Crystal structure from X-ray powder diffraction data, DFT-D calculation, Hirshfeld surface analysis, and energy frameworks of (RS)-trichlormethiazide

Robert A. Toro, Analio Dugarte-Dugarte, Jacco van de Streek, José Antonio Henao, José Miguel Delgado and Graciela Díaz de Delgado*

Grupo de Investigación en Química Estructural (GIQUE), Escuela de Química, Facultad de Ciencias, Universidad Industrial de Santander, Bucaramanga, Colombia, Laboratorio de Cristalografía-LNDRX, Departamento de Química, Facultad de Ciencias, Universidad de los Andes, Mérida 5101, Venezuela, and Avant-garde Materials Simulation, Alter Str. 2, D-79249 Merzhausen, Germany. *Correspondence e-mail: gdiazdedelgado@gmail.com

The structure of racemic (RS)-trichlormethiazide [systematic name: (RS)-6-chloro-3-(dichloromethyl)-1,1-dioxo-3,4-dihydro-2H-1,1',2,4-benzothiadiazine-7-sulfonamide], C₈H₈Cl₃N₃O₄S₂ (RS-TCMZ), a diuretic drug in the treatment of oedema and hypertension, was determined from laboratory X-ray powder diffraction data using DASH [David et al. (2006). J. Appl. Cryst. 39, 910–915.], refined by the Rietveld method with TOPAS-Academic [Coelho (2018). J. Appl. Cryst. 51, 210–218], and optimized using DFT-D calculations. The extended structure consists of head-to-tail dimers connected by π–π interactions which, in turn, are connected by C–Cl···π interactions. They form chains propagating along [101], further connected by N···H···O hydrogen bonds to produce layers parallel to the ac plane that stack along the b-axis direction, connected by additional N···H···O hydrogen bonds. The Hirshfeld surface analysis indicates a major contribution of H···O and H···Cl interactions (32.2 and 21.7%, respectively). Energy framework calculations confirm the major contribution of electrostatic interactions (E_{elec}) to the total energy (E_{tot}). A comparison with the structure of S-TCMZ is also presented.

1. Chemical context
Trichlormethiazide (TCMZ), systematic name 6-chloro-3-(dichloromethyl)-1,1-dioxo-3,4-dihydro-2H-1,1',2,4-benzothiadiazine-7-sulfonamide (C₈H₈Cl₃N₃O₄S₂), is a diuretic drug derived from thiazide, the precursor of a classic family of diuretic compounds, discovered in the 1950s. The first approved drug of this class, chlorothiazide, was marketed under the trade name Diuril in 1958 (Beyer, 1993). The compound under study, trichlormethiazide, has a similar chemical structure to hydrochlorothiazide, the most prescribed member of the group (Hripcsak et al., 2020). The difference is the substitution of one hydrogen atom of the methylene group by a CHCl₂ dichloromethyl group. Thiazide diuretics and their derivatives are primarily used in the treatment of mild to moderate hypertension and oedema associated with Na⁺ and K⁺ retention and expansion of the extracellular fluid volume. They also increase Ca²⁺ excretion, a potentially useful effect in patients with hypercalciiuria, a condition that could lead to the formation of kidney stones (Menè, 2004). It is commonly used around the world under different brand names such as Achletin, Aquacot, Diu-hydrin.
Diurese, Metahydrin, Naqua, Trilumen, as well as with the generic trichlormethiazide name. Given our interest in the structure of materials involved in pharmaceutical formulations or with potential pharmaceutical applications, it was decided to undertake the structure determination of the racemic form of this active pharmaceutical ingredient (API).

2. Structural commentary

The refinement of the final structural model using powder diffraction data recorded showed bond distances and angles within the range suggested in the statistical analysis performed with the Mogul geometry check (Bruno et al., 2004). Only two out of 56 distances and bond angles in the structure are classified in the analysis as ‘unusual’. However, these two ‘unusual’ parameters are close to the values suggested by the Mogul geometry analysis, with Z-scores below 3. These parameters are similar to the values reported for the S-isomer (Cambridge Structural Database refcode KIKCUD; Fernandes et al., 2007) and for the DFT-D-optimized racemic structure.

The asymmetric unit contains one TCMZ molecule (Fig. 1): the stereogenic centre C7 has an S configuration but crystal symmetry generates a racemic mixture. The thiazide ring (A) exhibits a conformation that could be described as distorted half-chair to distorted envelope at N3 (Spek, 2020). The substituents in the ring are in bisecting (S1—O3), axial (S1—O4, N3—H3A, C7—H7) and equatorial (C7—C8, C4—C3, C5—C6, N2—H2A) conformations. The almost planar benzosulfonamide ring (ring B) makes an angle of 8.2 (2)° with the best plane through the thiazide ring. The molecule is oriented almost parallel to the a-axis as indicated by a 3.11 (8)° angle (PLATON; Spek, 2020), which corresponds to the angle between the a-axis and the perpendicular to the normal of the best least-square plane defined by the atoms of the two rings. The angle between the corresponding A and B rings in S-TCMZ is smaller than in RS-TCMZ [4.7 (2)°].

Fig. 2 shows a superposition of the molecule with an S-configuration in racemic TCMZ with the molecule of the S-enantiomer in KIKCUD. When flexibility is allowed in the superposition (Fig. 2a), the r.m.s.d. deviation is 0.070 and the maximum deviation (max. D) is 0.146 Å. Without flexibility, the values for r.m.s.d. and max. D are 0.785 and 2.763 Å, respectively (Fig. 2b). The difference between the two conformations lies in the orientation of the sulfonamide group and leads to differences in the hydrogen-bonding patterns between the two compounds as discussed below.

**Intramolecular hydrogen bonds**

Three different intramolecular hydrogen bonds are present in RS-TCMZ (Fig. 3a, Table 1). The shortest contact involves C6—H6···O1 with an H···A distance of 2.372 (8) Å and a D—H···A angle of 106.9 (5)°. A second intramolecular hydrogen bond occurs between C7—H7 and O4 [2.584 (10) Å, 106.1 (5)°]. The third contact, N3—H3A···O1, has geometric parameters 2.767 (8) Å and 102.1 (5)°. The three hydrogen bonds can all be represented by the graph-set symbol S(5) (Etter et al., 1990; Bernstein et al., 1995). The S-isomer displays the same intramolecular hydrogen bonds observed in RS-TCMZ. However, as a result of the orientation of the —NH2 group, an additional intramolecular interaction between N1—H1B and Cl1 is possible in S-TCMZ (Fig. 3b).
3. Supramolecular features

**Intermolecular hydrogen bonds**

Given the number of potential hydrogen-bond donors and acceptors, the hydrogen-bonding pattern in RS-TCMZ is very rich and relevant geometric parameters are summarized in Table 1. Fig. 4 depicts selected views of the intermolecular hydrogen bonds present in racemic TCMZ where the O and H atoms involved in hydrogen bonds are labelled. As shown in Fig. 4a, an \( R^2(16) \) loop, with O2 as the acceptor, N3 as the donor, and H3A as the donated H ([\( R^2(16) \)]\(_{S2} \), motif I) alternate with a motif [\( R^2(16) \)]\(_{N1} \) (H1A, motif II), forming tapes propagating along the c-axis direction. These tapes are joined by a sequence of [\( R^2(12) \)]\(_{N1,N3}^{O3} \) (H1A, H1B, III) and [\( R^2(16) \)]\(_{N1,N3}^{O2,O3} \) (H1B, H3A, IV) motifs, resulting in layers lying parallel to the bc plane. Perpendicular to these layers (Fig. 4b) the \( \text{I/II} \) motifs are connected by [\( R^2(20) \)]\(_{N1,N3}^{O2} \) (H2A, H1A, V) and [\( R^2(16) \)]\(_{S2,N3}^{O1,O2} \) (H2A, H3A, VI) motifs, forming layers parallel to the ac plane, resulting in an intricate three-dimensional hydrogen-bonded network. In the structure of S-TCMZ, N1 and N3 are also involved in hydrogen bonds based on the N—H···O heterosynthon. However, N2 participates in the homosynthon N2—H2···N1. A C8—H8···O3 hydrogen bond is also important in the packing arrangement of S-TCMZ.

![Figure 4](image-url)

(a) Graph-set analysis of the intermolecular N—H···O hydrogen bonds in RS-TCMZ projected onto the bc plane. (b) Sequence of hydrogen-bond motifs viewed down the b axis. The hydrogen-bonded motifs are labelled as I: \([R^2(16)]_{S2}^{O3}\); II: \([R^2(16)]_{N1}^{O1}\); III: \([R^2(12)]_{N1,N3}^{O1,O4}\); IV: \([R^2(16)]_{N1,N3}^{O2,O3}\); V: \([R^2(20)]_{N1,N3}^{O2}\); VI: \([R^2(16)]_{S2,N3}^{O1,O2}\).

![Figure 5](image-url)

Geometry of (a) \( \pi\)—\( \pi \) and (b) C—Cl···\( \pi \) interactions in RS-TCMZ; (c) sequence of head-to-tail \( \pi\)–\( \pi \) connected dimers and head-to-tail C—Cl···\( \pi \) connected dimers in RS-TCMZ.
\( \pi-\pi \) and C—Cl⋅⋅⋅π interactions

In addition, \( \pi-\pi \) and C—Cl⋅⋅⋅π interactions (Spek, 2020) provide connectivity between the molecules (Fig. 5). Short \( \pi-\pi \) interactions \( [d = 4.401 (3) \text{ Å}] \), occur between molecules related by the symmetry operation \(-x, 2-y, -z\) (Fig. 5a). At the same time, the original molecule interacts via a C—Cl⋅⋅⋅π contact of 3.761 (5) Å with another molecule related by symmetry operation \( 1-x, 2-y, 1-z \) (Fig. 5b). The molecules are arranged as head-to-tail dimers producing chains along [101] as depicted in Fig. 5c. In contrast, in the structure of S-TCMZ only C—Cl⋅⋅⋅π interactions are observed (Table 1). This contact is shorter \( [d = 3.456 (2) \text{ Å}] \) than in RS-TCMZ.

The structure of RS-TCMZ is a complex arrangement of hydrogen bonds, \( \pi-\pi \) and C—Cl⋅⋅⋅π interactions as shown in Fig. 6a and 6b. It can be described in terms of chains of head- to-tail dimers connected by \( \pi-\pi \) interactions, which are further connected via C—Cl⋅⋅⋅π interactions, also in a head-to-tail fashion. These chains are connected by N—H⋅⋅⋅O hydrogen bonds, producing layers parallel to the ac plane. The layers stack along the b-axis, connected by other N—H⋅⋅⋅O hydrogen bonds. In contrast, the structure of S-TCMZ can be described as chains of S-TCMZ molecules connected by C—Cl⋅⋅⋅π interactions (Fig. 6c), which form columns along the b-axis. These columns are further connected by N—H⋅⋅⋅O and N—H⋅⋅⋅N hydrogen bonds (Fig. 6d).

4. Database survey

A search in the Cambridge Structural Database (CSD, version 5.42, November 2020, updated September 2021; Groom et al., 2016) by name and by molecular diagram resulted in only one
5. Synthesis and crystallization

(RS)-Trichlormethiazide was kindly provided by Tecnoquímicas (Cali, Colombia). Based on the FT-IR spectra and the quality of the preliminary diffraction patterns, the present study was carried out on the sample as it was received. Crystallization experiments in different solvents, in search of possible polymorphs, are underway in our laboratories.

6. Refinement and DFT-D calculations

Crystal data, data collection and structure refinement details are summarized in Table 2. The powder diffraction pattern recorded (Fig. 7) was indexed with DICVOL14 (Loureõ & Boultif, 2014) using the first 30 peaks, producing a triclinic cell with \( a = 8.431 \, \text{Å}, b = 8.8919 \, \text{Å}, c = 9.720 \, \text{Å}, \alpha = 91.30 \, (1)^\circ, \beta = 106.07 \, (2)^\circ, \gamma = 97.19 \, (1)^\circ, V = 693.4 \, (2) \, \text{Å}^3. \)

![Figure 7](image_url)

Rietveld plot obtained after the structure refinement of RS-TCMZ.
Cartesian displacement (RMSCD) of 0.539 Å. This value is beyond the limit of 0.35 Å considered acceptable for correct structures determined from powder diffraction data (van de Streek & Neumann, 2014). The examination of the structure with Mercury (Macrae et al., 2020) showed that the structure displayed short N—H···Cl—C contacts. The charge distribution on a C—Cl bond is such that at the ‘tip’ (the other side of the atom away from the bond to the carbon atom), the Cl atom has a positive charge. Surprisingly, a hydrogen-bond donor points to this region of the Cl atom. There are several O···O contacts around 3.0 Å, which are possible, but surprising given the presence of four N—H hydrogen bond donors. By rotating the O—S(O)—N group around the C1—S1 bond axis by 120° all these inconsistencies disappeared and, therefore, this model was adopted.

The refinement performed with TOPAS-Academic (Coelho, 2018), using the energy-minimized structure as the starting model, was very stable and proceeded smoothly. Fig. 7 shows the final Rietveld refinement plot. The refinement included an overall scale parameter, the background, the peak shapes (including anisotropic broadening), unit-cell parameters, atomic coordinates and, initially, an overall Biso parameter. The bond distances and angles were restrained based on the values of the energy-minimized structure. A planar restraint for the molecule with a standard deviation of 0.01 Å was also established for atoms C1—C6/Cl1/S1. The positions of the hydrogen atoms were refined with restrictions on bond lengths and angles to the atoms to which they are attached, as in the related hydrochlorothiazide form II structure (Florence et al., 2005). The standard uncertainties of the hydrogen atoms, calculated by TOPAS, reflect the propagation of statistical errors from the raw data and do not reflect contributions from systematic errors. More realistic values are somewhat larger than those reported. The isotopic atomic displacement parameters for S and Cl were constrained to be equal and those for C, N, and O were also constrained to be equal. For the hydrogen atoms, they were 1.2 times the Uiso of the C or N atom to which they are attached.

In total, 177 parameters were refined against 3922 data points, 48 restraints and 2 constraints. The final whole pattern fitting converged with good figures of merit: Rexp = 0.02577, Rp = 0.0512, Rwp = 0.0694, R factor = 0.0397, and GoF = 2.704. Table 2 shows the crystal data, experimental parameters, and the refinement parameters obtained. The DFT-D calculations of the new model led to an RMSCD of 0.126 Å, which is lower than the 0.35 Å value (van de Streek & Neumann, 2014), indicating that the structure determined can be assumed to be correct.

### 7. Computational studies

#### Hydrogen-bond propensity analysis

As several donor and acceptor groups are present in trichlormethiazide, which could form different hydrogen bonding schemes, it was considered of interest to carry out a hydrogen-bond propensity (HBP) analysis for this molecule. The HBP analysis was carried out with Mercury (Macrae et al., 2020) for RS-TMZ and for the S-TCMZ enantiomer using data from the CSD entry KIKCUD.

The HBP tool provides an insight into the expected intra- and intermolecular hydrogen bonds in the structures. For the analysis, the donor atoms considered were N1 (sulfonamide), N2 (secondary amine) and N3 (next to the sulfonyl group). The acceptors were Cl1 (aryl chloride), Cl2/Cl3 (alkyl chloride), N2 (secondary amine), O1/O2 (sulfonamide), and O3/O4 (sulfonyl). The area under the receiver operating characteristics (ROC) curve was 0.865, indicating good statistical discrimination in the analysis. The results of the calculations are presented in the supporting information.

The intramolecular hydrogen bond with the highest propensity is N1—H1B···Cl1 (0.60). This hydrogen bond is observed only in the S-enantiomer. The intramolecular interaction involving N3—H3A···Cl3, observed in the two structures, has the second highest propensity value (0.48).

Regarding the intermolecular interactions, two hydrogen bonds involving the hydrogen atoms bonded to the nitrogen of the sulfonamide group and the two oxygen atoms of the sulfonyl group (N1—H1B···O3 and N1—H1A···O4) have the highest propensities (0.69). They are present in the structure of RS-TMZ (motifs II and III). However, only one of them (N1—H1A···O4) is present in the S-enantiomer. The next two interactions with highest propensities (0.68) are between the H and O atoms of the sulfonamide groups of two neighboring molecules. One of them (N1—H1B···O2) is observed only in the S-enantiomer.

The CSD statistics predicts hydrogen bonds for the sulfonl nitrogen atom (N3—H3A) and for the secondary amine (N2—H2A) with the sulfonyl O atoms (propensity values are 0.44 and 0.42, respectively), which are not present in either structure. However, N3—H3A···O1 and N3—H3A···O2 contacts with 0.42 propensities are displayed in S-TMZ and RS-TMZ (motifs I and IV), respectively. In addition, the hydrogen bond N2—H2A···O1 is present in RS-TMZ (motifs V and VI) but not in S-TMZ. The hydrogen bond N2—H2A···N1 was not predicted because the N1 atom was not considered an acceptor. The hydrogen-bond patterns found in the two structures are consistent with the hydrogen-bond propensity analysis results. Every donor and acceptor in RS-TMZ and S-TMZ have a hydrogen-bond coordination with a high likelihood. Figure S2 of the additional supporting information shows the putative landscape for trichlormethiazide. The two structures fall in the high propensity and hydrogen-bond coordination zone.

#### Hirshfeld surface analysis and energy frameworks

The software CrystalExplorer21 (Spackman et al., 2021) was used to produce fingerprint plots of the intermolecular interactions occurring in RS-TMZ and in CSD entry KIKCUD. The parameter dnorm, mapped onto the Hirshfeld surface (Spackman & Jayatilaka, 2009) is useful to visualize the atoms involved in intermolecular contacts and the strength of such contacts. Energy frameworks were also calculated with CrystalExplorer21.

Fingerprint plots representing dnorm interactions were calculated for RS-TMZ and are shown in Fig. 8.
comparison, plots for $S$-TCMZ were also calculated and shown in the same figure, along with the contributions of all contacts in $RS$-TCMZ and $S$-TCMZ to the Hirshfeld surface area. As can be seen, there are significant differences between the fingerprint plots for both compounds. The full set of parameters calculated are presented in Fig. S3 of the additional supporting information.

Fig. 8a–8l show that the most important interactions in $RS$-TCMZ are the $H \cdot \cdot \cdot O$ and $H \cdot \cdot \cdot Cl$ contacts, which represent 32.2 and 21.7% of the surface, respectively. In $S$-TCMZ, they are also the most important contacts (Fig. 8m–8x) with 36.0 and 16.9%, respectively. The next interaction, $O \cdot \cdot \cdot Cl$, is slightly less important in $RS$-TCMZ than in $S$-TCMZ (8.7% versus 9.6%). The remaining interactions differ in order of

![Fingerprint plots for $RS$-trichlormethiazide: (a) all contacts; (b) $H/O$ 32.2%; (c) $H/Cl$ 21.7%; (d) $O/Cl$ 8.7%; (e) $H/H$ 8.5%; (f) $Cl/Cl$ 6.0%; (g) $H/C$ 5.9%; (h) $N/Cl$ 4.1%; (i) $O/C$ 3.8%; (j) $C/Cl$ 2.8%; (k) $H/N$ 2.1%; (l) $C/C$ 1.8%. Fingerprint plots for $S$-Trichlormethiazide: (m)–(x). The percentage of surface area included is shown for each plot: $RS$-TCMZ 95.3% and $S$-TCMZ 99%. (y) Comparison of the contribution of intermolecular contacts (%) to the Hirshfeld surface area for $RS$-TCMZ and $S$-TCMZ.](image)
importance. For example, the H⋯H interaction is more important (8.5%) in RS-TCMZ than in S-TCMZ (7.2%). It is worth noting that the fingerprint plot delineated into the H⋯H interaction for RS-TCMZ shows a tip at $d_e + d_i = 2.20 \text{ Å}$, which is less than 2 times the van der Waals radii of hydrogen. In contrast, in S-TCMZ this interaction is dispersed over a range of $d_e + d_i$ values. Weaker interactions such as $\pi$–$\pi$ contacts are present only in racemic TCMZ and they represent 1.8% of the contribution to the Hirshfeld surface. The Cl⋯$\pi$ interaction is more important in S-TCMZ, contributing 9.1% in contrast to RS-TCMZ where it represents 2.8%. This is the result of two interactions in the S-enantiomer that lead to layers parallel to the $ab$ plane. In RS-TCMZ, the Cl⋯$\pi$ interactions alternate with $\pi$–$\pi$ contacts to produce chains nearly along [101]. Another interesting feature is displayed by the H⋯N contacts. There is a lower degree of directionality and strength of this interaction in RS-TCMZ (2.1%) than in S-TCMZ (3.3%) as a result of the additional $\text{N2}—\text{H2}$⋯$\text{N1}$ interaction in the latter.

In addition, the electrostatic ($E_{\text{ele}}$), dispersive ($E_{\text{dis}}$), and total energies ($E_{\text{tot}}$) for the intermolecular interactions in RS-TCMZ and S-TCMZ were calculated with CrystalExplorer21.

**RS-Trichloromethiazide**

![Energy frameworks calculated for RS-TCMZ viewed down the $b$-axis: (a) $E_{\text{ele}}$, red; (b) $E_{\text{dis}}$, green; (c) $E_{\text{tot}}$, blue. Energy contributions are represented within 4 × 4 × 4 unit cells. The cylinder radii were scaled to 50 arbitrary units with a cut-off value of 10 kJ mol$^{-1}$. Energy frameworks calculated for S-TCMZ viewed down the $b$-axis represented within 2 × 2 × 2 unit cells: (d) $E_{\text{ele}}$, red; (e) $E_{\text{dis}}$, green; and (f) $E_{\text{tot}}$, blue. The cylinder radii were scaled to 80 arbitrary units with a cut-off value of 5 kJ mol$^{-1}$.](image_url)
(Spackman et al., 2021). They are represented in Fig. 9. The summary of calculated energy values is presented in the supporting information and the detailed interactions are collected in Table S1 of the supporting information.

As depicted in Fig. 9, in RS-TCMZ the topologies of the electrostatic ($E_{ele}$, Fig. 9a) and dispersive ($E_{dis}$, Fig. 9b) components are similar although their contributions are quite different. They result in an offset tile arrangement for $E_{tot}$ when viewed down the b-axis direction (Fig. 9c). In the structure of S-TCMZ, $E_{ele}$ and $E_{dis}$ make similar contributions to $E_{tot}$ and their topology is similar (Fig. 9d and 9e). The pattern viewed down the b-axis direction resembles a herringbone arrangement (Fig. 9f).

8. Spectroscopic and thermal characterization

The FT-IR spectrum shows the absorption bands expected for TCMZ (Fig. S4 of the supporting information). The stretches for the secondary N-H grouping of the sulfonamide group appear at 3387 and 3322 cm$^{-1}$ followed by the stretching bands of the S-N-H and N-H groups of the amine on the dihydrothiadiazine at 3281 and 3232 cm$^{-1}$, respectively. The stretches of the $C_{sp}^2$—H (3150–3100 cm$^{-1}$) and $C_{sp}^3$—H (3000–2900 cm$^{-1}$) bonds are observed as weak bands. The $C_{sp}^2$—$C_{sp}^2$ stretch of the aromatic ring appears at 1596 cm$^{-1}$ while the C=N and S=N stretches overlap at 1351 and 1332 cm$^{-1}$. The stretches of the two S=O groups appear as strong absorptions at 1176 and 1157 cm$^{-1}$. Table S2 summarizes the assignment of the most important absorptions for RS-TCMZ.

The TGA curve (Fig. S5a) recorded indicates the material is stable up to 240°C. A series of weight loss events occur from 240°C to 450°C. A 24.2% weight loss (2.270 mg) between 245 and 301°C coincides with the first two transitions in the DSC (Fig. S5b). The endotherm at 281.1°C ($\Delta H = 81.19$ J g$^{-1}$) is associated with melting of the material. This transition is followed by an exotherm with peak temperature 287.9°C ($\Delta H = 103.70$ J g$^{-1}$). The TGA curve shows two continuous weight loss processes at 302–384°C (1.354 mg, 14.4%) and 384–448°C (1.032 mg, 11.0%), associated with ill-defined transitions in the DSC. The total weight loss due to decomposition is 49.6%.

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Crystal structure from X-ray powder diffraction data, DFT-D calculation, Hirshfeld surface analysis, and energy frameworks of (RS)-trichlormethiazide

Robert A. Toro, Analio Dugarte-Dugarte, Jacco van de Streek, José Antonio Henao, José Miguel Delgado and Graciela Díaz de Delgado

Computing details

Data collection: DIFFRAC.Suite (Bruker, 2011); cell refinement: TOPAS-Academic (Coelho, 2018); data reduction: TOPAS-Academic (Coelho, 2018); program(s) used to solve structure: DASH (David et al., 2006); program(s) used to refine structure: TOPAS-Academic (Coelho, 2018); molecular graphics: DIAMOND (Brandenburg, 1999); software used to prepare material for publication: enCIFer (Allen et al., 2004) and publCIF (Westrip, 2010).

(RS)-6-Chloro-3-(dichloromethyl)-1,1-dioxo-3,4-dihydro-2H-1λ6,2,4-benzothiadiazine-7-sulfonamide

Crystal data

C₈H₈Cl₃N₃O₄S₂  
Mr = 380.64  
Triclinic, P̅  
Hall symbol: -P 1  
am = 8.4389 (6) Å  
b = 8.8929 (7) Å  
c = 9.7293 (8) Å  
α = 91.315 (3)°  
β = 106.113 (2)°  
γ = 97.1580 (17)°  
V = 694.73 (9) Å³  
Z = 2  
Dₐ = 1.820 Mg m⁻³  
Melting point: 554.25 K  
Cu Kα₁ radiation, λ = 1.5418 Å  
T = 298 K  
Particle morphology: fine powder  
white  
flat sheet, 24.5 × 24.5 mm  
Specimen preparation: Prepared at 298 K and 100 kPa

Data collection

Bruker D8 ADVANCE diffractometer  
Radiation source: sealed X-ray tube  
Specimen mounting: Flat plate low-background Si single crystal specimen holder  
Data collection mode: reflection  
Scan method: step  
2θmin = 5.007°, 2θmax = 60.006°, 2θstep = 0.015°  
2 constraints

Refinement

Least-squares matrix: full  
R_p = 0.051  
R_wp = 0.069  
R_exp = 0.026  
R_mags = 0.040  
3922 data points
Profile function: PseudoVoight  
177 parameters  
48 restraints

2 constraints

Only H-atom coordinates refined  
Weighting scheme based on measured s.u.'s (Δ/σ)max = 0.001
Background function: Chebychev polynomial  
Preferred orientation correction: Simple March-Dollase correction, March-Dollase parameter:0.742(2)
**Special details**

**Experimental.** The FT-IR spectrum was registered in a IS50 FT-IR Nicolet Thermo Scientific spectrophotometer, in the 4000–400 cm\(^{-1}\) range with 32 scans at an optical speed of 0.4747 cm s\(^{-1}\). Thermogravimetric and differential scanning calorimetry measurements (TGA/DSC) were performed in a thermal analyzer DTA/DSC Instrument, Serie Discovery, under a dynamic nitrogen atmosphere at 50.0 mL min\(^{-1}\). The instrument was equilibrated at 28.00 °C. A heating ramp of 10.00 °C min\(^{-1}\) up to 450.00 °C was used.

*RS*-Trichlormethiazide was gently ground in an agate mortar. Small portions of the material were dusted on top of a flat plate low-background Si single crystal specimen holder. Powder diffraction patterns were registered at room temperature on a Bruker D8 ADVANCE diffractometer working in the Bragg-Brentano geometry using CuKa radiation, operating at 40 kV and 30 mA, equipped with a LynxEye position-sensitive detector. The pattern used in the structure determination was recorded from 5.007 to 60.006° (2θ) in steps of 0.01526°, at 1.5 sec/step. The standard instrument settings (Ni filter of 0.02 mm, Soller slits of 2.5°, Divergence Slit of 0.2 mm, scatter screen height of 3 mm) were employed.

**Geometry.** Bond distances, angles etc. have been calculated using the rounded fractional coordinates. All su’s are estimated from the variances of the (full) variance-covariance matrix. The cell esds are taken into account in the estimation of distances, angles and torsion angles.

**Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å\(^2\))**

|   | x      | y      | z      | U\(_{eq}\)/*U\(_{eq}\) |
|---|--------|--------|--------|-------------------------|
| Cl1 | 0.1706 (5) | 1.3869 (4) | 0.0737 (6) | 0.077 (2)* |
| Cl2 | 0.6976 (5) | 0.6228 (5) | 0.4823 (5) | 0.077 (2)* |
| Cl3 | 0.6169 (5) | 0.6852 (6) | 0.1807 (4) | 0.077 (2)* |
| S1  | −0.1719 (4) | 1.2122 (3) | 0.1245 (3) | 0.077 (2)* |
| S2  | 0.1781 (3) | 0.7747 (3) | 0.3633 (3) | 0.077 (2)* |
| O1  | −0.2933 (6) | 1.0957 (6) | 0.1498 (8) | 0.067 (3)* |
| O2  | −0.1923 (8) | 1.2685 (7) | −0.0171 (5) | 0.067 (3)* |
| O3  | 0.0321 (6) | 0.6764 (7) | 0.2898 (8) | 0.067 (3)* |
| O4  | 0.2180 (8) | 0.8015 (8) | 0.5171 (5) | 0.067 (3)* |
| N1  | −0.1595 (5) | 1.3476 (4) | 0.2391 (3) | 0.067 (3)* |
| N2  | 0.4634 (3) | 0.9538 (4) | 0.2834 (4) | 0.067 (3)* |
| N3  | 0.3382 (4) | 0.7092 (4) | 0.3292 (3) | 0.067 (3)* |
| C1  | 0.0177 (3) | 1.1394 (4) | 0.1699 (5) | 0.067 (3)* |
| C2  | 0.1642 (4) | 1.2130 (4) | 0.1445 (6) | 0.067 (3)* |
| C3  | 0.3096 (3) | 1.1530 (4) | 0.1835 (5) | 0.067 (3)* |
| C4  | 0.3185 (3) | 1.0161 (4) | 0.2523 (5) | 0.067 (3)* |
| C5  | 0.1731 (4) | 0.9465 (4) | 0.2836 (5) | 0.067 (3)* |
| C6  | 0.0246 (3) | 1.0070 (3) | 0.2418 (5) | 0.067 (3)* |
| C7  | 0.4870 (3) | 0.8221 (3) | 0.3700 (3) | 0.067 (3)* |
| C8  | 0.6447 (4) | 0.7593 (3) | 0.3576 (3) | 0.067 (3)* |
| H1A | −0.1365 (14) | 1.3166 (7) | 0.3346 (5) | 0.080 (3)* |
| H1B | −0.1025 (9) | 1.4428 (6) | 0.2271 (6) | 0.080 (3)* |
| H2A | 0.5578 (6) | 1.0136 (7) | 0.2680 (12) | 0.080 (3)* |
| H3  | 0.4081 (6) | 1.2080 (7) | 0.1708 (12) | 0.080 (3)* |
| H3A | 0.3087 (8) | 0.6781 (10) | 0.2301 (5) | 0.080 (3)* |
| H6  | −0.0758 (6) | 0.9513 (7) | 0.2507 (8) | 0.080 (3)* |
| H7  | 0.5057 (8) | 0.8495 (7) | 0.4690 (5) | 0.080 (3)* |
| H8  | 0.7352 (7) | 0.8393 (6) | 0.3793 (7) | 0.080 (3)* |
### Geometric parameters (Å, °)

| Bond/Distance          | Value     |
|------------------------|-----------|
| Cl1—C2                 | 1.708 (6) |
| Cl2—C8                 | 1.746 (5) |
| Cl3—C8                 | 1.771 (5) |
| S1—O1                  | 1.439 (6) |
| S1—O2                  | 1.449 (6) |
| S1—N1                  | 1.596 (4) |
| S1—C1                  | 1.747 (5) |
| S2—O3                  | 1.417 (7) |
| S2—O4                  | 1.447 (5) |
| S2—N3                  | 1.647 (4) |
| S2—C5                  | 1.729 (5) |
| N2—C4                  | 1.366 (4) |
| N2—C7                  | 1.460 (4) |
| N3—C7                  | 1.461 (4) |
| C1—C2                  | 1.412 (5) |
| O1—S1—O2               | 120.4 (4) |
| O1—S1—N1               | 104.7 (4) |
| O1—S1—C1               | 106.3 (3) |
| O2—S1—N1               | 110.6 (3) |
| O2—S1—C1               | 106.4 (4) |
| N1—S1—C1               | 107.9 (3) |
| S3—O2                  | 119.4 (4) |
| S3—O3                  | 108.0 (3) |
| S3—C3                  | 108.2 (3) |
| S4—O2                  | 117.2 (3) |
| S4—S2                  | 109.4 (4) |
| N3—S2                  | 103.4 (2) |
| C4—N2                  | 122.0 (3) |
| S5—N3                  | 111.5 (3) |
| C5—N3                  | 123.5 (3) |
| S6—C1                  | 117.3 (2) |
| C6—C1                  | 119.1 (3) |
| S6—N1                  | 117.3 (5) |
| H1B—N6                 | 115.6 (7) |
| S7—N1                  | 113.0 (5) |
| C8—C6                  | 121.7 (3) |
| C9—C8                  | 116.8 (3) |
| C10—C9                 | 116.9 (5) |
| C11—C10                | 119.3 (6) |
| C12—C11                | 121.5 (4) |
| S1—C1                   | 172.5 (5) |
| S2—C2                   | −11.3 (5) |
| S3—C3                   | 43.1 (5)  |

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O2—S1—C1—C6 −140.8 (4) C6—C1—C2—C3 3.0 (7)
N1—S1—C1—C2 −75.6 (5) S1—C1—C6—C5 −178.4 (4)
N1—S1—C1—C6 100.6 (4) C2—C1—C6—C5 −2.0 (7)
O3—S2—N3—C7 165.6 (4) C1—C2—C3—C4 175.2 (4)
O4—S2—N3—C7 −64.4 (4) N3—C7—C8—Cl2 169.9 (3)
C5—S2—N3—C7 51.2 (3) N3—C7—C8—Cl3 −66.3 (3)
O3—S2—C5—C4 −134.0 (4) N3—C7—C8—Cl3 57.5 (3)
O3—S2—C5—C6 41.0 (5) N3—S2—C5—C4 178.0 (4)
O4—S2—C5—C6 −90.6 (5) N3—S2—C5—C6 3.1 (7)
N3—S2—C5—C4 −19.6 (4) S2—C5—C6—C1 −175.9 (4)
N3—S2—C5—C6 155.4 (4) S2—C5—C6—C1 −1.0 (7)
C7—N2—C4—C3 172.4 (4) C4—C5—C6—C1 169.9 (3)
C7—N2—C4—C5 −9.1 (6) C4—C5—C6—C1 −66.3 (3)
N3—C4—C5—C6 42.5 (5) C4—C5—C6—C1 57.5 (3)
C4—C5—C6—C1 167.7 (3) C4—C5—C6—C1 0.41 (3)
N3—C4—C5—C6 167.7 (3) C4—C5—C6—C1 0.42 (3)
N3—C4—C5—C6 167.7 (3) C4—C5—C6—C1 0.42 (3)
N2—N3—C7—N2 −64.5 (3) C4—C5—C6—C1 0.42 (3)
S2—N3—C7—C8 172.8 (2) C4—C5—C6—C1 0.42 (3)

Summary of calculated energies (kJ mol⁻¹) for RS-TCMZ and S-TCMZ (from CSD Refcode KIKCUD)

|      | \( E_{\text{ele}} \) | \( E_{\text{pot}} \) | \( E_{\text{dis}} \) | \( E_{\text{rep}} \) | \( E_{\text{tot}} \) |
|------|------------------|------------------|------------------|------------------|------------------|
| RS-TCMZ | -71.8 | -50.6 | -240.5 | 260.7 | -161.6 |
| S-TCMZ (KIKCUD) | -147.7 | -41.4 | -146.1 | 185.6 | -199.6 |

Energy Model

| Energy Model | \( k_{\text{ele}} \) | \( k_{\text{pot}} \) | \( k_{\text{disp}} \) | \( k_{\text{rep}} \) |
|-------------|------------------|------------------|------------------|------------------|
| CE-B3LYP    | 1.057            | 0.740            | 0.871            | 0.618            |
| B3LYP/6-31G(d,p) | electron densities | | | |

Predicted and realized intermolecular hydrogen bonds for TCMZ

| Donor-Intermolecular interactions | Acceptor | Propensity | RS-TCMZ | S-TCMZ |
|----------------------------------|----------|------------|---------|--------|
| N1–H1B                           | O3       | 0.69       | *Observed* |        |
| N1–H1A                           | O4       | 0.69       | *Observed* | *Observed* |
| N1–H1A                           | O1       | 0.68       |         |        |
| N1–H1B                           | O2       | 0.68       | *Observed* |        |
| N3–H3A                           | O3       | 0.44       |         |        |
| N3–H3A                           | O4       | 0.44       |         |        |
| N3–H3A                           | O1       | 0.42       |         | *Observed* |
| N3–H3A                           | O2       | 0.42       | *Observed* |        |
| N2–H2A                           | O3       | 0.42       |         |        |
| N2–H2A                           | O4       | 0.42       |         |        |
| N2–H2A                           | O1       | 0.41       | *Observed* |        |
| N2–H2A                           | O2       | 0.41       | *Observed* |        |
| N1–H1A/H1B                       | N2       | 0.08       |         |        |
|          | Interactions | Distances (Å) |
|----------|--------------|---------------|
| N1–H1A/H1B | Cl1          | 0.04          |
| N1–H1A/H1B | Cl2          | 0.04          |
| N1–H1A/H1B | Cl3          | 0.04          |
| N3–H3A     | N2           | 0.03          |
| N2–H2A     | N2           | 0.02          |
| N3–H3A     | Cl1          | 0.02          |
| N2–H2A     | Cl1          | 0.01          |
| N3–H3A     | Cl2          | 0.01          |
| N3–H3A     | Cl3          | 0.01          |
| N2–H2A     | Cl2          | 0.01          |
| N2–H2A     | Cl3          | 0.01          |

**Intramolecular interactions**

|          | Interactions | Distances (Å) |
|----------|--------------|---------------|
| N1–H1B   | Cl1          | 0.60          |
| N3–H3A   | Cl3          | 0.48          |

*Observed*