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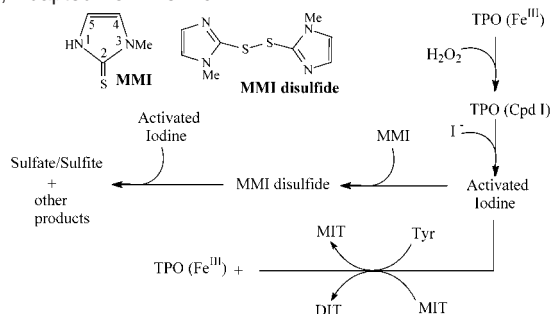
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Anti-Thyroid Drug Methimazole: X-ray Characterization of Two Novel Ionic Disulfides Obtained from Its Chemical Oxidation by I₂M. Carla Aragoni,[†] Massimiliano Arca,[†] Francesco Demartin,[‡] Francesco A. Devillanova,[†] Alessandra Garau,[†] Francesco Isaia,^{*,†} Vito Lippolis,[†] and Gaetano Verani[†]*Dipartimento di Chimica Inorganica ed Analitica, S.S. 554 bivio per Sestu, I-09042 Monserrato (CA), Italy, and Dipartimento di Chimica Strutturale e Stereochimica Inorganica, I-20133 Milano, Italy*

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Owing to its effective antithyroid activity, methimazole (1-methyl-imidazole-2-thione, **MMI**) has been studied for many years.¹ The mechanism of action of this drug has been investigated by many researchers.¹ Taurog et al.^{1c} demonstrated that **MMI** is a potent inhibitor of the thyroperoxidase (TPO)-catalyzed iodination of tyrosine or tyrosyl residues of thyroglobulin, and that the drug itself is readily oxidized by the TPO system to form **MMI disulfide** (bis[1-methylimidazole(2)]disulfide), which then evolves toward other metabolites. The identification of the oxidation products of anti-thyroid agents reacted with I₂ is therefore crucial in understanding the mechanism of action in vivo of these drugs. (Scheme 1)

Scheme 1. Inhibition Mechanism of TPO-Catalyzed Iodination by **MMI**, Adapted from Ref 1c



To the best of our knowledge no **MMI**-I₂ adducts have been structurally characterized to date and only the structures of two different crystalline modifications of the 1,3-dimethylimidazole-2-thione-I₂ CT complex are reported in the literature.²

The equilibrium reaction between **MMI** and I₂ in CH₂Cl₂ has recently been reinvestigated by C. Laurence et al.,³ who have also calculated that the resulting 1:1 CT complex of the thione tautomer of **MMI** is favored by 13.2 kJ mol⁻¹ compared to that of the thiol tautomer. The formation constant at 25 °C for the **MMI**-I₂ complex in CH₂Cl₂ is reported to be 84 700 or 92 400 M⁻¹ when the influence of **MMI** self-association is considered.³ Both values locate **MMI** among the strongest S-donors toward I₂ and this explains why **MMI** acts as an efficient "diiodine sponge" in the thyroid gland.

As previously reported,^{2,3} treatment of **MMI** with 1 equiv of I₂ in CH₂Cl₂ and subsequent concentration of the solution yields a dark red oil (**A**) that fails to crystallize on long standing. The FT-Raman spectrum of **A** in the ν(I-I) region shows intense peaks at 175, 141, and 110 cm⁻¹. We monitored the formation of these peaks by recording a series of Raman spectra on solutions with a 1:1

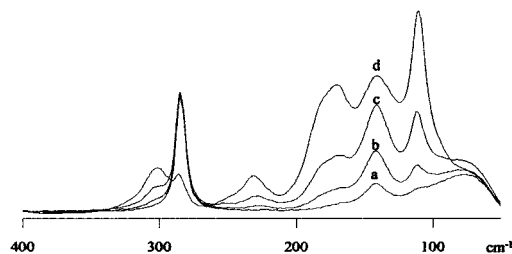


Figure 1. FT-Raman spectra for reaction mixtures of **MMI** with I₂ (1:1 molar ratio) in CH₂Cl₂: 0.06 (a), 0.12 (b), 0.24 (c), and 0.96 M (d).

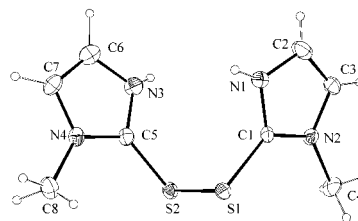


Figure 2. View of the dication **2**. C-S 1.748(5), 1.735(5) Å; S-C-N 1.347(6)–1.331(6) Å.

molar ratio of **MMI** and I₂ at different concentrations (from 6.0 × 10⁻² to 9.6 × 10⁻¹ M) obtained by evaporation of the solvent (Figure 1). From the single Raman peak at 141 cm⁻¹, due to the 1:1 **MMI**-I₂ complex, two new peaks at 175 and 110 cm⁻¹ form as the solution concentrates. They indicate the formation of weakly perturbed I₂ molecules and I₃⁻ species, respectively.⁴

The reaction of **MMI** with I₂ in a 1:2 molar ratio in CH₂Cl₂ yielded a deep red-brown solution, from which jet-black crystals were obtained in good yield on standing at ca. -15 °C. The X-ray crystal structure⁵ shows formation of compound [(C₄H₆N₂S)₂]₂I₈ (**1**), which consists of the dication **2** (Figure 2) containing a disulfide bond [S-S 2.085(2) Å] and I₈²⁻ as counterion. The Z-shaped I₈²⁻ anions are formed by the interaction of two triiodides with a diiodine molecule [2(I₃⁻)·I₂]. They display head-to-tail contacts of 3.783-(1) Å, giving rise to infinite zigzag chains running along [011] (Supporting Information). The reaction was also carried out in H₂O. The insoluble black powder obtained was recrystallized from CH₂Cl₂ at ca. -20 °C to give black crystals of the salt [2(C₄H₅N₂S-SN₂C₄H₆)]₂I₃I₅ (**3**) as identified by X-ray diffraction analysis. Compound **3** contains two independent disulfide monocations [S-S 2.085(3), 2.094(3) Å] located around two different 2-fold axes at 1/2, y, 3/4 and 0, y, 1/4, respectively, which interact with their symmetry equivalents through N-H...N [(N...H 1.82(1), 1.85(1) Å, >N-H-N 175(1)°] hydrogen bonds to form dimeric units (**4**)

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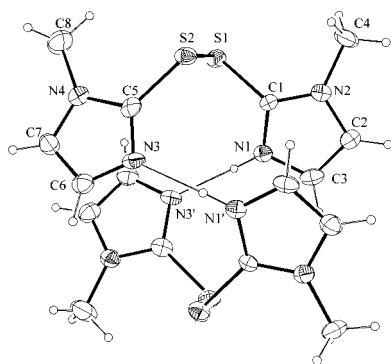


Figure 3. View of one of the independent monocations **4**. C–S 1.700(11)–1.744(9) Å; S–N 1.308(11)–1.375(12) Å.

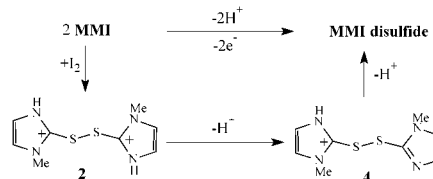
(Figure 3) with overall charge 2+. The charge balance in the crystal is achieved by the presence of I_3^- and I_5^- anions in a general position.

Open-chain stable dications and monocations having an S–S bond are not very common in the literature and to the best of our knowledge the other structurally characterized compounds of this type are $\{[(NH_2)_2CS]_2^{2+} 2X^- \cdot H_2O\}$ ($X = Br, I$), both of which were obtained by reacting iodine or bromine with thiourea in water.⁷ The formation of these species was first explained by Husebye⁸ as the result of the attack of a chalcogen donor (D) on the $[DI]^+$ species. The key role played by the $[DI]^+$ cation in the formation of the numerous products that can be obtained from the initially formed $D \cdot I_2$ CT adducts has recently been confirmed by us on the basis of DFT calculations.⁹ We have also shown that among all the considered thioketonic compounds, imidazoline-2-thione derivatives have the highest tendency to form dicationic species and the formation of **2** and **4** confirms this hypothesis.⁹

The mechanism by which **MMI** interacts with the active iodine (I^+ , I^\bullet , or $TPO-I^+$) (Scheme 1) in the thyroid gland is not fully understood and the identification of the iodinating species is still under investigation. On this matter Po et al.¹⁰ studied the electrochemistry of the **MMI/MMI disulfide** system in HCl/ethanenitrile solution at 26.0 °C. An irreversible electron-transfer reaction was observed [$E_{pa} = 0.51$ V, $E_{pc} = -0.015$ V, vs Ag/AgCl] in which 2 mol of **MMI** are oxidized to give the **MMI disulfide** species presumably via dimerization of $[MMI]^\bullet$ free radicals. However, the chemical way through which **MMI** is transformed into **MMI disulfide** in vivo is unknown, and the ionic species **2** and **4** could indeed represent two possible intermediates in this process through which the ionic species **2**, first formed from the reaction of **MMI** with I_2 , undergoes two consecutive deprotonations to give **MMI disulfide** via **4** (Scheme 2).

In our studies, the choice of the solvent and its polarity has been of paramount importance in the stabilization of **2** and **4**. In fact, the formation of **2** is easily accomplished in CH_2Cl_2 but its subsequent imido proton dissociation is favored in water. Moreover, the deprotonation of **4** to **MMI disulfide** is not observed in water because of the low solubility of its polyiodide salt **3** in this solvent. However, the two consecutive deprotonations of **2** to form **4** and then **MMI disulfide** are easily achieved in CH_3CN , where **1**, **3**,

Scheme 2. Intermediates **2** and **4** in the Oxidation of **MMI**



and **MMI disulfide** are soluble. This process was monitored by ^{13}C NMR. When dissolved in CH_2Cl_2 or CH_3CN (δ 150.1 and 138.1 respectively), compound **1** shows a very different chemical shift for carbon C(2). Assignment of the signal at δ 138.1 to **MMI disulfide** is straightforward and supported by comparison with the spectrum of the pure compound recorded in CH_3CN , (δ 140.1). In support of this, the molar conductivity of **1** increases from 4.8 to 148 $mS\ cm^2\ mol^{-1}$ on passing from CH_2Cl_2 to CH_3CN due to the release of protons.

In conclusion, the interaction of the drug methimazole with I_2 in solvents having different polarity gives two new stable compounds containing the dication disulfide **2** and a monocation disulfide arranged in dimers **4**, respectively. These species can also be seen as two different protonated forms of the final disulfide product and therefore might be effective intermediates in the reaction of **MMI** with an active iodine species depending on the pH and I_2 concentration conditions in the thyroid gland.

Supporting Information Available: Experimental procedures and FT-Raman spectra (PDF) and X-ray data (CIF) for **1** and **3**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (5) Crystal data for (**1**): $C_8H_{12}I_8N_4S_2$, M_r 1243.57, triclinic, space group $P\bar{1}$ (no. 2), $a = 7.9848(7)$ Å, $b = 11.8610(11)$ Å, $c = 14.1180(13)$ Å, $\alpha = 80.29(2)^\circ$, $\beta = 85.29(2)^\circ$, $\gamma = 87.07(2)^\circ$, $V = 1312.5(2)$ Å³, $Z = 2$, $D_{calc} = 3.147$ g cm⁻³, $\mu(Mo\ K\alpha) = 96.12$ cm⁻¹, $T = 20$ °C, $R = 0.026$, $wR = 0.045$, $GOF = 0.859$. ^{13}C NMR (CH_2Cl_2 25 °C): δ 150.1 C(2), 123.3 C(4), 117.8 C(5), 35.9 NCH₃. FT-Raman: 102 (sh), 111 (I_3^- , ν_s), 140, 149 (sh) (I_3^- , ν_{as}), 174 cm⁻¹ (I_2 , $\nu(I-I)$).
- (6) Crystal data for (**2**): $C_{16}H_{22}I_8N_8S_4$, M_r 1469.88, monoclinic, space group $P2_1/c$ (no. 13), $a = 14.278(2)$ Å, $b = 13.516(2)$ Å, $c = 20.452(2)$ Å, $\beta = 106.06(1)^\circ$, $V = 3792.8(9)$ Å³, $Z = 4$, $D_{calc} = 2.574$ g cm⁻³, $\mu(Mo\ K\alpha) = 67.84$ cm⁻¹, $T = 20$ °C, $R = 0.046$, $wR = 0.115$, $GOF = 1.190$. ^{13}C NMR ($CH_2Cl_2/DMSO$, 25 °C): δ 147.5 C(2), 123.0 C(4), 118.8 C(5), 35.6 NCH₃. FT-Raman: 166 (I_2 , $\nu(I-I)$), 153 (I_2 , $\nu(I-I)$), 113 cm⁻¹ (I_3^- , ν_s).
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