Brief Articles

Interaction of Methimazole with I_2: X-ray Crystal Structure of the Charge Transfer Complex Methimazole−I_2. Implications for the Mechanism of Action of Methimazole-Based Antithyroid Drugs

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Received February 21, 2008

The antithyroid drug methimazole (MMI) reacts with molecular iodine to form, in a multistep process, 1-methylimidazole as final product. In this process, the charge transfer complex MMI−I_2 and the ionic disulfide $[(C_4H_6N_2S–)_2]^{2+}$ (**1**, dication MMI disulfide) have been isolated and their X-ray crystal structures solved. Dication MMI disulfide perchlorate acts effectively both in reducing I_2 to I^- ions and in showing antioxidant properties in inactivating the enzyme lactoperoxidase compound **I**.

Introduction

Hyperthyroidism is a pathological condition resulting from the effects of overproduction of thyroid hormones, which is effectively cured with drugs containing the thiocarbamide group like methimazole (1-methyl-3*H*-imidazole-2-thione, MMI[a]) or 6-propyl-2-thiouracile (PTU) (Figure 1).[1] The mechanism through which MMI exerts its antithyroidal activity is currently attracting great interest in developing new drugs with fewer adverse side effects.[2] The primary effect of MMI is to inhibit the synthesis of thyroid hormone precursors monoiodotyrosine (MIT) and diiodotyrosine (DIT) by competing with the tyrosine residues of the enzyme thyroperoxidase (TPO) for an oxidized form of iodine (Scheme 1). In the thyroid gland, the mechanism by which the drug MMI interacts with the iodinating species (TPO-Iox) or the I_2 molecule, the latter generated from the reaction of I^- anion with TPO-Iox, is not still well understood, and the chemical pathway through which MMI is oxidized in vivo to bis-[1-methylimidazole(2)] disulfide (MMI disulfide) is still under investigation.[2] Recently, we reported on the reaction of MMI with molecular I_2 that led to the identification of two novel oxidation products of MMI that we postulated to be of interest in elucidating the mechanism of action of the antithyroid drug MMI.[3] Pursuing our interest in this particular topic, we report here on the isolation of the 1:1 adduct between MMI and I_2, along with its crystal structure, on the reactions of this adduct with MMI and I_2 that lead to the formation of the ionic disulfide $[(C_4H_6N_2S−)_2]^{2+}$ (**1**, dication MMI disulfide) and on the ability of **1** in reducing I_2 to I^- ions and in inactivating the enzyme lactoperoxidase compound **I** (LPO compound **I**).

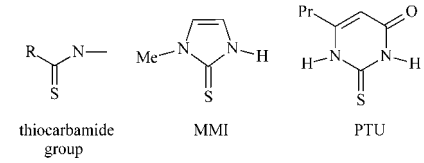
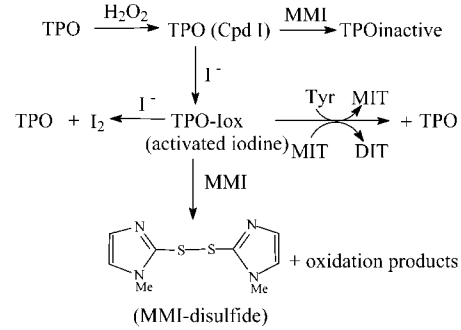


Figure 1. Antithyroidal drugs containing the thiocarbamide group: methimazole (MMI) and 6-propyl-2-thiouracile (PTU).

Scheme 1. Schematic Representation of the Synthesis of Prohormones MIT and DIT and Inhibition Mechanism of TPO-Catalyzed Iodination by MMI[a]



[a] Cpd: Compound. Adapted from refs 1b and 2a.

Results and Discussion

As previously reported, in nonpolar solvents MMI and I_2 form a 1:1 CT complex [K_f(25.0 °C) of 106 905 L mol^{-1} in CH_2Cl_2 and 27 096 L mol^{-1} in CCl_4] with MMI binding in the thioketo tautomeric form to I_2.[4,5] Conversely, in aqueous solutions, MMI

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[a] Abbreviations: ABTS, 2,2′-azinobis(3-ethylbenzthiazoline-6-sulfonic acid); CT, charge transfer; DIT, diiodothyrosine; DMSO, dimethyl sulfoxide; IC_{50}, half-maximal inhibitory concentration; LPO, enzyme lactoperoxidase; LPO compound **I**, enzyme lactoperoxidase compound **I**; MAS, magic angle spinning; MIT, monoiodothyrosine; MMI, 1-methyl-3*H*-imidazole-2-thione, methimazole; MMI disulfide, bis-[1-methylimidazole(2)] disulfide; PTU, 6-proyl-2-thiouracile; TPO, enzyme thyroperoxidase; TPO compound **I**, enzyme thyroperoxidase compound **I**.

10.1021/jm8001857 CCC: $40.75
Published on Web 06/05/2008

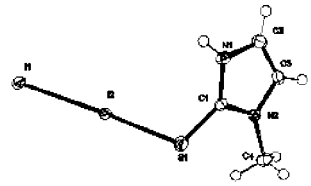


Figure 2. Molecular structure of the adduct MMI−I_2. Selected bond distances (Å) and angles (deg): I1−I2 2.9912(2), I2−S1 2.593(1), S1−C1 1.725(3), I1−I2−S1 175.01(2), I1−S1−C1 101.66(9).

is readily oxidized by I_2 to MMI disulfide involving a sulfenyl iodide (−SI) as an intermediate.[2a] We have gained other useful information about the nature of the adduct MMI−I_2 by isolating and solving, as part of this contribution, its X-ray crystal structure, which, because of the difficulties faced by us and other authors in obtaining a solid sample, had not been reported in the literature so far.[4,5] In fact, oils were always obtained by evaporation of solution of MMI and I_2 in apolar solvents. As far as the nature of these oils is concerned, in a previous study[3] we demonstrated the presence of them in the adduct MMI−I_2 and of polyiodides species, which presumably hampered the crystallization of the adduct. The addition of cadmium in powder to an MMI and I_2 solution in CH_2Cl_2 (see Experimental Section), initially to study the oxidation properties of MMI−I_2 toward zerovalent metals,[6a] made possible the obtaining of a crystalline sample of MMI−I_2, presumably by affecting the amount of polyiodides in solution. The structure of MMI−I_2 (Figure 2) features a linear S−I−I arrangement; the observed *d*(I−I) bond distance of 2.9912(2) Å is markedly elongated with respect to the I−I bond distance in crystalline iodine (2.715 Å, at −163.1 °C).[6b] As a consequence, the C−S bond (1.725(3) Å) is also elongated (average of 1.684 Å in MMI),[6c] indicating a reduced C═S double-bond character. Moreover, although iodine binds to sulfur on the less sterically crowded side, no NH···I intramolecular hydrogen bonding, within the sum of the van der Waals radii (3.18 Å), is detectable.[4] These data clearly indicate that the adduct could be better described as an [MMI−I]$^+$···I^- ion pair.[6a] Conversely, in the case of the molecular structure of the CT complex PTU−I_2 the *d*(I−I) and *d*(S−I) bond distances (2.8264(4) and 2.7805(10) Å, respectively) show that PTU forms a medium-weak CT complex with I_2.[6d] The different nature of the S−I−I moiety in compounds MMI−I_2 and PTU−I_2 supports the proposal of Nagasaka et al. on the difference in the inhibition mechanism of these drugs.[7] Recently, we have reported on the reaction of MMI−I_2 with an equimolar amount of I_2 in CH_2Cl_2 that leads to the formation of compound [$(C_4H_6N_2S-)_2$]I_8 (**1**I_8), which consists of the dication MMI disulfide (**1**) containing a disulfide bond and I_8^{2-} as counterion.[3,8]

Interestingly, dication **1** might represent a possible intermediate in the oxidation process of MMI by an active iodinating species because MMI disulfide has been identified as transient species evolving in the formation of sulfate/sulfite ions as found by Taurog et al. in an in vitro incubation system.[2a] In this context, we have extended our studies to investigate the reactivity of dication **1** toward I_2 in a polar solvent and to determine its inhibition ability for the LPO/H_2O_2 system since LPO has been shown to have similar properties as TPO.[2b] Dication **1** was employed as a perchlorate salt obtained from the reaction of **1**I_8 with MMI and ^{n}Bu$_4$N(ClO_4), since a direct metathesis reaction of **1**I_8 with a perchlorate salt was not successful. The crystal structure of **1**(ClO_4)$_2$ (Figure 3) consists of discrete dications containing two MMI moieties joined by a disulfide bond and two NH hydrogen-bonded perchlorate anions

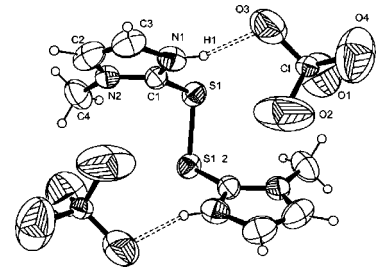


Figure 3. Structure of [$(C_4H_6N_2S-)_2$](ClO_4)$_2$, **1**(ClO_4)$_2$. Selected bond distances (Å) and angles (deg): C1−N1 1.322(10), C1−N2 1.323(8), C3−N1 1.375(12), C2−C3 1.330(15), C2−N2 1.333(11), C1−S1 1.717(8), S1−S1_S2 2.065(5), N1−C1−S1 124.0(6), N2−C1−S1 128.2(6).

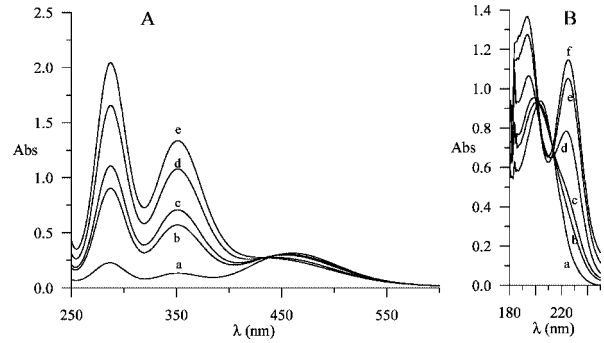


Figure 4. Absorption spectra for the reaction of I_2 with **1**(ClO_4)$_2$ in water: (A, left) (a) [I_2] = 4.4 × 10^{-4} M. [I_2]/[**1**(ClO_4)$_2$]: (b) 40, (c) 30, (d) 20, and (e) 10. (B, right) (a) [I_2] = 4.4 × 10^{-5} M. [I_2]/[**1**(ClO_4)$_2$]: (b) 15, (c) 10, (d) 5, (e) 3, and (f) 2. All measurements were carried out at 25.0 °C.

as counter-ions (see also Supporting Information). The reaction of **1** with I_2 in water was studied spectrophotometrically in the UV−vis region to verify the ability of **1** to reduce I_2 to I^- ion. The progressive addition of **1**(ClO_4)$_2$ to a solution of I_2[9] causes an absorbance increase in the bands at 287 and 351 nm and a concomitant decrease in the intensity of the band at 460 nm (Figure 4A), indicating the progressive formation of the I_3^- anion at the expense of the free I_2. In particular, spectra analyses revealed that for the range of I_2/**1**(ClO_4)$_2$ reaction molar ratios used (40−10) the reaction of dication **1** with I_2 affords the overall formation of two I_3^- anions according to reactions 1 and 2.[9,10]

$$\mathbf{1}(ClO_4)_2 + I_2 \rightarrow 2I^- + \text{1-methylimidazole} + \text{oxidation products} \quad (1)$$

$$2I^- + 2I_2 = 2I_3^- \quad (2)$$

When the reaction between **1**(ClO_4)$_2$ and I_2 is carried out at lower I_2 to **1** molar ratios (15−2), the formation of a new band at 226 nm due to I^- is observed (Figure 4B).[9a] In fact, at these reagent molar ratios the formation of the I_3^- species cannot be experimentally observed as a consequence of its very low concentration.[9] Further insights into reaction 1 have been obtained by recording the ^{13}C NMR spectrum of a 1:1 solution of **1**(ClO_4)$_2$ and I_2 in water. The resonances at δ 34.3, 121.5, 126.0, and 137.0 ppm are, according to the studies of Taurog[2a] and Doerge,[11] attributable to the formation of 1-methylimidazole (^{13}C NMR (D_2O): δ 33.1, 121.2, 128.5, and 138.4 ppm), whereas two other small resonances at δ 29.3 and 78.2 ppm have not been attributed.

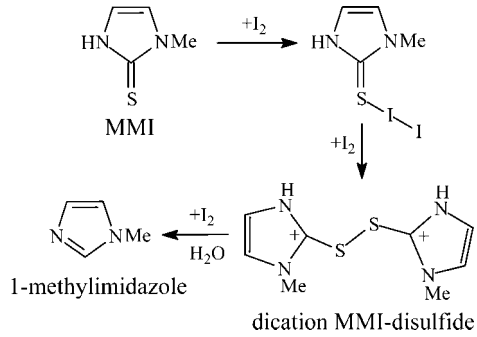
The unexpected reduction properties of **1**(ClO_4)$_2$ toward I_2 has led us to consider this compound to be able to inactivate

Table 1. Half-Maximal Inhibitory Concentration (IC_{50})[a] Values for Inhibition by **1**$(ClO_4)_2$ and MMI of LPO-Catalyzed Oxidation of ABTS

compd	IC_{50} (μM)	reference
1$(ClO_4)_2$	1.4	this work
MMI	5.6	this work
MMI	6.6	13

[a] pH 7.0, $T = 25.0$ °C.

Scheme 2. Compounds Obtained from the Reaction of MMI with I_2



the enzyme TPO. In fact, as reported in many studies,[2] the inhibitory action of MMI in thyroid hormone biosynthesis is also the consequence of the reaction of the drug with TPO compound **I** to form an inactive form of the enzyme (Scheme 1). In this view, the inhibitory activity of **1**$(ClO_4)_2$ and MMI was evaluated via their inhibition of the LPO-catalyzed oxidation of 2,2′-azinobis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS). A half-maximal inhibitory concentration (IC_{50}) value of 1.4 and 5.6 μM (Table 1) was determined for **1**$(ClO_4)_2$ and MMI, respectively. These values show that **1**$(ClO_4)_2$ has a nearly 4-fold higher inhibitory activity than that of MMI toward LPO compound **I**. Doerge[12] reported that LPO catalyzed S-oxygenation of thiocarbamides produces a reactive intermediate (MMI−sulfenic acid) that binds covalently to the active-site heme; it seems likely, therefore, that the formation of such intermediate might more easily be achieved from **1** than MMI.

Conclusion

In summary, the antithyroid drug MMI reacts with I_2 to form the stable-to-air MMI−I_2 solid adduct when a 1:1 reagents molar ratio is employed. According to the X-ray crystal structure, MMI−I_2 can be described as a CT complex featuring an almost linear S−I···I arrangement and an elongated I−I bond distance, which supports the nature of MMI as a strong donor toward iodine. When the reaction between MMI and I_2 is carried out using a 1:2 molar ratio or when MMI−I_2 is added to an equimolar amount of I_2, the ionic disulfide species dication **1** is separated. We have shown that in water dication **1** acts effectively in reducing I_2 to I^- ions (reactions 1 and 2) and has shown antioxidant properties in inactivating the enzyme LPO compound **I**. These results indicate that (i) the overall oxidation of MMI to 1-methylimidazole by iodine is a multistep process, as shown in Scheme 2, (ii) the nature of the CT complex antithyroid drug−I_2 (strong in MMI−I_2, weak in PTU−I_2) might be at the basis of the reactivity of the drugs and of their different mechanism of action, (iii) the reactivity of dication MMI disulfide toward I_2 and its high inhibitory activity toward LPO support an active role of this species in the mechanism of action of MMI.

Experimental Section

Materials and Methods. All reagents for the syntheses and 2,2′-azinobis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) were purchased from Sigma-Aldrich (St. Louis, MO) and used without further purification. Lyophilized powder lactoperoxidase from bovine milk (LPO, RZ value $A_{412}/A_{280} = 0.9$) was from Sigma. The enzyme concentration was determined spectrophotometrically using an ε_{412} of 1.12×10^5 M^{-1} cm^{-1}.[14] Hydrogen peroxide was from Merck (Darmstadt, Germany), and $\varepsilon_{240} = 43.6$ M^{-1} cm^{-1} was used to determine its concentration.[14] UV−vis absorption spectra were measured on a Nicolet Evolution 300 spectrophotometer. $^{13}C\{^1H\}$ NMR spectra were recorded on a Varian INOVA 400 MHz spectrometer operating at 100.5 MHz at 25 °C and referenced to $Si(CH_3)_4$, or adamantane in the case of MAS ^{13}C NMR spectra. Data from all LPO activity assays were obtained with an Ultrospec 2000 spectrophotometer (Biochrom Ltd., Cambridge, England) using cells with a 1 cm path length. Elemental analyses were obtained using a Fisons Instruments 1108 CHNS elemental analyzer.

Synthesis of the CT Complex MMI−I_2. To a solution of 1-methyl-3*H*-imidazole-2-thione (MMI) (500 mg, 44.1 mmol) in CH_2Cl_2 (50 mL) was added a solution of I_2 (1119 mg, 44.1 mmol) in CH_2Cl_2 (50 mL) and cadmium in powder (247.8 mg, 22.05 mmol). The red-brown solution was stirred at room temperature for 24 h. In the course of the reaction a yellow powder separated from the solution and was discarded. Then the solution was slowly concentrated to produce dark-red crystals, which were washed with *n*-hexane. Yield: 800 mg (49%). Anal. ($C_4H_6I_2N_2S$) C. H: calcd, 1.64; found, 1.40. N: calcd, 7.61; found, 7.70. S: calcd, 8.71; found, 8.81.

Synthesis of the Dication MMI Disulfide Perchlorate $[(C_4H_6N_2S–)_2][ClO_4]_2$. Caution! Perchlorate containing compounds are potentially explosive. To a solution of dication MMI disulfide octaiodide (**1**I_8),[3] (1000 mg, 0.8 mmol) and 1-methyl-3*H*-imidazole-2-thione (548.0 mg, 2.4 mmol) in CH_2Cl_2 (200 mL) was added $^nBu_4N(ClO_4)$ (815 mg, 2.4 mmol). The mixture was stirred at room temperature for 4 h and then allowed to slowly concentrate in air. Yellow crystals were filtered from the solution and washed with *n*-hexane, then were stored in a desiccator. Yield 154 mg (45%). Anal. ($C_8H_{12}Cl_2N_4O_8S_2$) C, H, N, S. ^{13}C NMR (D_2O) δ: 35.3, 122.8, 127.3, 137.2.

Crystal data for MMI−I_2: $C_4H_6I_2N_2S$, $M_r = 367.97$, monoclinic, space group $P2_1/n$ (No.14), $a = 7.7136(2)$ Å, $b = 9.3302(2)$ Å, $c = 12.5582(2)$ Å, $\beta = 94.439(1)°$, $V = 901.10(3)$ Å^3, $Z = 4$, $D_{calc} = 2.712$ g cm^{-3}, μ(Mo Kα) = 7.138 mm^{-1}, $R = 0.0179$ (1986 reflections), $wR^2 = 0.0401$ (2055 reflections), $T = 120$ K, GOF = 1.219. The 13 084 reflections were measured in the range $5.82° \le 2\theta \le 54.96°$ on a Bruker-Nonius CCD diffractometer equipped with a rotating anode using graphite monochromatized Mo Kα radiation ($\lambda = 0.710\,73$ Å) and employing a 0.20 mm × 0.20 mm × 0.07 mm crystal (2055 unique, $R_{int} = 0.028$).

Crystal data for 1$(ClO_4)_2$: $C_8H_{12}Cl_2N_4O_8S_2$, $M_r = 427.24$, monoclinic, space group $P2/c$ (No.13), $a = 9.4595(19)$ Å, $b = 6.3700(13)$ Å, $c = 13.927(3)$ Å, $\beta = 102.98(3)°$, $V = 817.8(3)$ Å^3, $Z = 2$, $D_{calc} = 1.735$ g cm^{-3}, μ(Mo Kα) = 6.99 cm^{-1}, $R = 0.1119$ (1105 reflections), $wR^2 = 0.3273$ (1588 reflections), $T = 294(2)$ K, GOF = 1.303. The 894 reflections (1588 unique, $R_{int} = 0.030$) were collected in the range $4.42° \le 2\theta \le 52.00°$, employing a 0.21 mm × 0.10 mm × 0.05 mm crystal mounted on a Bruker SMART area-detector diffractometer with graphite monochromatized Mo Kα radiation ($\lambda = 0.710\,73$ Å). Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC-663179 and CCDC-663180 for MMI−I_2 and **1**$(ClO_4)_2$, respectively.

Determination of LPO Activity. LPO activity was determined using ABTS as substrate. Activity measurements were made in 100 mM potassium phosphate buffer, pH 7.0, at 25 °C, using 5 μg of LPO, 200 μM hydrogen peroxide, 90 μM of the reducing substrate ABTS, by following the increase in absorbance at 415 nm resulting from the formation of the ABTS cation radical product ($\varepsilon_{415} = 36$ mM^{-1} cm^{-1}). Enzyme activity after the addition of the inhibitors was expressed as the percentage of that observed in the absence of the inhibitors. The inhibitor MMI and

dication MMI disulfide perchlorate were used in the range 1−7.5 μM (Tables S1 and S2). The activities were expressed as a percentage of remaining activity. The inhibition constant (K_i) was determined from a Dixon plot.[14] The inhibition curves for MMI and **1**$(ClO_4)_2$ are shown in Figure S1.

Acknowledgment. This study was partially supported by PRIN 2006 (Progetti di Ricerca di Interesse Nazionale).

Supporting Information Available: Elemental analysis results, melting point, and X-ray crystallographic structure determination details of compounds MMI–I_2 and **1**$(ClO_4)_2$; comments on the structure of **1**$(ClO_4)_2$; determination of LPO activity; inhibition curves for MMI and **1**$(ClO_4)_2$. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The compound **1**I_8 was also separated from the reaction in CH_2Cl_2 of MMI−I_2 with an equimolar amount of MMI.

(9) (a) The UV−vis spectrum of iodine in water (Figure 4A, curve a) shows three bands at 287 (ε = 40 000 M^{-1} cm^{-1}), 351 (ε = 26 400), and 462 (ε = 746) nm, the last of which is related to the free iodine into the solution whereas the other two bands are related to the presence of the I_3^- anion in equilibrium with I_2. (b) Awtrey, A. D.; Connick, R. E. The absorption spectra of I_2, I_3^-, I^-, IO_3^-, $S_4O_6^{-2}$ and $S_2O_3^{-2}$. Heat of the reaction $I_3^- = I_2 + I^-$. *J. Am. Chem. Soc.* **1951**, *73*, 1842–1843. (c) McIndoe, J. S.; Tuck, D. G. Studies of polyhalide ions in aqueous and non-aqueous solution by electrospray mass spectrometry. *Dalton Trans.* **2003**, 244–248.

(10) I_2(aq) + I^- (aq) = I_3^- (aq); K_c(25 °C) = 723. Daniele, G. Misura della costante di equilibrio del triioduro di potassio con un metodo spettrofotometrico. *Gazz. Chim. Ital.* **1960**, *90*, 1068–1075.

(11) The nature of the oxidation products was not investigated. According to Taurog (ref 2a) and Doerge (U.S. Patent 5,371,102, year 1994), the formation of 1-methylimidazole and sulfate/sulfite anions is expected.

(12) Doerge reported that LPO catalyzed S-oxygenation of thiocarbamides produces a reactive intermediate (MMI−sulfenic acid) that binds covalently to the active-site heme. We think that the formation of such intermediate might more easily be achieved from **1** than MMI. Doerge, D. Mechanism-based inhibition of lactoperoxidase by thiocarbamide goitrogens. Identification of turnover and inactivation pathways. *Biochemistry* **1988**, *27*, 3697–3700.

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JM8001857