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Anti-Thyroid Drug Methimazole: X-ray Characterization of Two Novel Ionic Disulfides Obtained from Its Chemical Oxidation by I_2

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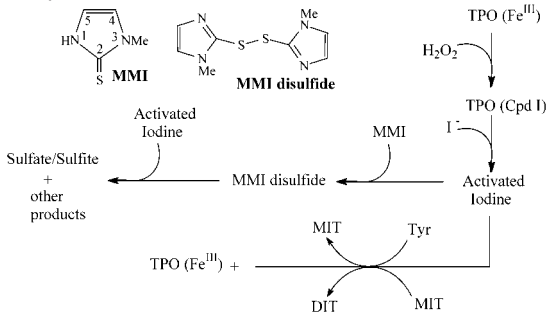
Owing to its effective antithyroid activity, methimazole (1-methyl-imidazole-2-thione, **MMI**) has been studied for many years.[1] The mechanism of action of this drug has been investigated by many researchers.[1] Taurog et al.[1c] demonstrated that **MMI** is a potent inhibitor of the thyroperoxidase (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 I_2 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**-I_2 adducts have been structurally characterized to date and only the structures of two different crystalline modifications of the 1,3-dimethylimidazole-2-thione-I_2 CT complex are reported in the literature.[2]

The equilibrium reaction between **MMI** and I_2 in CH_2Cl_2 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**-I_2 complex in CH_2Cl_2 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 I_2 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 I_2 in CH_2Cl_2 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 molar ratio of **MMI** and I_2 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**−I_2 complex, two new peaks at 175 and 110 cm^{-1} form as the solution concentrates. They indicate the formation of weakly perturbed I_2 molecules and I_3^- species, respectively.[4]

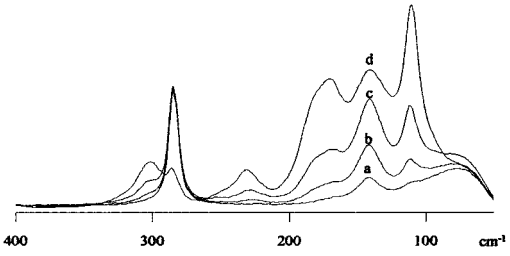


Figure 1. FT-Raman spectra for reaction mixtures of **MMI** with I_2 (1:1 molar ratio) in CH_2Cl_2: 0.06 (a), 0.12 (b), 0.24 (c), and 0.96 M (d).

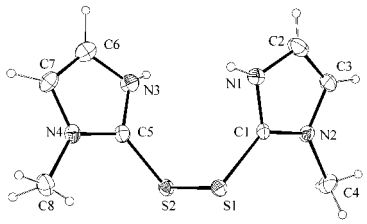


Figure 2. View of the dication **2**. C−S 1.748(5), 1.735(5) Å; SC−N 1.347(6)−1.331(6) Å.

The reaction of **MMI** with I_2 in a 1:2 molar ratio in CH_2Cl_2 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 structure[5] shows formation of compound $[(C_4H_6N_2S\text{-})_2]I_8$ (**1**), which consists of the dication **2** (Figure 2) containing a disulfide bond [S−S 2.085(2) Å] and I_8^{2-} as counterion. The Z-shaped I_8^{2-} anions are formed by the interaction of two triiodides with a diiodine molecule $[2(I_3^-)\cdot I_2]$. 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 H_2O. The insoluble black powder obtained was recrystallized from CH_2Cl_2 at ca. −20 °C to give black crystals of the salt $[2(C_4H_5N_2S{-}SN_2C_4H_6)]I_3I_5$ (**3**) as identified by X-ray diffraction analysis. Compound[6] **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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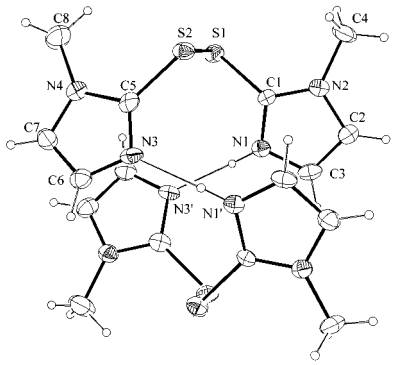


Figure 3. View of one of the independent monocations **4**. C−S 1.700(11)−1.744(9) Å; SC−N 1.308(11)−1.375(12) Å.

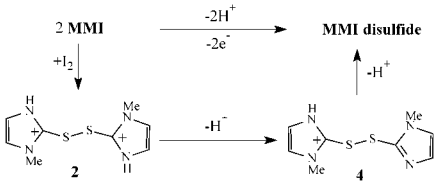
(Figure 3) with overall charge 2+. The charge balance in the crystal is achieved by the presence of I_3^- and I_5^- anions in a general position.

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 Husebye[8] 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**, 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.

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



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, $\alpha = 80.29(2)°$, $\beta = 85.29(2)°$, $\gamma = 87.07(2)°$, $V = 1312.5(2)$ Å^3, $Z = 2$, $D_{calc} = 3.147$ g cm^{-3}, μ(Mo Kα) = 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 NCH_3. FT-Raman: 102 (sh), 111 (I_3^-, ν_s), 140, 149(sh) (I_3^-, ν_{as}), 174 cm^{-1} (I_2, ν(I−I)).

(6) Crystal data for (**2**): $C_{16}H_{22}I_8N_8S_4$, M_r 1469.88, monoclinic, space group $P2/c$ (no. 13), $a = 14.278(2)$ Å, $b = 13.516(2)$ Å, $c = 20.452(2)$ Å, $\beta = 106.06(1)°$, V= 3792.8(9) Å^3, $Z = 4$, $D_{calc} = 2.574$ g cm^{-3}, μ(Mo Kα) = 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 NCH_3. FT-Raman: 166 (I_2, ν(I−I)), 153 (I_2, ν(I−I)), 113 cm^{-1}(I_3^-, ν_s).

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