

UDC 541.6:548.737

**N—H···S HYDROGEN BONDING MOTIFS IN CRYSTALLINE SOLIDS  
OF 1,2,4-TRIAZOLE-5-THIONES: APPLICATION OF THE CAMBRIDGE  
STRUCTURAL DATABASE.  $R_2^2(8)$  RING MOTIF**

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*Received October, 9, 2012*

A database study on the N—H···S hydrogen bonding ring motif ( $R_2^2(8)$ ) for 1,2,4-triazole-5-thiones is reported. The  $R_2^2(8)$  ring is one of the most general ring motifs observed in the crystallographic literature, however, up to now the ring synthon built by the N—H···S interaction has not been particularly described. Probably, in multi-heteroatom systems, other structure-determining stronger interactions may take precedence over weaker N—H···S interactions. On the other hand, in recent years, considerable importance has been given to structures determined through N—H···S interactions. It is also common in the crystals of 1,2,4-triazole-5-thione derivatives.

**Keywords:** N—H···S hydrogen bond,  $R_2^2(8)$  ring motif, 1,2,4-triazole-5-thiones, dimer, Hirshfeld surface, fingerprint plot, CSD, Cambridge Structural Database.

**INTRODUCTION**

Over the past decade, considerable importance has been given to the structures of 1,2,4-triazole-5-thione derivatives, which are mainly determined through N—H···S hydrogen bonds [ 1, 2 ]. Moreover, the biological relevance of the N—H···S hydrogen bonding has been noted [ 3 ]. Desiraju [ 4 ] and others [ 5, 6 ] in their review papers described various types of supramolecular synthons, but it is noteworthy that the supramolecular synthon built by the N—H···S interaction was not mentioned there. Probably, in multi-heteroatom systems, other structure-determining stronger interactions (e.g. N/O—H···O/N) may take precedence over weaker N—H···S interactions and the supramolecular synthon formed by N—H···S becomes rarer, which does not imply that it is less significant [ 1, 2 ].

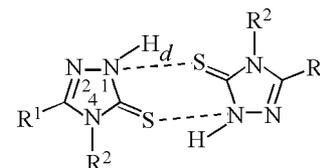
**METHODOLOGY**

In view of the above mentioned facts, the Cambridge Structural Database (CSD, version 5.32 + 5 updates [ 7 ]) was surveyed using the ConQuest program [ 8 ] to identify 1,2,4-triazole-5-thione derivatives and their N—H···S hydrogen bond ring motifs. In total, a subset was created containing 149 crystal structures of 1,2,4-triazole-5-thione derivatives. This subset was attended as the base for all further searches and analyses (only organic compounds having 3D coordinates, no errors or disorders and  $R < 10$  %; additionally, entries were inspected visually using the ConQuest 3D Visualiser, multiple and structures which did not have hydrogen atoms were removed manually). All search queries were built manually exerting the *Draw* button in the *Build Queries* area, and geometric constrains of nonbonded contacts were added by the *Contact* button in the *Draw* window.

In order to describe and classify the hydrogen bond ring motifs, the graph set notation  $G_d^a(r)$  (where  $G$  is the pattern designator —  $R$  ring,  $C$  chain,  $S$  self/intramolecular,  $D$  finite patterns,  $a$  is the number of acceptors,  $d$  is the number of donors, and  $r$  is the number of atoms in the motifs) was used [9].

In the initial subset, two structures (refcodes [7]: WIWJOC, HOLQAB) have H-substituents at N4 atoms, and finally, the subset containing 147 1,2,4-triazole-5-thione derivatives was used to retrieve the N—H $\cdots$ S hydrogen bonding ring motif. The query of the  $R_2^2(8)$  ring synthon was created as shown in Scheme 1. The only contact considered was the 1,2,4-triazole $\cdots$ thione hydrogen bond (homo-ring motif), defined with a N $\cdots$ S distance cutoff of 3.45 Å between N(triazole) and S(thione) atoms.

Scheme 1. Search protocol for the  $R_2^2(8)$  ring motif formation by N—H $\cdots$ S interactions;  $R^1, R^2 =$  any non-metal,  $d(\text{N}\cdots\text{S}) < 1.5 + 1.85 + 0.1 < 3.45$  Å



## RESULTS AND DISCUSSION

As a result of the described methodology, 77 structures were found (there were no hydrates and/or solvates amongst them) which represent 52.4 % of the entire subset, and the remaining 70 (= 47.6 %) form non-cyclic arrangements. The 77 structures containing the described motif were then divided into two sections in Table 1: (i) 72 structures, including one chemical entity in the asymmetric

Table 1

1,2,4-Triazole-5-thione derivatives<sup>a</sup> (and their space groups) which form the  $R_2^2(8)$  motif<sup>b</sup>

ABEFUJ ( $Z' = 1$ )	$P2_1/n$	KODZIN	$P2_1/n$	HADCUL	$P\bar{1}$	TIGTUZ	$P2_1/n$
ABEMEA	$P2_1/c$	LEPFAO	$P\bar{1}$	HAMSIY	$P2_1/n$	VOPMAP01	$P2_1/n$
ABHYTZ	$C2/c$	LIJQOL	$P\bar{1}$	HAMZOL	$P2_1/c$	VUJZAB	$P\bar{1}$
APOXOS01	$P2_1/n$	LOHQUV	$P\bar{1}$	HEBKEF	$C2/c$	VUJZAB01	$P2_1/n$
AWUTUI	$P\bar{1}$	LUHCIB	$P2_1/c$	HIGWIE	$P\bar{1}$	WAGKOG	$P2_1/n$
BZAMTZ	$P2_1/c$	LUPHEK	$P2_1/c$	HIQKOH01	$P\bar{1}$	WIYGEQ	$P\bar{1}$
CIQLIY	$P2_1/c$	MOFVUZ	$P2_1/n$	HISPEF	$P\bar{1}$	WUMPUP	$P\bar{1}$
CIZVIQ	$P\bar{1}$	MUSVUR	$P2_1/n$	HOMCUI	$P2_1/c$	XEZBEK	$P\bar{1}$
CIZVUC	$P\bar{1}$	NERZUG	$P\bar{1}$	HOYCAA	$P\bar{1}$	YIRBAD	$P\bar{1}$
COJLAO01	$P\bar{1}$	NOBJAQ	$P\bar{1}$	HPMTZT	$P2_1/c$	YIXYUA	$P\bar{1}$
CUPXOB	$P2_1/n$	OCAMEL	$P2_1/n$	HUCRUT	$P\bar{1}$	YIZDAN	$P2_1/c$
ETICOZ	$P\bar{1}$	OGEJIU	$P\bar{1}$	HUDZEM	$P2_1/c$	YODGAA	$P\bar{1}$
ETIWAF	$P2_1/n$	PIZDIM	$P\bar{1}$	IDUPON	$P\bar{1}$	YODHAB	$P\bar{1}$
EVAMAQ	$P2_1/n$	POWXAB	$P\bar{1}$	INEVAZ	$P2_1/c$		
FAXRUS	$P2_1/c$	QETNOT	$P2_1/c$	IYAZEN	$C2/c$	NEYBOJ ( $Z' = 2$ )	$P\bar{1}$
FEVKAT	$P2_1/n$	QOFGUO	$Pbcn$	IZAMOL	$P\bar{1}$	PEZDUU	$P2_1/c$
GISNOM	$P\bar{1}$	SIKTIQ	$P2_1/a$	JAXQAB	$P2_1/a$	QIYQUK	$P\bar{1}$
GOMBUG	$P2_1/c$	SIMTOY	$P2_1/n$	JEYFEZ	$P2_1/n$	REHHOC	$P\bar{1}$
GOMCIV	$P2_1/n$	SOHDUP	$P2_1/c$	JEYFID	$P2_1/n$	YERSOE	$P\bar{1}$
GURCAY	$P\bar{1}$	TIGTOT	$P2_1/n$				

<sup>a</sup> Refcodes from CSD [7].

<sup>b</sup> See Scheme.

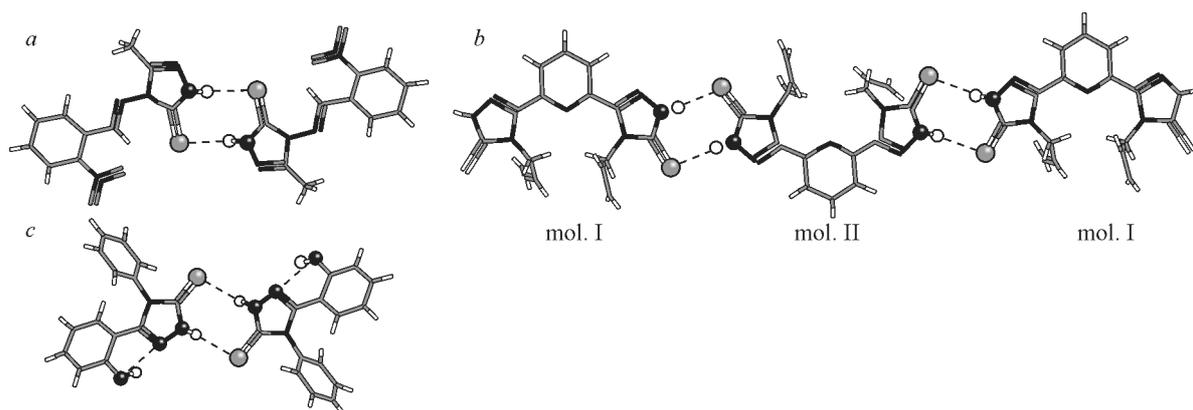


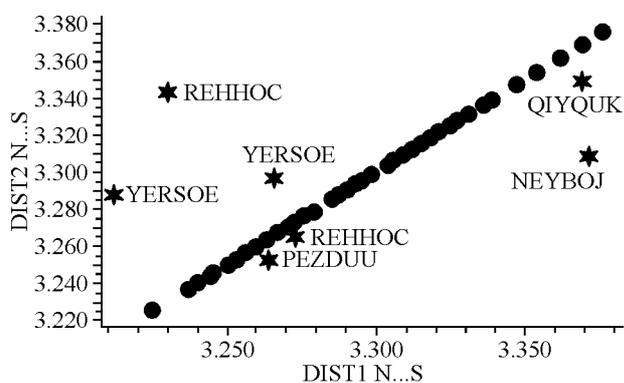
Fig. 1. Examples of the N—H $\cdots$ S dimer formation: JEYFID ( $Z' = 1$ ) (a), YERSOE ( $Z' = 2$ ) (b), ABEMEA ( $Z' = 1$ ) (c)

unit ( $Z' = 1$ ) (**Z'1**) and (ii) 5 structures, including more than one chemical entity in the asymmetric unit (in this case  $Z' = 2$ ) (**Z'2**). Crystallographically, two molecules in the asymmetric unit are totally independent, and must be clearly distinguished and treated separately to generate graph set notations of hydrogen bonds. The representation of the hydrogen bonding motifs observed in this study is shown in Fig. 1.

The scatter plot (Fig. 2) clearly indicates that in **Z'1** structures the ring motif is centrosymmetric, and is described by the first-level graph set  $R_2^2(8)$  (Fig. 1, a). So, in this ring motif "good" proton donors and acceptors are used in the hydrogen bonding [10]. In addition to the base pairing, intramolecular hydrogen bonds in six-membered rings are also common (as an example, Fig. 1, c): the triazole N2 atom participates in this  $S(6)$  motif. In **Z'2**, the recognized motif is pseudo-centrosymmetric and is denoted by the second-level graph set. It can be seen that the inversion center plays a significant role in the structures of 1,2,4-triazole-5-thione derivatives of the hydrogen ring motifs with the graph set  $R_2^2(8)$ .

For PEZDUU, NEYBOJ, and QIYQUK there are two different triazole $\cdots$ thione hydrogen bonds, each one of these combinations is the  $D$  motif, so the first-level graph set is  $N_1 = DD$ . A combination of these two motifs in a binary graph set results in the ring, consequently is simply  $N_2(a,b) = R_2^2(8)$ . In REHHOC and YERSOE, the molecules have two 1,2,4-triazole-3-thione moieties. The two H(—N1) atoms from molecule **I** form hydrogen bonds with S(=C) atoms from molecule **II**, and *vice versa* (Fig. 4, b). Hence, the first-level graph set is  $N_1 = DDDD$ , while two of the binary graph sets, (a,b) and (c,d), are  $R_2^2(8)$ . As seen from Fig. 2, the shortest N $\cdots$ S distance is 3.212 Å (YERSOE), whereas the longest one is 3.376 Å (HISPEF).

It should be noted here that among the structures which do not form triazole $\cdots$ triazole rings (within the 147-subset) there are only eight hydrates (FIDYEX, NIJSAB, QEXKOU, RIYQUM,



VEKVAJ, XAZMAN and two dimethylformamide solvates PAMQUQ, YIFYIW). Within those crystals, O—H $\cdots$ S<sub>thione</sub> (FIDYEX) and N—H<sub>triazole</sub> $\cdots$ O<sub>H<sub>2</sub>O/DMF</sub> (other) hydrogen bonds are created. Thus, in multi-heteroatom molecules, other structure-determining stronger interactions take precedence over N—H $\cdots$ S interactions.

Fig. 2. Scatter plot of the N $\cdots$ S distances observed in the  $R_2^2(8)$  ring

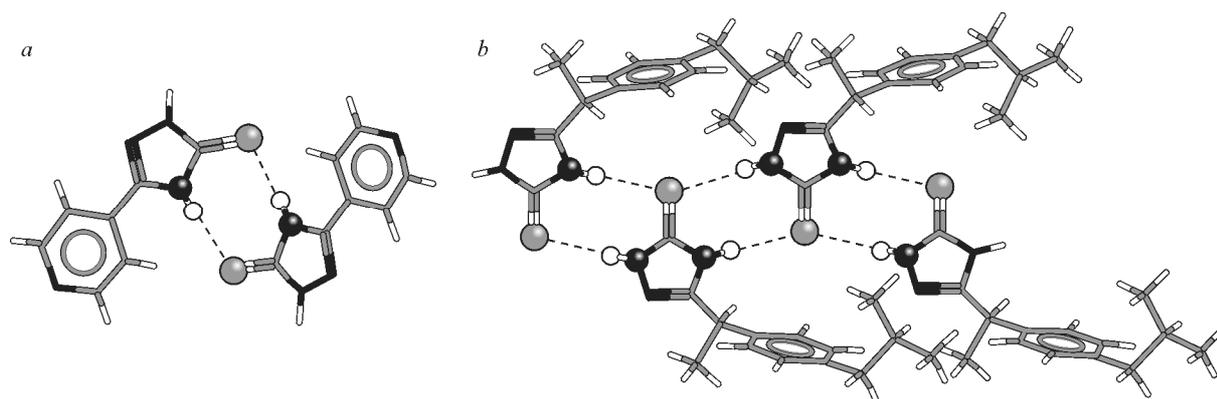


Fig. 3. Arrangement of N—H···S hydrogen bonds in the structures which are H-substituted at N4 atoms: WIWJOC (a) and HOLQAB (b)

Returning to the structures, which are H-substituted at N4 atoms (WIWJOC and HOLQAB — not mentioned in Table 1), and analyzing their arrangement of hydrogen bonds, we can observe the  $R_2^2(8)$  motifs, too. In contrast to N4-substituted structures, in that ring motif, either N4—H groups (WIWJOC) or both N4—H and N1—H groups (HOLQAB) participate as donors of N—H···S interactions (Fig. 3).

For example, Hirshfeld surfaces of N—H···S dimers for two crystals (JEYFID (**Z'1**) and YER-SOE (**Z'2**)) were generated. Furthermore, 2D fingerprint plots were produced to show the relative contribution of N—H···S intermolecular interactions to the Hirshfeld surfaces. Surfaces mapped with the  $d_{\text{norm}}$  and decomposed fingerprint plots are shown in Fig. 4. From this simple analysis, it appears, that for YER-SOE the crystal structure is determined by S···H/H···S interactions (contacts make 25.4 % and 22.5 % of the surface area, for two independent molecules in the asymmetric unit, respectively,

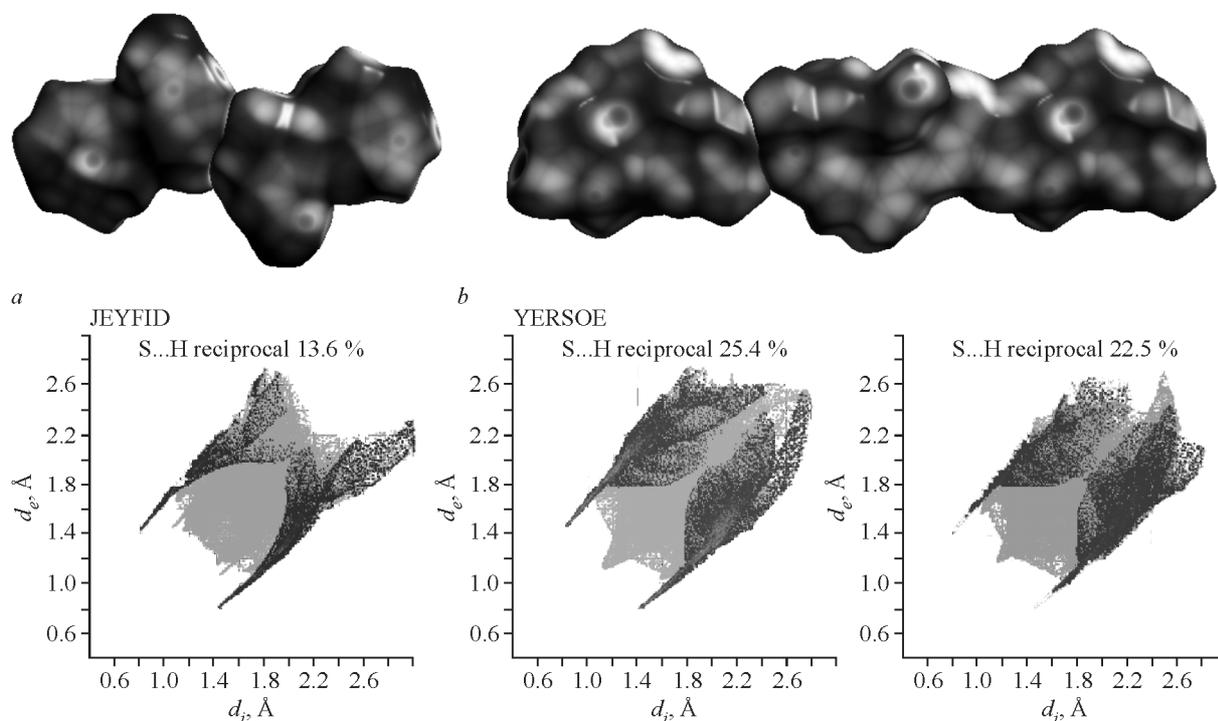


Fig. 4. Hirshfeld surfaces mapped with  $d_{\text{norm}}$  and decomposed fingerprint plots showing N···S contacts: JEYFID ( $Z' = 1$ ) (a), YER-SOE ( $Z' = 2$ ) (b)

Fig. 4, b). The 2D plot for JEYFID shows that S $\cdots$ H/H $\cdots$ S interactions not determine primarily its crystal structure (contacts make 13.6 % of the surface area, Fig. 4, a). Further inspection of contacts between other atom types pointed out that there are O $\cdots$ H/H $\cdots$ O significant interactions within the crystal (contacts make 24.3 % of the surface area — data not shown).

### CONCLUSIONS

In conclusion, it should be noted, the  $R_2^2(8)$  ring is one of the most general ring motifs observed in the crystallographic literature (for example, aliphatic and aromatic carboxylic acids [11], amides [12, 5], sulfonamides [13], thioureas [14]). It is also common (centrosymmetric or pseudo-centrosymmetric) in the crystals of 1,2,4-triazole-5-thione derivatives; in 77 (= 52.4 %) of the 147 crystals, which means it is not so much predominate. There does not seem to be any clear correlation between the graph set  $R_2^2(8)$  and  $R^1$  and  $R^2$  substituents (Scheme 1). Nevertheless, from Hirshfeld surfaces analyses it can be concluded that in **Z'**1 crystals, the network of intermolecular interactions is delineated by N—H $\cdots$ S hydrogen bonds (Fig. 4).

As regards hydrates or solvates of the discussed triazoles, the presence of a guest results in the formation of stronger host $\cdots$ guest interactions and ring triazole $\cdots$ triazole motifs are not created.

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