Struct Chem (2011) 22:313–317
DOI 10.1007/s11224-010-9710-y

ORIGINAL RESEARCH

# Solvent mediated reaction of 1-methyl-1*H*-tetrazoline-5-thione with iodine

**Nataliya V. Aleshina · Margarita S. Chernov'yants ·
Igor N. Shcherbakov · Zoya A. Starikova**

Received: 16 September 2010 / Accepted: 9 December 2010 / Published online: 24 December 2010

**Abstract** 1-Methyl-1*H*-tetrazoline-5-thione (1) reacts with iodine in $CHCl_3$ with formation of 1:1 stable $\sigma$-complex ($\log\beta = 3.8 \pm 0.1$ is found by spectrophotometry). In the ethanol solution irreversible oxidation with formation of disulfide product 5,5′-dithiobis(1-methyl-1*H*-tetrazole) (2) is observed. The structure of (2) was determined by X-ray diffraction. Strong intermolecular interactions with shortened contacts are observed between sulfur atom of disulfide bridge and heterocyclic nitrogen of the neighboring molecule (S···N 3.0179(15) Å) forming infinite supramolecular chains which are further linked with $\pi$–$\pi$ stacking interaction of tetrazole rings (interplane distance is 3.1685(6) Å).

**Keywords** X-ray structure · Heterocyclic compounds · Stability constant · Iodine chemistry

## Introduction

Tetrazole compounds have a wide range of pharmaceutical applications, where they act as stimulants or sedatives on the central nervous system. These compounds have anti-inflammatory, antilipemic, antimicrobial, and antiallergic activities [1]. Moreover, such compounds possess anti-thyroidal effect same *N*-methylimidazoline-2-thione (methimazole) or 3-methyl-2-thioxo-4-imidazoline-1-ethylcarboxylate (carbimazole) [2].

Studies on the formation of heterocyclic thiones *n*–$\sigma$* complexes such as *N*-methylbenzothiazole-2-thione, *N*-methylimidazoline-2-thione, 2-imidazolidinethione with molecular iodine were motivated by an interest in elucidation of the mechanism of action of antithyroid drugs used for the treatment of hyperthyreosis [3]. It is known [4] that the reaction of 2-imidazolidinethione with an aqueous solution of $I_2$ in KI is accompanied by oxidation of thione to give the dimeric product, viz., 2,2′-dithiobis(imidazolidine). The reaction of methimazole with molecular iodine in $CH_2Cl_2$ in a molar ratio of 1:2 gave the $[(C_4H_6N_2S\text{-})_2]I_8$ compound containing the 2,2′-dithiobis(1-methylimidazolium) dication and the Z-shaped $I_8^{2-}$ counterion [5]. The crystal and molecular structure of the compound with composition $[(C_4H_6N_2)S]_2(I_3)_2I_2$—the oxidation product of methimazole with molecular iodine in $CHCl_3$ was established by X-ray diffraction [6]. The reaction of thiazolidine-2-thione with molecular iodine in a molar ratio of 1:2 affords the iodonium salt $[(C_3H_5NS_2)_2I^+]\ I_3^-I_2$ as a result of heterolytic disproportionation of the iodine molecule [2]. The crystal structure of the reaction product of 5-methyl-1,3,4-thiadiazoline-2-thion with molecular iodine in $CHCl_3$ consists of the iodonium cations $(C_3H_4N_2S_2)_2I^+$ and the pentaiodide anions $I_5^-$ [7]. Organic disulfide—5,5′-dithiobis(1-phenyl-1*H*-tetrazole), $C_{14}H_{10}N_8S_2$, have been isolated during an attempt to prepare an unsymmetrical disulfide [8].

It was shown [9, 10] that the mechanism of reaction (the formation of disulfide or iodonium salt) depends on the electron-releasing properties of the thione molecule

N. V. Aleshina
Southern Scientific Center of Russian Academy of Sciences
(SSC RAS), 41, Chehova Str., Rostov-on-Don 344006,
Russian Federation

M. S. Chernov'yants · I. N. Shcherbakov (✉)
Southern Federal University, 7, Zorge Str.,
Rostov-on-Don 344090, Russian Federation
e-mail: shcherbakov@sfedu.ru

Z. A. Starikova
A. N. Nesmeyanov Institute of Organoelement Compounds,
Russian Academy of Sciences, Moscow 119991,
Russian Federation

determined by the nature of heteroaromatic moiety and the character of the oxidizing agent and the solvent used. The adiabatic ionization potentials of heteroaromatic thiones are rather low due to which they are readily oxidized to form radical cations or thiyl radicals as a result of the loss of the hydrogen atom from thione [11]. Ability of heteroaromatic thioamides to interact with iodine, stoichiometry and stability of charge transfer complexes, molecular and crystal structures have been studied by several authors [12–19].

The aim of the present study was to study the reaction of 1-methyl-1*H*-tetrazoline-5-thione (1) with elemental iodine in chloroform and ethanol solutions.

## Results and discussion

In chloroform solution reversible complex formation was observed and studied by UV/vis spectroscopy.

$$L + nI_2 \rightleftharpoons L \cdot nI_2$$

The number of $I_2$ molecules coordinated by thione (L) in solution and the stability constant of the molecular adduct of (I) with iodine were estimated by spectrophotometry based of the shift of the reaction equilibrium:

$$\beta = \frac{[L \cdot nI_2]}{[L][I_2]^n} \qquad (1)$$

The UV/visible absorption spectra of solutions containing thione at a constant concentration and iodine at concentrations varied from $4 \times 10^{-5}$ up to $1.2 \times 10^{-3}$ mol/L are presented in Fig. 1.

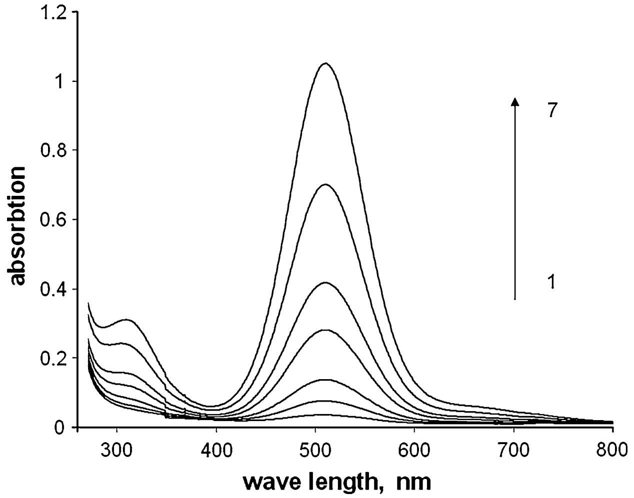

**Fig. 1** Electronic absorption spectra of solutions of thione ($4.0 \times 10^{-5}$ mol/L) and molecular iodine at the concentrations: $4.0 \times 10^{-5}$ (*1*), $8.0 \times 10^{-5}$ (*2*), $1.6 \times 10^{-4}$ (*3*), $3.2 \times 10^{-4}$ (*4*), $4.8 \times 10^{-4}$ (*5*), $8.0 \times 10^{-4}$ (*6*), and $1.2 \times 10^{-3}$ mol/L (*7*)

The stability constant was calculated by the least squares method according to Eq. 2, the linearized form of Eq. 1:

$$\log\frac{A_i}{A_{\max} - A_i} = \log\beta + n\log\left[c_{I_2} - n\frac{A_i}{A_{\max}}c_L\right] \qquad (2)$$

where $A_{\max}$ is the absorbency of a solution, in which thione L is almost completely involved in the adduct ($\lambda_{\max} = 308$ nm); $A_i$ is the absorbency of solutions containing thione L and the molecular adduct; $\beta$ is the stability constant, $n$ is the number of iodine molecules coordinated by thione L; $c_{I_2}$, $c_L$ are the total concentrations of molecular iodine and thione, respectively.

The calculated from experimental data least squares line (2) is $y = 0.972x + 3.83$ ($\rho = 0.992$). From which it can be concluded that L coordinates only one iodine molecule and estimated $\log\beta = 3.8 \pm 0.1$.

Mixing of the same reagents in ethanol solution resulted in rapid irreversible oxidation of the thione with formation of disulfide 5,5′-dithiobis(1-methyl-1*H*-tetrazole), which molecular and crystal structure was studied by X-ray diffraction data.

The molecular structure of 5,5′-dithiobis(1-methyl-1*H*-tetrazole) with the atom-numbering scheme is shown in Fig. 2 and selected geometric parameters are given in Table 1.

The conformation of the molecule in crystal is not symmetrical, two formally identical thiotetrazole moieties interconnected with disulfide bridge are rotated relative to each other around S–S line (the C1–S1–S2–C2 torsion angle is 80.83(8)°). Both tetrazole rings are strictly planar due to $\pi$-conjugation (larges deviation of atoms from the least squares planes is 0.006(2) Å).

The bond lengths and angles are rather close in the two thiotetrazole moieties of the molecule, the most deviating are two N–N bond pairs: N1–N2, 1.341(2) Å and N6–N7, 1.352(2) Å) and (N3–N4, 1.356(2) Å and N8–N9, 1.367(2) Å). S–C bond lengths are nearly the same (S1–C1, 1.7512(18) Å and S2–C3, 1.7532(18) Å) though orientation of tetrazole rings $\pi$-systems relative to S–S bond are different. The angle between ls plane of "first" tetrazole ring (with C1 atom) and S1–S2 bond is 59.67(7)°, whilst the same one for the second ring (with C3 atom) is 15.86(7)° (Table 1).

The S1–S2 bond length (2.0484(6) Å) is rather short for acyclic disulfide bridge connecting five-membered heterocycles (common range is 2.013–2.141 Å) which is typical for bis-thiotetrazole derivatives (compare with 2.0128(9) Å in 5,5′-dithiobis(1-phenyl-1*H*-tetrazole [8] and 2.026(2) Å in bis(1-(2,6-dimethylphenyl)-1,2,3,4-tetrazol-5-yl)disulfane [20].

Hydrogen atoms on both methyl groups are disordered over two sets of positions with equal occupancy corresponding to internal rotation of methyl groups around N–C bond.

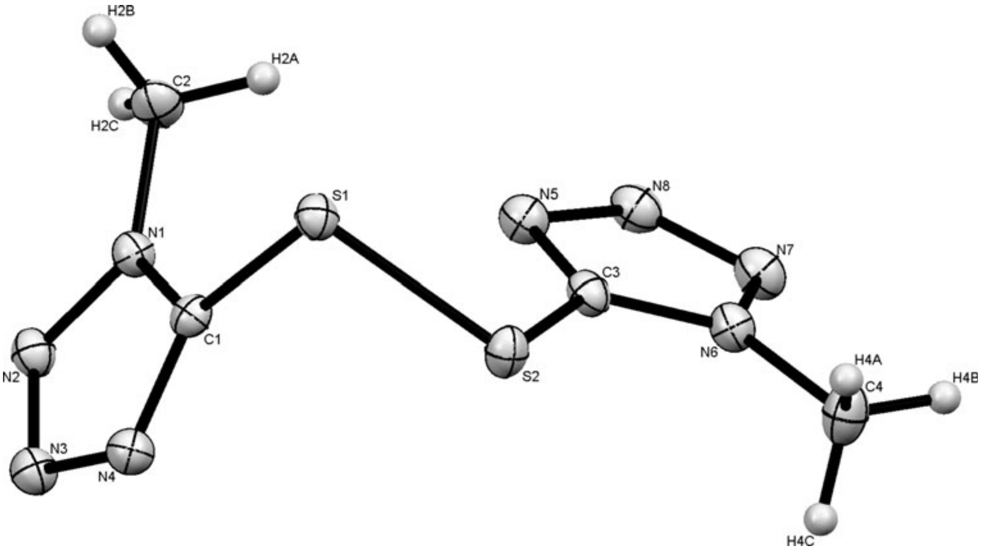

**Fig. 2** Structure of the compound $C_4H_6N_8S_2$ (2) (thermal ellipsoids are drawn at 50% probability)

**Table 1** Selected geometric parameters (Å, °)

| Parameter | Value |
|---|---|
| Bond lengths (Å) | |
| S1–C1 | 1.7520(16) |
| N1–C1 | 1.3415(19) |
| N1–N2 | 1.3414(18) |
| N3–N2 | 1.3031(19) |
| N4–N3 | 1.3564(19) |
| N4–C1 | 1.323(2) |
| N1–C2 | 1.456(2) |
| S1–S2 | 2.0482(6) |
| S2–C3 | 1.7530(16) |
| N6–C3 | 1.336(2) |
| N6–N7 | 1.3528(19) |
| N8–N7 | 1.293(2) |
| N9–N8 | 1.3704(19) |
| N5–C3 | 1.326(2) |
| N6–C4 | 1.459(2) |
| Bond angles (°) | |
| C1–S1–S2 | 101.60(5) |
| C3–S2–S1 | 102.02(6) |
| Torsion angles (°) | |
| C1–S1–S2–C3 | 80.83(8) |

Crystal packing of the molecules appears to be very interesting and worth discussing. Intensive intermolecular interaction between S1 and N3$^{i}$ atoms is observed with very short interatomic distance of 3.0179(17) Å between atoms (symmetry code: (i) $1 - x, -1/2 + y, 1/2 - z$). It is 0.33 Å shorter than sum of the van der Waals radii and is the shortest intermolecular contact registered in Cambridge Structural Database up to date (CSD [21], version 5.31 + updates November 2009) between heterocyclic nitrogen and acyclic disulfide sulfur atom. C1 and N3$^{i}$ contact is also extremely short—2.932(2) Å (0.32 Å less than vdW radii sum). Also not common is the arrangement of the interacting moieties of the molecules which are placed in the crystal in such a way that S–S···N$^{i}$ angle is 166.82(6)° and S1 goes out of the mean plane of tetrazole moiety of N3$^{i}$ only by 0.305 Å, S–S bond is nearly parallel to this plane.

Nitrogen atom N3 of the same thiotetrazole moiety is involved into similar with earlier described interaction with S1$^{ii}$ and C1$^{ii}$ atoms of another molecule (symmetry code: (ii) $1 - x, 1/2 + y, 1/2 - z$). Connected in such "head-to-tail" manner molecules of disulfide form infinite one-dimensional zigzag chains which propagate along (b) axis of the crystal as shown in Fig. 3. These chains are formed due to interactions in which only one of the two tetrazole moieties present in the molecule is involved (with S1 and C1 atoms in it).

Infinite one-dimensional supramolecular chains are "zipped" with one another into two-dimensional layer (which is paralleled to (01-1) plane) by interaction in which the "second" thiotetrazole moiety of the molecules is taking part (with S2 and C3 atoms within it). Connection between infinite chains is accomplished by $\pi$–$\pi$ stacking interactions of tetrazole rings (Fig. 3).

Least squares planes of interacting rings are strictly parallel to each other and are separated by 3.1687(7) Å (distance between tetrazole ring's centroids is 3.2256(10) Å). Rings slip relative to each other in such a way that C3 and N8 atoms are almost directly above N8$^{iii}$ and C3$^{iii}$ atoms of another molecule, correspondingly (symmetry code: (iii) $1 - x, 2 - y, -z$). Interatomic distances in C3···N8$^{iii}$ and C3$^{iii}$···N8 contacts are 3.179(2) Å long and by 0.07 Å shorter than sum of interacting atom's vdW radii. In CSD there is no example of such arrangement of tetrazole rings in the crystal state and the rings

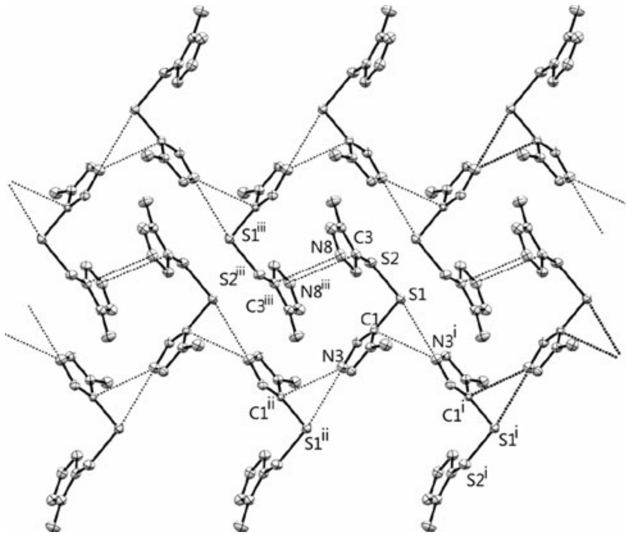

**Fig. 3** Supramolecular interactions in the crystal structure of $C_4H_6N_8S_2$ (hydrogen atoms are omitted for clarity). Symmetry codes: (*i*) $1 - x, -1/2 + y, 1/2 - z$; (*ii*) $1 - x, 1/2 + y, 1/2 - z$; (*iii*) $1 - x, 2 - y, -z$

interplane separation is one of the shortest found for interacting five-membered heteroaromatic systems.

The infinite quasi two-dimensional layers are linked by two infinite chains of CH···N interactions of tetrazole ring nitrogen atoms and H atom of the methyl group of another molecule, both propagating along (a) crystal axis. First chain is formed by $N4\cdots H2E^{iv}$ and $H2E\cdots N4^{v}$ interactions which are 2.47 Å long (0.28 Å less than vdW sum), second—by contacts $N8\cdots H4A^{v}$ and $H4A\cdots N4^{iv}$—which are 2.54 Å long (0.21 Å less than vdW sum; symmetry codes: (iv) $1 - x, y, z$; (v) $1 + x, y, z$).

To summarize, we showed that the weakly polar aprotic solvent ($CHCl_3$) favors formation of the stable molecular complex of thione (1) with iodine. The dipolar amphiprotic solvent ($C_2H_5OH$) forms the $n$–$\sigma^*$ complex with iodine molecule characterized by a substantial charge transfer and initiates the formation of oxidation disulfide product (2). These facts were confirmed by the UV/vis-spectrophotometric and X-ray diffraction data. In the crystal state unusual intermolecular interactions are observed.

## Experimental

1-Methyltetrazoline-5-thione (1) (98%, Aldrich) was used without additional purification. 5,5′-Dithiobis(1-methyl-1*H*-tetrazole) (2) was synthesized by mixing ethanol solutions (15 mL) of compound (1) (1 mmol, 0.1162 g) and iodine (2 mmol, 0.5076 g). The solvents were purified according to known procedures [22].

MS spectra of 2 were recorded in positive and negative electrospray mode with a Thermo Finnigan Surveoyor MSQ spectrometer (energy of ionization about 1–3 eV).

ESI(+)-MS $m/z$ ($I_r$, %): 230.9 $[M + H]^+$ (100); 174.9 $[M + H\text{-}2N_2]^+$ (17.9); 147.9 $[M + 2H\text{-}3N_2]^{+\bullet}$ (15.5); 118.9 $[M + H\text{-}4N_2]^+$ (20.2).

ESI(−)-MS $m/z$ ($I_r$,%): 115.1 $[M/2]^{-\bullet}$ (100).

The electronic absorption spectra of chloroform solutions containing thione (1) and molecular iodine in different ratios were registered on a Cary 100 UV–visible spectrophotometer in quartz cells with a 1.0 cm in the 250–800 nm region. Chloroform solutions of thione ($2.0 \times 10^{-3}$ mol/L) and iodine ($2.0 \times 10^{-3}$ mol/L) were used as starting solutions. Equilibrium constant measurements were performed at 22 ± 0.5 °C.

The crystals were obtained by mixing ethanol solutions of thione (1) and molecular iodine in a molar ratio of 2:3 followed by slow evaporation of the solvent in air. The resulting light brown oil was recrystallized from ethanol with replacement of solvent to obtain needle-like beige crystals.

Crystal data are shown in Table 2. The crystal structure was solved by direct methods followed by calculations of Fourier maps with the use of the SHELXS-97 [23] program package. C-bound H atoms were positioned geometrically (C–H 0.96 Å) and were refined as riding on their parent atoms, with $U_{iso}(H) = 1.5\ U_{eq}$(parent atom). The experimental data had been corrected for absorption effects with a sadabs procedure [24] with $T_{min}/T_{max} = 0.847/0.893$. PLATON [25] and Mercury v. 2.3 software [26] were used to prepare material for publication.

CCDC-783408 contains the supplementary crystallographic data for this paper. These data can be obtained free

**Table 2** Crystal data

| | |
|---|---|
| $C_4H_6N_8S_2$ | $V = 898.97(13)$ Å$^3$ |
| $M_r = 230.29$ | $Z = 4$ |
| Monoclinic, $P2_1/c$ | Mo $K\alpha$ |
| $a = 6.2740(5)$ Å | $\mu = 0.57\ \text{mm}^{-1}$ |
| $b = 8.0175(7)$ Å | $T = 100(2)$ K |
| $c = 18.1878(14)$ Å | $0.45 \times 0.20 \times 0.15$ mm |
| Bruker APEX II CCD area detector' diffractometer | 2386 independent reflections |
| Absorption correction: multi-scan SADABS (Bruker, 2005) | 1952 reflections with $I > 2\sigma(I)$ |
| $T_{min} = 0.873$, $T_{max} = 0.919$ | $R_{int} = 0.043$ |
| 10415 measured reflections | |
| $R[F^2 > 2\sigma(F^2)] = 0.030$ | 129 parameters |
| $wR(F^2) = 0.073$ | H atom parameters constrained |
| $S = 1.01$ | $\Delta\rho_{max} = 0.33$ e Å$^{-3}$ |
| 2386 reflections | $\Delta\rho_{min} = -0.29$ e Å$^{-3}$ |

of charge at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033; email: deposit@ccdc.cam.ac.uk).

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