Conformation and Bonding in Unsymmetrically 3,6-Disubstituted Dihydro-1,2,4,5-Tetrazine

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The molecular structure of the title compound, I, has been determined by single-crystal X-ray diffraction. The crystals are triclinic, space group P$\bar{1}$. The analysis revealed that the dihydro-*s*-tetrazine molecule is in a slightly twisted boat conformation with the nitrogen atoms carrying the two hydrogens, N(2) and N(4), pointing upward. All substituents on the dihydro-*s*-tetrazine ring exist in *pseudo*-equatorial configurations. Adjacent hydrogen and bulky groups (CF_3 and *p*-Cl-C_6H_4) have *cis*-relationships. The *p*-chlorophenyl group is twisted with respect to the dihydro-*s*-tetrazine ring. The unit cell for I contains six molecules. Each dihydro-*s*-tetrazine ring participates in four intermolecular hydrogen bonds (N···H bond distance 2.23 to 2.41 Å), two hydrogen bonds to each adjacent tetrazine ring in the same unit cell.

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One of the longstanding uncertainties in heterocyclic chemistry have been the structures of the dihydro-derivatives of 1,2,4,5-tetrazines, being referred to almost at random as 1,2- and/or 1,4-dihydro derivatives. An additional source of confusion is the ready isomerization under the influence of heat or light of dihydro-1,2,4,5-tetrazines to 4-amino-1,2,4-triazoles, being mistaken by many workers in this field for dihydrotetrazines [1].

Only one X-ray crystallographic analysis of a dihydro-1,2,4,5-tetrazine has been published. Hunter, Neilson, and Weakley [2] reported an X-ray determination of the structure of 3,6-bis(4-chlorobenzyl)-1,4-dihydro-1,2,4,5-tetrazine. While these data showed that this *s*-tetrazine exists as the 1,4-dihydro compound, the molecule was shown to be disordered. Their data suggested that the disorder involves two 1,4-dihydrotetrazine moieties each occurring in an acentric boat conformation with equal probability. In the present study of an unsymmetrically-3,6-disubstituted-dihydrotetrazine, 3-(4-chlorophenyl)-6-(trifluoromethyl)-dihydro-1,2,4,5-tetrazine, I, single-crystal X-ray crystallographic analysis showed no disorder and permitted unequivocal confirmation of the 1,4-dihydro structure. In addition, these data provided insight on the nature of the intermolecular bonding between adjacent molecules.

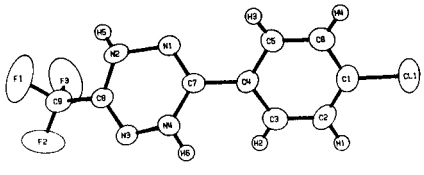

Figure 1. Ortep plot of X-ray crystallographic structure for I.

Table 1

Crystallographic Data

Molecular formula	$C_9H_6ClF_3N_4$
Formula weight	262.62
Space group	Triclinic P$\bar{1}$
Calculated density (p).	1.61 g/cm^3
Cell dimensions	a = 10.294 (1) Å
	b = 12.395 (1) Å
	c = 13.720 (1) Å
	α = 68.21 (1) deg
	β = 89.58 (1) deg
	γ = 86.76 (1) deg
	Z = 6
	V = 1622.7 Å^3

Table 2

Structure Solution and Refinement

Solution	Direct methods
Hydrogen atoms	Located and refined isotropically
Refinement	Full-matrix least-squares
Minimization function	$\Sigma w(\|Fo\|-\|Fc\|)^2$
Least-squares weights	$4Fo^2/\sigma^2(Fo^2)$
"Ignorance" factor	0.050
Anomalous dispersion	All non-hydrogen atoms
Reflections included	2335 with $Fo^2 > 2.0\sigma(Fo^2)$
Parameters refined	532
Unweighted agreement factor	0.052
Weighted agreement factor	0.059
Factor including unobs. data	0.161
Esd of obs. of unit weight	1.42
Convergence, largest shift	0.35σ
High peak in final diff. map	0.48 (6) e/A^3
Computer hardware	PD-11/45
Computer software	Enraf-Nonius SDP and private programs of Molecular Structure Corporation

Results and Discussion.

The crystals of I are triclinic with space group P$\bar{1}$. The crystal structure was found to be unusual, *i.e.*, containing three crystallographically unique molecules per asymmetric unit. Details of the X-ray crystallographic analysis and unit cell are given in the Experimental Section and in Tables 1 and 2. These data and an ORTEP plot of the

X-ray crystallographic structure of a typical molecule in a unit cell of I (Figure 1) clearly show that this dihydro-*s*-tetrazine exists as the 1,4-dihydro isomer in the solid state. This conclusion is in agreement with the data reported by Hunter, Neilson, and Weakley [2] for the structure of the symmetrically-3,6-disubstituted tetrazine, 3,6-bis(4-chlorobenzyl)-1,4-dihydro-1,2,4,5-tetrazine, II.

The bond distances, bond angles, and torsional angles for the dihydro-*s*-tetrazine ring for each crystallographically unique molecule in a unit cell are listed in Tables 3, 4, and 5. These data show no significant structural differences between the three crystallographically unique molecules in an asymmetric unit. The bond distances between N(1)-C(7) and N(3)-C(8) have average values of 1.286 and 1.277 Å, respectively, which is consistent with localized carbon-nitrogen double bonds [3]. These values are in excellent agreement with the value of 1.268 Å reported by Hunter, *et al.* [2] for the same bond in II. The N(1)-N(2) and N(3)-N(4) bond distances have average values of 1.434 and 1.416 Å, respectively, which are consistent with localized nitrogen-nitrogen single bonds. These values are slightly shorter than those reported by Hunter, *et al*, [2] namely 1.504 and 1.473 Å. Finally, the carbon-nitrogen single bonds between N(2)-C(8) and N(4)-C(7) are 1.375 and 1.396 Å, respectively. These values are also slightly less than reported earlier [2]. The X-ray study shows that the

Table 3

Selected Bond Distances in Angstroms

Atom 1	Atom 2	Molecule 1	Molecule 2	Molecule 3
N1	N2	1.438 (5)	1.436 (6)	1.437 (5)
N2	H5	0.78 (4)	0.72 (4)	0.85 (4)
N2	C8	1.382 (6)	1.380 (6)	1.364 (6)
C8	C9	1.473 (7)	1.491 (6)	1.501 (7)
C8	N3	1.277 (5)	1.278 (5)	1.276 (5)
N3	N4	1.411 (5)	1.417 (5)	1.421 (5)
N4	H6	0.90 (5)	0.82 (4)	0.80 (4)
N4	C7	1.390 (6)	1.399 (6)	1.399 (6)
C7	N1	1.285 (5)	1.280 (6)	1.293 (6)
C7	C4	1.464 (6)	1.459 (6)	1.459 (6)

Numbers in parentheses are estimated standard deviations in the least significant digits.

Table 4

Selected Bond Angles in Degrees

Atom 1	Atom 2	Atom 3	Molecule 1	Molecule 2	Molecule 3
N1	N2	C8	114.5 (4)	113.7 (4)	113.4 (4)
H5	N2	N1	109.0 (4)	108.4 (4)	106.0 (3)
H5	N2	C8	115.0 (4)	109.0 (4)	121.0 (3)
N2	C8	N3	121.6 (5)	122.1 (5)	122.9 (5)
C9	C8	N2	119.2 (5)	119.7 (5)	119.2 (5)
C9	C8	N3	119.2 (5)	118.1 (5)	117.9 (5)
C8	N3	N4	111.1 (4)	111.2 (4)	110.0 (4)
N3	N4	C7	116.0 (4)	115.2 (4)	115.0 (4)
H6	N4	N3	104.0 (4)	111.0 (3)	111.0 (3)
H6	N4	C7	119.0 (4)	112.0 (3)	113.0 (3)
N4	C7	N1	120.4 (5)	120.8 (5)	119.4 (5)
C7	N1	N2	111.2 (4)	111.6 (4)	111.4 (4)
C4	C7	N4	119.2 (4)	119.4 (5)	120.1 (5)
C4	C7	N1	120.3 (5)	119.8 (5)	120.5 (5)

Numbers in parentheses are estimated standard deviations in the least significant digits.

Table 5

Selected Torsional Angles in Degrees

Atom 1	Atom 2	Atom 3	Atom 4	Molecule 1	Molecule 2	Molecule 3
C7	N1	N2	C8	-39.9 (5)	-40.6 (5)	-41.5 (5)
C7	N1	N2	H5	-170.2 (30)	-161.1 (30)	-177.0 (20)
N2	N1	C7	N4	2.5 (5)	3.1 (6)	2.5 (6)
N2	N1	C7	C4	-175.7 (4)	-177.2 (4)	-177.1 (4)
N1	N2	C8	N3	39.6 (6)	40.5 (6)	41.5 (7)
N1	N2	C8	C9	-140.3 (5)	-140.2 (4)	-136.2 (5)
H5	N2	C8	N3	167.1 (30)	160.6 (30)	169.6 (40)
H5	N2	C8	C9	-12.8 (40)	-20.0 (30)	-8.0 (40)
C8	N3	N4	C7	-39.5 (6)	-38.7 (6)	-41.4 (6)
C8	N3	N4	H6	-171.7 (30)	-166.4 (30)	-171.4 (30)
N4	N3	C8	N2	1.0 (7)	0.3 (7)	1.0 (7)
N4	N3	C8	C9	-179.1 (4)	-179.0 (4)	-178.7 (5)
N3	N4	C7	N1	38.6 (6)	38.0 (6)	40.4 (6)
N3	N4	C7	C4	-143.2 (4)	-141.8 (4)	-140.0 (4)
H6	N4	C7	N1	163.5 (30)	165.2 (20)	-169.4 (30)
H6	N4	C7	C4	-18.3 (30)	-14.6 (20)	-11.0 (3)
C3	C4	C7	N1	-145.4 (5)	-141.4 (5)	-143.2 (5)
C3	C4	C7	N4	36.4 (6)	38.4 (7)	37.2 (7)
C5	C4	C7	N1	35.0 (6)	39.0 (7)	34.5 (7)
C5	C4	C7	N4	-143.2 (4)	-141.3 (5)	-145.1 (5)

Numbers in parenthesis are estimated standard deviations in the least significant digits.

Table 6

Distances (Å) from the Best Planes through C(9), C)8), N(2), N(3), N(4) (A) and C(4), C(7), N(1), N(2), N(4) (B).

Molecule 1

Plane A		Plane B	
Atom	Distance	Atom	Distance
	Atoms in Plane		
C(9)	0.008 (6)	C(4)	-0.030 (5)
C(8)	0.000 (5)	C(7)	0.015 (5)
N(2)	-0.003 (5)	N(1)	0.027 (4)
N(3)	-0.007 (4)	N(2)	-0.027 (4)
N(4)	0.007 (4)	N(4)	0.007 (4)
	Other Atoms		
N(1)	-0.845 (4)	N(3)	0.803 (4)
C(7)	-0.773 (5)	C(8)	0.733 (5)
H(5)	-0.157 (38)	H(5)	0.106 (37)
H(6)	-0.125 (50)	H(6)	0.222 (49)

Numbers in parenthesis are estimated standard deviations in the least significant digits.

dihydro-*s*-tetrazine ring has a boat conformation, shown schematically in Figure 2. The boat conformation is actually slightly twisted as shown by a least squares fit of the atoms to planes forming the two halves of the boat configuration, see Table 6. One plane, *A* consists of N(4) plus all atoms bonded to the trigonal sp^2 carbon C(8), namely, N(2), N(3), and C(9). The other plane, *B*, consists of N(2) plus all atoms bonded to the trigonal sp^2 carbon C(7), namely, N(1), N(4) and C(4). The significant deviations from planarity for the atoms in plane *B* arise from the slightly twisted boat conformation. The dihedral angle between the planes for molecule I is 38.2°. This angle for molecules 2 and 3 is 39.1 and 41.6°, respectively. All substituents on the dihydro-*s*-tetrazine ring exist in *pseudo*-equatorial configurations. Adjacent hydrogen and bulky groups (trifluoromethyl and *para*-chlorophenyl) have *cis*-relationships. However, the conformations of the *cis*-substituents are not exactly eclipsed; *i.e.* typical torsional angles between hydrogens and adjacent groups range from 13 to 20°.

The trifluoromethyl groups were found to be relatively localized. No major rotational disorder was observed. The *p*-chlorophenyl groups were also found to have a fixed orientation. The *p*-chlorophenyl groups are twisted with respect to the dihydro-*s*-tetrazine ring. The dihedral angle between the planar *p*-chlorophenyl ring and plane *B* of the dihydro-*s*-tetrazine ring (see above) is 35.6°.

A stereoscopic view of the molecular packing in the unit cell of I is shown in Figure 3. The unit cell contains six molecules and, presumably due to a favorable packing arrangement, three molecules per asymmetric unit were located and determined. The dihydro-*s*-tetrazine ring is highly hydrogen bonded in the solid state. A typical hydrogen bonded unit is shown schematically in Figure 4. Each tetrazine ring participates in four intermolecular hydrogen bonds, two hydrogen bonds to each adjacent tetrazine ring in the same plane of the unit cell. The observed intermolecular N···H bond distances of 2.23 to 2.41 Å fall in the typical range for nitrogen-hydrogen bond formation [4].

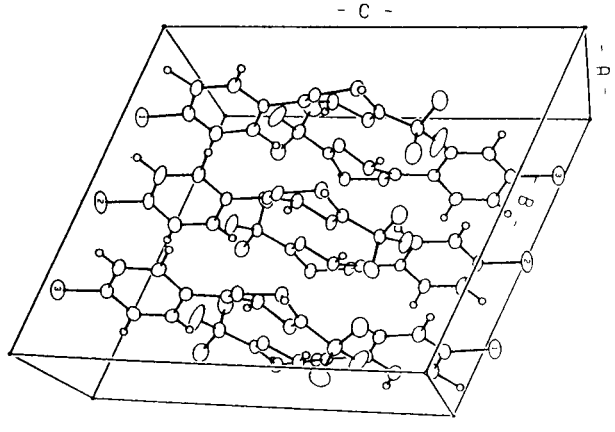

Figure 3. Packing Diagram for I.

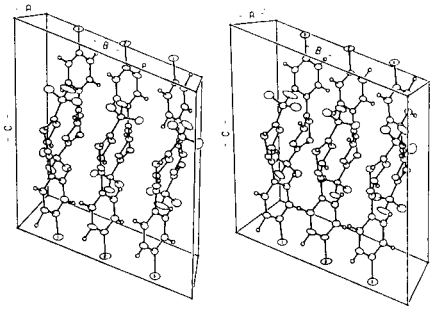

Figure 4. Typical hydrogen bonded unit of I.

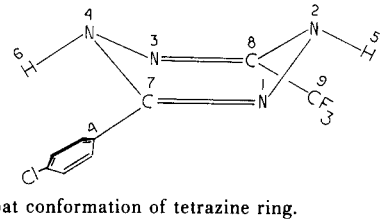

Figure 2. Boat conformation of tetrazine ring.

EXPERIMENTAL

1,4-Dihydro-3-(4-chlorophenyl)-6-(trifluoromethyl)-1,2,4,5-tetrazine, I.

This compound was prepared in 57% yield by the reaction of 1,4-dichloro-1-(4-chlorophenyl)-4-(trifluoromethyl)azine with hydrazine following the reported [5,6] procedure, light yellow crystalline solid, mp 177-179° (from ether); nmr (deuteriochloroform): δ 9.38 (1, NH, s), 7.4 and 7.7 (4, (CH=)$_4$, *p*-substituted-phenyl, q); ir (potassium bromide): 3320 and 3260 (NH), 1420 (C=N str.), 1200(s) cm^{-1} (CF_3); uv (methanol): λ max 243 (log ε 4.28) and 355 (log ε 2.74); λ max (diethyl ether): 243 (log ε 4.28)

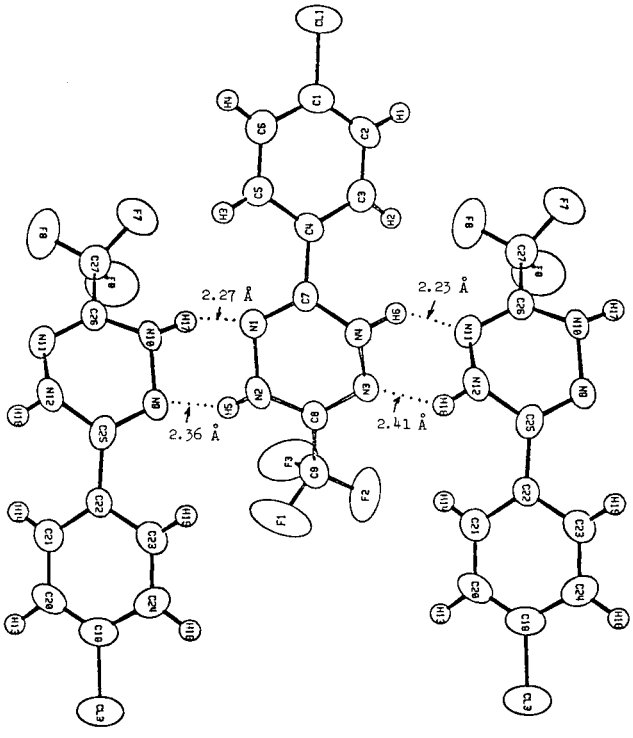

Figure 5

and 355 (log ε 2.75); λ max (cyclohexane): 243 (log ε 4.31) and 347 nm (log ε 2.80); EI-ms: (m/z) 262 (M^+), 138 ($ClC_6H_4CNH^+$), 137 ($ClC_6H_4CN^+$), 111 ($C_6H_5Cl^+$), 102 (m/z 138-HCl), 96 (CF_3CN^+), 75 (m/z 102-HCN), 69 (CF_3^+).

Anal. Calcd. for $C_9H_6ClF_3N_4$: C, 41.1; H, 2.3; N, 21.3. Found: C, 41.2; H, 2.2; N, 21.1.

X-ray Crystallographic Analysis.

A pale yellow prismatic crystal of I having the approximate dimensions of 0.05 × 0.12 × 0.20 mm was analyzed. X-ray intensities were measured on an Enraf-Nonius CAD4 computer controlled kappa axis diffractometer equipped with a graphite crystal incident beam monochromator using Cu Kα radiation (λ = 1.54184 Å). Cell constants and an orientation matrix for data collection were obtained from least-squares refinement, using the setting angles of 25 reflections in the range $9 < \theta < 29°$, measured by the computer controlled diagonal slit method of centering. As a check on crystal quality, omega scans of several intense reflections were measured; the width at half-height was 0.15° with a take-off angle of 2.8°, indicating good crystal quality. The data were collected at a temperature of 23 + 1° using the W-θ scan technique [7]. The variable scan rate allows rapid data collection for intense reflections where a fast scan rate is used and assures good counting statistics for weak reflections where a slow scan rate is used. Data were collected to a maximum 2θ of 120.0°. The scan range (in deg.) was determined as a function of θ to correct for the separation of Kα doublet, the scan width was calculated as follows:

$$\theta \text{ scan width} = 0.5 + 0.300 \tan\theta$$

Moving-crystal moving counter background counts were made by scanning an additional 25% above and below this range. Thus the ratio of peak counting time to background counting time was 2:1. The counter aperture was also adjusted as a function of θ. The horizontal aperture width ranged from 2.0 to 3.7 mm; the vertical aperture was set at 2.0 mm. A total of 4991 reflections were collected, of which 4827 were unique.

As a check on crystal and electronic stability three representative reflections were measured every 33 minutes. The intensities of these standards remained constant within experimental error throughout data collection. No decay correction was applied. Lorentz and polarization corrections were applied to the data. The linear absorption coefficient is 34.4 cm^{-1} for Cu Kα radiation. No absorption correction was made. An extinction correction was not necessary. A summary of the crystal data is given in Table 1. The structure was solved by direct methods. Using 325 reflections (minimum E of 2.07) and 2573 relationships, a total of 32 phase sets were produced. The 51 non-hydrogen atoms were located from an E-map prepared from the phase set with probability statistics: absolute figure of merit = 1.14, residual = 0.05, and psi zero = 1.560. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located and their positions and isotropic thermal parameters were refined. The structure was refined in full-matrix least-squares where the function minimized was $\Sigma w(|Fo| - |Fc|)^2$ and the weight w is defined as $4Fo^2/\sigma^2(Fo^2)$. The standard deviation on intensities, $\sigma(Fo^2)$, is defined as follows where S is the scan rate, C is the total integrated peak count, R is

$$\sigma^2(Fo^2) = [S^2(C + R^2B) + (pFo^2)^2]Lp^2$$

the ratio of scan time to background counting time, B is the total background count, Lp is the Lorentz-polarization factor, and the parameter p is a factor introduced to downweight intense reflections. Here p was set to 0.050.

Scattering factors were taken from Cromer and Weber [8]. Anomalous dispersion effects were included in Fc [9]; the values for Δf' and Δf'' were those of Cromer [10]. Only the 2335 reflections having intensities greater than 2.0 times their standard deviation were used in the refinements. The final cycle of refinement included 532 variable parameters and converged (largest parameter shift was 0.35 times its esd) with unweighted and weighted agreement factors of:

$$R1 = \Sigma||Fol - |Fc||/\Sigma|Fo| = 0.052$$

$$R2 = SQRT(\Sigma w(|Fo| - |Fc|)^2/\Sigma w Fo^2) = 0.059$$

The standard deviation of an observation of unit weight was 1.42. The highest peak in the final difference Fourier had a height of 0.48 e/A^2 with and estimated error based on ΔF [11] of 0.07. Plots of $\Sigma w(|Fo| - |Fc|)^2$ versus |Fo|, reflection order in data collection, sin θ/λ, and various classes of indices showed no unusual trends.

All calculations were performed on a PDP-11/45 computer using the Enraf-Nonius Structure Determination Package as well as private programs of Molecular Structure Corporation. The details of the structure solution and refinement are summarized in Table 2.

Supplementary Material Available.

Complete X-ray data on compound I are available upon request from the author (LHG) including tables of fractional atomic coordinates for non-hydrogen atoms, thermal parameters, bond lengths, bond angles, intermolecular contacts, mean planes, and torsion angles (43 pages).

Acknowledgement.

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