–z; (iii) x, 0.5–y, –0.5+z; (iv) 1.5–x, 1–y, 0.5+z; (v) 2–x, 0.5+y, 0.5–z; (vi) x, 0.5–y, 0.5+z.

Ib in Table S1; see Supporting Information). An ORTEP drawing for the two independent molecules, **Ia** and **Ib**, in the title compound is depicted in Fig. 2. Observations of the bond angle in N2–C4–C5 between **Ia**, **Ib** and **I** are 113.3(4)°, 112.6(4)° and 111.5(2)°, respectively.

The molecular packing of the title compound is shown in Fig. S1. An analysis of the molecular packing in the unit cell reveals that each independent molecule is linked with three other molecules by intermolecular hydrogen bonds (Table 2 and Fig. 3). Each independent molecule is linked into the $C_1^1(6)$ graph set association via N–H···O hydrogen bond interactions (Fig. 3 notation [a], [b] for **Ia** and [e], [f] for **Ib**). Meanwhile, each independent molecule is linked into the $R_2^2(8)$ graph set association via two N–H···N hydrogen bond interactions (Fig. 3 notation [c], [d] for **Ia** and [g], [h] for **Ib**). Furthermore, another type of hydrogen bond involves interactions via N–H···N combined with N–H···O that are linked into the $R_4^4(12)$ graph set association; this situation is just in the two independent molecules, **Ia** and **Ib**, not exist in crystal **I**. For example, the amino atom N8ⁱⁱ in type I **Ia** acts as a hydrogen-bond donor, via H8Aⁱⁱ, to nitrogen atom N3^{vii} (Fig. 3; symmetry codes: (vii) 2–x, –y, –z) to form a N–H···N hydrogen bond interaction (Fig. 3 notation [i]). Meanwhile, the amino atom N8ⁱⁱⁱ acts as a hydrogen-bond donor, via H8Bⁱⁱⁱ, to the oxygen atom O1^{vii} to form a N–H···O hydrogen bond interaction (Fig. 3 notation [j]). Therefore, type I **Ia**, together with four hydrogen-bond [b], [c], [j], and [i] form a $R_4^4(12)$ graph set association. In type II **Ib** the $R_4^4(12)$ graph set association is linked by the hydrogen-bond [f],

Fig. 3 Intermolecular N–H···O, N–H···N and Br···Br contacts in **Ia** and **Ib**. For the notation and symmetry codes see Table 2 and in the text.

[g], [i], and [k] (Fig. 3; symmetry codes: (viii) 2–x, 1–y, 1–z). Another interesting feature of the crystal structure is a short contact analysis (shown in Fig. 3), which revealed a slightly short Br1···Br2^{ix} for **Ia** and Br2···Br1^x for **Ib** having the same short contact distance of 3.4675(7)Å (Symmetry codes: (ix) 0.5+x, y, 0.5–z; (x) –0.5+x, y, 0.5–z), but not found in crystal **I**.

The above-mentioned evidence suggests that the extra hydrogen-bond interactions system graph set $R_4^4(12)$ and Br1···Br2 short contact association make the title compound **Ia** and **Ib** have a higher density, D_{calc} , of 1.726 g/cm³ than compound **I** for a density, D_{calc} , of 1.677 g/cm³. The assignment of the H-bond descriptors is based on the graph-set theory.⁸

Supporting Information

A comparison of a selected bond distances and angles for compounds **I**, **Ia** and **Ib** is summarized in Table S1. Additionally, the molecular packing of the title compound is shown in Fig. S1.

References

1. H. Neunhoeffer and P. F. Wiley, "Chemistry of 1,2,3-Triazines and 1,2,4-Triazines, Tetrazines and Pentazines", ed. A. Weissberger and E. C. Taylor, **1978**, J. Wiley and Sons, New York, Chichester, Brisbane, Toronto, 1001 – 1004.
2. L. C. Hwang, R. R. Wu, S. Y. Jane, and G. H. Lee, *Anal. Sci.*, **2003**, 19, x73.
3. L. C. Hwang, J. H. Wang, C. C. Tzeng, G. H. Lee, and S. M. Peng, *Anal. Sci.*, **2002**, 18, 723.
4. B. L. Mylari, M. W. Miller, H. L., Jr. Howes, S. K. Figdor, J. E. Lynch, and R. C. Koch, *J. Med. Chem.*, **1977**, 20, 475.
5. R. Sarges, R. C. Schnur, J. L. Belletire, and M. J. Peterson, *J. Med. Chem.*, **1988**, 31, 230.
6. L. C. Hwang, Yu. C. Su, T. P. Wang, L. T. Liu, and G. H. Lee, *X-ray Struct. Anal. Online*, **2010**, 26(8), 61.
7. L. C. Hwang, C. H. Tu, and J. H. Wang, *J. Heterocycl. Chem.*, **2006**, 43, 889.
8. J. Bernstein, R. E. Davis, L. Shimoni, and N. L. Chang, *Angew. Chem. Int. Ed. Engl.*, **1995**, 34, 1555.