Structure and molecular interactions of anti-thyroid drugs. Part 3.[1] Methimazole: a diiodine sponge

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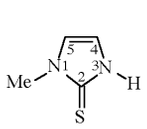
The anti-thyroid drug methimazole functions as a diiodine sponge. Its thione tautomer forms with diiodine a very stable electron donor–acceptor complex (K_f = 36 600 l mol^{-1} in CCl_4), stabilized in a more polar medium (K_f = 92 400 l mol^{-1} in CH_2Cl_2). Two stereoisomeric complexes, one planar on the non-bonding sulfur lone pair and the other perpendicular on the sulfur π electrons, are found in solution to be under steric control. The position of the charge-transfer band of many diiodine complexes of thioamides and thioureas allows the prediction of their geometry. The sulfur–iodine coordination is assisted by intramolecular hydrogen bonding NH ··· I. This iodine amphoterism is explained by the anisotropy of its electrostatic potential surface. Hard and soft acid–base chemistry might explain the two mechanisms of action of anti-thyroid drugs, the inhibition of thyroid peroxidase *via* coordination to the hard heme group and the trapping of oxidized iodides *via* complexation of soft iodinated Lewis acids.

Introduction

Methimazole (MMI; **1**), carbimazole (CBZ; **2**) and propylthiouracil (PTU; **3**) are currently the most commonly employed



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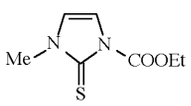

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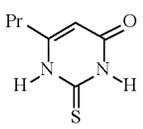

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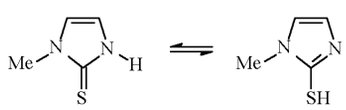
drugs in the treatment of hyperthyroidism.[2] They depress the formation of thyroid hormones 3,5,3′-triiodothyronine (T_3) and 3,5,3′,5′-tetraiodothyronine (T_4) by inhibiting the first step of the hormonal biosynthesis which is the incorporation of oxidized iodides into tyrosine residues in the large thyroid hormone precursor molecule, thyroglobulin.[3]

These molecules possess the thiourea pharmacophore which is known to form very stable electron donor–acceptor complexes with the Lewis acid diiodine.[4–6] A good correlation has been found[7] between the thyroid activity *in vivo* in the rat (assays of T_3 and T_4, and histology of the thyroid gland) and the formation constants of the diiodine complexes of various organic bases. This correlation suggests[7,8] a possible mechanism of action of anti-thyroid agents: by forming stable complexes with diiodine, they could divert it from the second oxidation step of iodides ($I_2 \longrightarrow 2I^+ + 2e^-$) and consequently prevent the electrophilic substitution of I^+ on the tyrosine residues of thyroglobulin.

The properties of the diiodine complexes of anti-thyroid agents **1**–**3** seem therefore an important area of interest. We have already determined the formation constants of the diiodine–CBZ complex in various solvents,[1] and shown that diiodine is coordinated only to sulfur. PTU is difficult to study because of its insolubility in organic solvents, but there are indications[1] that the thiourea pharmacophores of PTU and CBZ might have similar basicities. This paper reports a thermodynamic and structural study of the diiodine–MMI complex. Raby *et al.*[9] and Suszka[10] have already determined by visible or UV spectroscopy the formation constant of this complex. However Raby *et al.*[9] have attributed the high formation constant of MMI–I_2 to a coordination of iodine to the sulfur atom of the thiol tautomer **1b**, whereas Suszka[10] suggests that both thione **1a** and thiol **1b** tautomers of MMI are involved in com-



1a **1b**

plex formation. Neither work takes into account the influence of methimazole self-association on its diiodine basicity. We have therefore reinvestigated the stability and tautomerism of the MMI–I_2 complex by UV spectroscopy. We have also discovered two stereoisomeric complexes: the first is quasi-planar and in the other one diiodine stands quasi-perpendicularly to the MMI plane. IR spectroscopy shows that the iodine atom coordinated to sulfur is hydrogen-bonded by the NH group in the planar complex. Thus iodine acts simultaneously as electron acceptor when attached along its molecular axis, but as electron donor, *i.e.* hydrogen bond acceptor, when vertical to it. This interesting amphoteric behaviour of heavy halogens in chemistry is discussed and possible mechanisms of action of anti-thyroid drugs are examined.

Experimental

Methimazole (99+%), diiodine (99.99+%), thioamides and thioureas were commercial compounds (except the three Δ^2-1,2,4-triazoline-5-thiones of Table 7, generously given by Professor Saidi Idrissi, Rabat) used without further purification. Spectroscopic solvents (CCl_4 and CH_2Cl_2) were dried on 4 Å molecular sieves. All experiments were performed in a dry glove-box. IR spectra were recorded on a Bruker IFS 48 Fourier transform spectrometer by selecting 1 cm^{-1} resolution. Overlapping bands were mathematically decomposed into their

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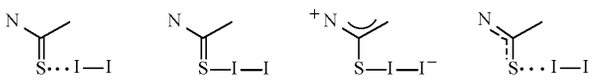
Gausso-Lorentzian components by the Curve Fit™ Bruker programme. The diiodine complexes were studied as CCl_4 and/or CH_2Cl_2 solutions with an infrasil 1 cm cell.

UV spectra were measured with a Cary 219 spectrometer. The CCl_4 and CH_2Cl_2 solutions were thermoregulated at 25 °C in a 1 cm suprasil cell. Equilibrium constants were obtained by the method of Rose and Drago[11] from absorbance measurements on the charge-transfer band of diiodine complexes.

Semi-empirical and *ab initio* quantum-mechanical calculations were performed on a Silicon graphics Indy workstation using the Spartan 4.0.3 suite of software.

Seventeen structures of solid diiodine complexes of thioamides and thioureas were retrieved from the Cambridge Structural Database (CSD). The October 1997 release (175 093 entries) was used. The various 2D chemical diagrams **a**–**d** given



a **b** **c** **d**

in the CSD for these complexes made this search difficult. The non-bonded search capabilities of QUEST3D were used with the condition that the S · · · I distance be less than the appropriate sum of van der Waals radii using $r(S) = 1.80$ and $r(I) = 1.98$ Å.

Results and discussion

Stability and tautomerism

The UV spectrum of methimazole shows an intense band at 265 nm ($\varepsilon = 12\,923$ l mol^{-1} cm^{-1}) in CCl_4, and at 268 nm ($\varepsilon = 16\,289$ l mol^{-1} cm^{-1}) in CH_2Cl_2. The progressive addition of diiodine to a CCl_4 or CH_2Cl_2 solution of methimazole causes an absorbance decrease of this band to the benefit of a new band at 298 nm in CCl_4, and at 302 nm in CH_2Cl_2, with a strong shoulder at 350 nm (Fig. 1). This new band is attributed to the complex and most probably, according to the Mulliken theory of charge-transfer (CT) complexes,[12] to the CT transition from the methimazole HOMO to the diiodine LUMO (σ_u*).

The formation constant of the 1 : 1 complex is related to the equilibrium molar concentrations by eqn. (1). We used very

$$\text{MMI} + I_2 \rightleftharpoons \text{complex}$$
$$K_f = [\text{complex}]/[I_2][\text{MMI}] \quad (1)$$

dilute and similar concentrations of methimazole (*ca.* 5×10^{-5} mol l^{-1}) and diiodine (from 2×10^{-4} to 2×10^{-5} mol l^{-1}) in order to form almost exclusively the 1 : 1 complex. From absorbance variations of the charge-transfer band (Fig. 1) we have calculated K_f by the Rose and Drago method.[11] However we only obtained apparent constants since we have shown elsewhere[13] that methimazole exists as a mixture of monomer and hydrogen-bonded cyclic dimer, even in dilute solution. The dimerization constant K_D, defined by eqn. (2), was found[13a] to

$$2\ \text{MMI} \rightleftharpoons \text{cyclic dimer}$$
$$K_D = [\text{cyclic dimer}]/[\text{monomer MMI}]^2 \quad (2)$$

be 3375 l mol^{-1} in CCl_4 and 60 l mol^{-1} in CH_2Cl_2. Eqn. (3)

$$K_f = 4K_D\,[\text{complex}]/[I_2]\{[1 + 8K_D\,([\text{MMI}]_0 - [\text{complex}])]^{1/2} - 1\} \quad (3)$$

allows us to take into account the self-association of methimazole. The results are summarized in Table 1. The self-association correction explains that in CCl_4 our value is significantly greater than those of Suszka[10] (16 470) and Raby *et al.*[9] (23 194 at 20 °C). In fact in CCl_4 only 68% of methimazole exists as monomer at 10^{-4} mol l^{-1}, the concentration used by Raby *et al.* The difference is much less important in CH_2Cl_2, a strongly unfavourable solvent for cyclic dimerization (see our results[13a] and ref. 13*b*).

Table 1 Formation constants of the diiodine–methimazole complex in CCl_4 and CH_2Cl_2 at 25 °C

Solvent	$[\text{MMI}]_0/10^{-5}$ M[a]	K_f/l mol^{-1} Apparent	Corrected
CCl_4	6.69	34 070[b]	39 694
	3.92	29 705[b]	33 561
		$K_f = 36\,628$	
CH_2Cl_2	7.10	88 799[b]	88 919
	6.53	83 232[b]	83 370
	7.42	104 752[b]	105 010
		$K_f = 92\,433$[c]	

[a] Initial molar concentration of methimazole. [b] Mean values calculated for five diiodine concentrations. [c] 84 730 according to Suszka.[10]

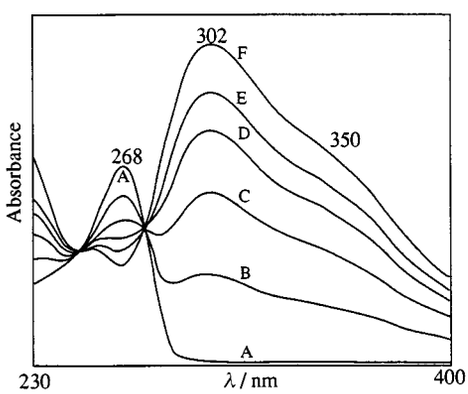
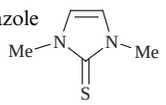
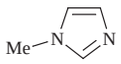


Fig. 1 UV spectrum of methimazole in CH_2Cl_2 (A) and appearance of a CT band when increasing quantities of diiodine are added (B–F). The CT band at 302 nm presents a shoulder at around 350 nm.

All the studies (ionization constants,[14] ^{13}C NMR,[15] ^{15}N NMR,[16,17] IR,[18] Raman[18] and theoretical calculations[19]) in various physical states (water,[14] DMSO,[15–17] $CDCl_3$,[17] CCl_4,[18] CH_2Cl_2[18] and *in vacuo*[19]) of the prototropic tautomerism **1a** $\rightleftharpoons$ **1b** conclude that methimazole exists almost exclusively as the thione tautomer **1a**. However Raby *et al.*[9] have explained the much higher diiodine basicity of methimazole compared with 1-methylimidazole **4** by the coordination of iodine to the sulfur atom of the thiol tautomer **1b**, and Suszka[10] has attributed the shoulder on the charge-transfer band (Fig. 1) to the diiodine–thiol **1b** complex. In order to determine the tautomeric form of methimazole in its diiodine complex, *i.e.* the site of diiodine fixation on the tautomer **1a** or **1b**, we have collected from the literature the formation constants in CCl_4 and CH_2Cl_2 of the diiodine complexes of: (i) 1,3-dimethyl-Δ^4-imidazoline-2-thione **5**,[10] for modelling the diiodine basicity of the sulfur atom of the thione tautomer **1a**; (ii) 1-methylimidazole **4**,[20] for modelling the imino nitrogen of the thiol tautomer **1b**, since the global electronic effect of the SH substituent is almost negligible, its withdrawing field effect ($\sigma_F = +0.28$)[21] almost compensating for its donating resonance effect ($\sigma_R^+ = -0.25$);[21] (iii) CF_3CH_2SH,[22] for modelling the sulfur of the thiol tautomer **1b**, since the field effects of CF_3CH_2 ($\sigma_F = +0.23$)[21] and of the 1-methylimidazol-2-yl substituent ($\sigma_F = +0.26$)[23] are not very different (the withdrawing resonance effect of the heterocyclic substituent still decreases the sulfur basicity).

The results are summarized in Table 2, on a logarithmic scale. It is clear that the thiol group, an extremely weakly basic one, and the imino nitrogen of the imidazole ring cannot seriously

Table 2 Comparison of the formation constants (logarithmic scale) of the diiodine complexes of **1**, **4**, **5** and CF_3CH_2SH

Solvent	Methimazole			CF_3CH_2SH
				
	1a or **1b**	**5**	**4**	
CCl_4	4.56	4.43	2.67	0.08
CH_2Cl_2	4.97	5.03	2.65	—
Δ^a	+0.41	+0.60	−0.02	—

^{a} $\Delta = \log K\,(CH_2Cl_2) - \log K\,(CCl_4)$.

Table 3 Formation constants[a] (l mol^{-1}) of diiodine complexes with representative organic bases[b]

Base	log K_f[b]	Base	log K_f[b]
C_6H_6	−0.62	$EtNH_2$	2.75
MeCN	−0.03	EtSeEt	3.18
MeCOMe	0.05	$MeCSNMe_2$	3.25
EtOEt	0.09	Et_3N	3.67
$MeCONMe_2$	1.18	Et_2NH	3.73
MeSOMe	1.27	Oct_3PS[c]	3.79
Pyridine	2.21	$Me_2NCSNMe_2$	4.00
EtSEt	2.26	MMI	4.56

[a] Ref. 18. [b] In CCl_4 or heptane. [c] Oct = oct-1-yl.

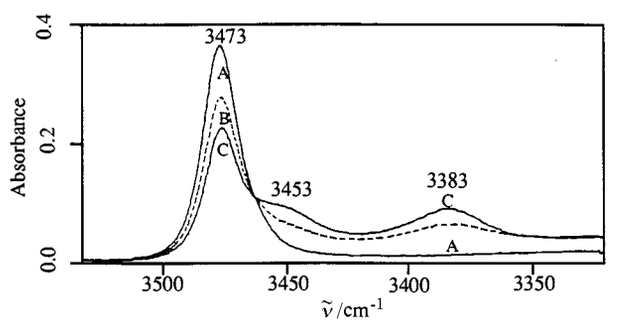


Fig. 2 IR spectrum (NH stretching band) of methimazole in CCl_4 (A) and appearance of two new ν(NH) bands of complex at 3453 and 3383 cm^{-1} when increasing quantities of diiodine are added (B, C)

compete with the thione sulfur in coordinating diiodine; the diiodine complex of the thione tautomer **1a** is favoured in CH_2Cl_2 by a Gibbs energy of 13.2 kJ mol^{-1} over the thiol tautomer **1b**. The conclusion that the diiodine–methimazole complex exists as the thione tautomer is reinforced by the observation of a strong stabilizing effect of the polar solvent CH_2Cl_2, which characterizes all diiodine–thiocarbonyl complexes[4b,6,24,25] but not the imidazole–diiodine one.[20]

We must emphasize the very high stability of the methimazole–diiodine complex, higher than previously found.[9,10] As shown in Table 3, this complex is among the most stable known. It might be biologically relevant that a polar medium still increases the complex stability: 0.41 log K unit is gained by increasing the relative permittivity from 2.30 (CCl_4) to 9.02 (CH_2Cl_2). In the thyroid methimazole might behave as an efficient diiodine sponge.

Stereoisomerism

The X-ray structure of the 1 : 1 methimazole–diiodine complex has not yet been elucidated, since it appears as a purple oil.[26] However we have obtained important structural information *via* IR spectrometry, by studying the N–H stretching band. By adding diiodine to a CCl_4 solution of methimazole, we observe (Fig. 2) that the sharp ν(NH) band of free methimazole at 3473 cm^{-1} disappears to the benefit of two broadened new bands

Table 4 NCSI torsion angle in I_2–thioamide complexes

Planar complexes		Perpendicular complexes	
CSD refcode	φ/°	CSD refcode	φ/°
CEWMOG	−174.2	BZHTIC 10	100.0
CEWNAT	−6.9	MSNROD	−76.7
KUWDEL	6.2	TURMEY	85.8
KUWDIP	11.1	TURMIC	90.4
KUWDIP	159.4	TOTWUU	−96.5
KUWDOW	−0.3	TOTXAB	−103.0
TCAPLI	178.5	VEBCEK	106.1
ZEBQOM	−178.2	ZARDOL	−100.8
GIGLOX	173	GEGNUB	−90.0
GIGLOX	175	GEGNUB 01	92.6
GIGLOX	148		
GIGLOX	−172		

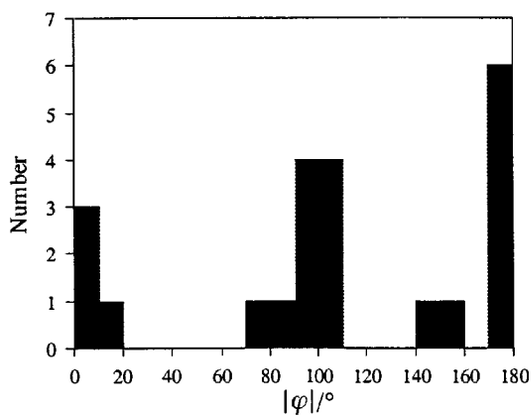
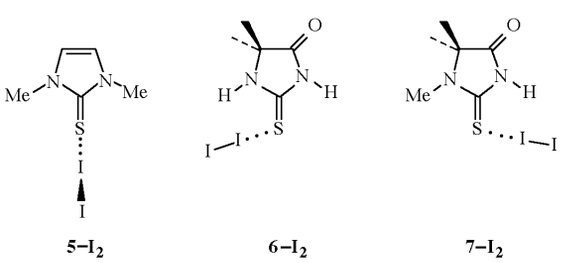


Fig. 3 Distribution of the NCSI torsion angles listed in Table 4

which are shifted to 3383 and 3453 cm^{-1}. This indicates the formation of two different complexes with two differently perturbed NH bonds, because of the different shifts (90 and 20 cm^{-1}) and different half-bandwidths (43 and 35 cm^{-1}).

A search in the CSD shows that I_2–thioamide complexes have many common geometrical features: no appreciable change in the C=S distance but lengthening of the diiodine bond upon complexation, S···I distance in the range 3.10–2.58 Å, nearly linear S···I–I fragment and C=S···I angle between 95.3 and 112°. However the torsion angles N–C=S···I around C=S suggest that two series of complexes are involved. In the first of these, the torsion angles are *ca.* 0 and ±180°; they indicate that the diiodine is not much displaced off the thioamide NCS plane. These complexes will be called planar. In the second series, torsion angles are close to ±90° and characterize so-called perpendicular complexes. Fig. 3 illustrates the tri-modal distribution of torsion angles listed in Table 4, with modes 5 and 175° for the planar complexes and 100° for the perpendicular ones. The crystal geometry of I_2–thioamide complexes seems mainly under steric control (hydrogen bonding can also contribute, *vide infra*). Steric shielding of the sulfur lone pair, on both sides, results in the perpendicular geometry (example **5**–I_2)[26] and in the planar geometry (example **6**–I_2) as iodine binds to sulfur always on the less sterically crowded side (example **7**–I_2).[27,28]



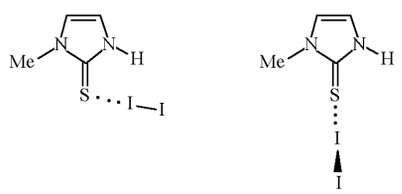
5–I_2 **6**–I_2 **7**–I_2

Table 5 PM3 and 3-21G* calculations of the NH stretching wavenumber (cm^{-1}) in the I_2–HCSNHD complex

	HCSNHD	I_2–HCSNHD (planar)		I_2–HCSNHD (perpendicular)	
	ν(NH)	ν(NH)	$\Delta\nu$(NH)[a]	ν(NH)	$\Delta\nu$(NH)
PM3	3479	3439	40	3466	13
3-21G*	3776	3734	42	3776	0

[a] $\Delta\nu$(NH) = ν(NH, free HCSNHD) − ν(NH, complex).

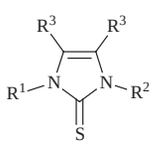
From these crystal structure data, we have attributed the more intense ν(NH) band to the planar **1**–$\mathbf{I_2}$ structure and the less intense one to the perpendicular **1′**–$\mathbf{I_2}$ structure. In order to



1–$\mathbf{I_2}$ **1′**–$\mathbf{I_2}$

support this hypothesis, we have tried to check by theoretical calculations that the NH stretching was shifted to a lower wavenumber in the planar than in the perpendicular complex. We have undertaken calculations on the simplest thioamide, thioformamide (monodeuterated in order to uncouple the NH_2 vibrators). The geometry of the I_2–HCSNHD complex was optimized with PM3 calculations, whereas single-point calculations were performed at the HF/3-21G* level, by using the microwave geometry of $HCSNH_2$[29] and, for the S···I–I fragment, the crystal geometry of the I_2–ethylenethiourea complex[30] with φ (NCSI) = 0 or 90°. The results given in Table 5 support our explanation of the ν(NH) shifts in the I_2–MMI complex.

In the UV spectrum we also observe two CT bands in CCl_4 or CH_2Cl_2 solutions (Fig. 1) and we attribute the more intense band at 302 nm to the planar complex and the shoulder at 350 nm to the perpendicular one. This attribution is supported by the Suszka results[10] on the diiodine complexes of substituted Δ^4-imidazoline-2-thiones **8** showing one band at *ca.* 350 nm



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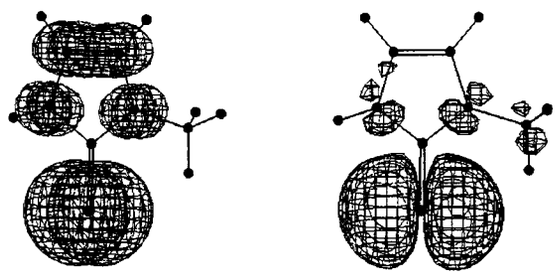
when the sulfur is sterically crowded on both sides ($R^1 = R^2$ = Me), and two bands at *ca.* 300 and *ca.* 350 nm with absorbance ratios A_{300}/A_{350} in the range 1.30–1.79 when one sulfur side is crowded (R^1 = H, R^2 = Me) and 2.46–2.79 when steric effects are minimal ($R^1 = R^2$ = H). Clearly, sterically dependent stereoisomerism, and not tautomerism, allows the interpretation of the CT bands of **8**–$\mathbf{I_2}$. This is confirmed by the Bouab results[31] on the diiodine complexes of non-tautomeric tertiary amides $RCSNMe_2$ (Table 6). The steric hindrance to iodine bonding in the SCN plane on the R side (the NMe_2 side is already crowded) increases from R = Me to R = Et, Pr^i and Bu^t. As a consequence a planar complex is expected for the small Me and Et groups and indeed we find the CT bands at 305 nm, whereas a perpendicular complex must be formed for the bulky Pr^i and Bu^t substituents and we observe the CT bands at 348 nm. Thus a large body of data on the CT bands of I_2–thiourea complexes (Table 7) can be rationalized by the following rule: in order to observe a CT band in the 294–302 nm range typical of planar complexes, sulfur must be sterically unhindered on at least one side, *i.e.* have an NH group s-*cis* to the thiocarbonyl group; otherwise the CT band absorbs at significantly longer wavelengths (321–350 nm) characterizing perpendicular complexes.

Table 6 CT bands of the diiodine complexes of tertiary thioamides $RCSNMe_2$ in heptane[a]

R	λ[b]/nm	ε[c]/l mol^{-1} cm^{-1}
Me	305[d]	38 000
Et	305[d]	35 600
Pr^i	348[e]	27 780
Bu^t	348[e]	28 830

[a] Ref. 31. [b] Wavelength of the CT band maximum. [c] Molar extinction coefficient at the CT band maximum. [d] Shoulder near 350 nm. [e] Unsymmetrical band at short wavelength.



HOMO HOMO–1

Fig. 4 HOMO (πS) and HOMO-1 (nS) of methimazole (PM3)

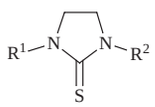
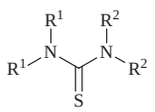
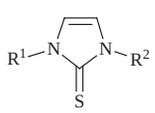
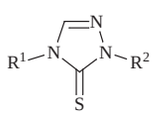
A theoretical rationale of stereoisomerism cannot presently be reached for complexes with so many electrons. We wish only to remark that the HOMO and HOMO-1 of methimazole, calculated at various levels of theory or deduced from ionization energies,[33] have similar energies, the theoretical differences ranging from 0.36 to 0.77 eV and the experimental one being 0.49 eV (Table 8). The contribution of AOs to these MOs, illustrated in Fig. 4, shows that they are relatively localized, with important πS (HOMO) and nS (HOMO-1) character, *i.e.* they have very different directional character. The experimental C=S···I angle range of 95.3–112° (*vide supra*) agrees with a significant overlap of the I_2 σ* LUMO with either nS (the planar complex) or πS (the perpendicular complex) MO of methimazole. We do not mean that the geometries and stabilities of I_2–MMI isomers are mainly under orbital control but that stereoisomerism partly originates in the existence of πS and nS orbitals of near energies.

Intramolecular hydrogen bonding

In the IR spectrum of the I_2–MMI complex (Fig. 1) the shift (90 cm^{-1}) and broadening ($\Delta\nu_{1/2}$ = 43 cm^{-1} instead of 17 cm^{-1} in free MMI) of the ν(NH) band characterizes a hydrogen-bonded vibrator. A PM3 molecular modelling of the complex shows that the S-bonded iodine [I(1)] is the hydrogen bond acceptor site since the H···I(1) distance (2.98 Å) is appreciably shorter than the sum of the van der Waals radii (3.18 Å). This constitutes another example of the NH···I(1) intramolecular hydrogen bonding first discovered by Devillanova and co-workers[27,28,34] in the diiodine complexes of many pentaatomic rings containing the thioamido group (*e.g.* **6**–$\mathbf{I_2}$ and **7**–$\mathbf{I_2}$). According to Devillanova and co-workers the NH···I(1) interaction brings an additional stability to the complex. We indeed observe a formation constant for **1**–$\mathbf{I_2}$ 0.13 log *K* unit (0.74 kJ mol^{-1} on the Gibbs energy scale) higher than for its methylated analog **5**–$\mathbf{I_2}$ in CCl_4. Other examples of hydrogen bonding-assisted complexation are assembled in Table 9 for the diiodine complexes of compounds **9**–**13** (R = H or Me).

We wish to emphasize the amphoteric behaviour of the inner

Table 7 Steric dependence of CT band wavelengths in diiodine–thiourea complexes

Thiourea	R^1	R^2	λ/nm Planar complex	λ/nm Perpendicular complex	Solvent	Ref.
	H	H	298		CH_2Cl_2	32
	Me	H	298		CH_2Cl_2	32
	Et	H	299		CH_2Cl_2	32
	Me	Me		322	CH_2Cl_2	32
	Et	Et		321	CH_2Cl_2	32
	H	H	294		CH_2Cl_2	*a*
	Me	Me		339	Heptane	31
				338	CCl_4	*a*
				328	CH_2Cl_2	*a*
	Me	Et		345	Heptane	31
	Et	Et		346	Heptane	31
	H	H	299		CH_2Cl_2	10
	Me	H	302		CH_2Cl_2	*a*
			298		CCl_4	*a*
	Me	Me		350	CH_2Cl_2	10
	Me	H	302		CH_2Cl_2	*a*
	H	Me	302		CH_2Cl_2	*a*
	Me	Me		334	CH_2Cl_2	*a*

[a] This work.

Table 8 Eigenvalues and ionization energies of methimazole

Method	Eigenvalues[a]/eV HOMO-1	HOMO	ΔE^b/eV
AM1	−8.52	−8.13	0.38
PM3	−8.55	−8.19	0.36
3-21G	−8.31	−7.54	0.77
6-31G**	−8.35	−7.59	0.76
	E_i/eV[c]		
	nS	πS	
	7.90	7.41	0.49

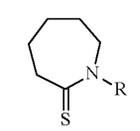
[a] This work. [b] $\Delta E = E(\text{HOMO}) - E(\text{HOMO-1})$. [c] Ref. 33.

Table 9 Comparison of the formation constants K_f (l mol^{-1}) of the diiodine complexes of secondary (R = H) and tertiary (R = Me) thioamides **9**–**13** in CH_2Cl_2 at 25 °C

	K_f/l mol^{-1} R = H	R = Me	Δ[a]	Ref.
9	83 721[b]	19 400	+0.64	24
10	2 826	1 081	+0.42	35
11	49 500	8 100	+0.79	32
12	10 800	4 740	+0.36	36
13	132	19	+0.84	28

[a] $\Delta = \log K_f(\text{R = H}) - \log K_f(\text{R = Me})$. [b] This work.

iodine atom in the diiodine–methimazole complex: iodine changes from acting as a Lewis acid towards the basic sulfur atom, to behaving as a Lewis base towards the acidic hydrogen atom. The Lewis acidity of heavy halogenated compounds (Fig. 5a) is well-documented in the literature[37] and a few reports on the Lewis basicity of haloalkanes (mainly as hydrogen bond acceptors, Fig. 5b)[38] allow conclusions to be drawn on the heavy halogens' amphoterism. These studies refer to halogens as electron donors or acceptors in different molecules. Examples of halogen amphoterism in the same molecule can



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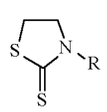

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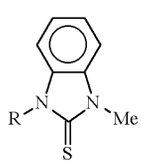

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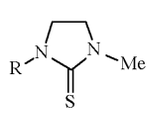

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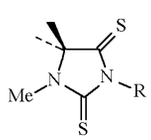

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be found in the complexes of stoichiometry 1 base: 2 I_2 (Fig. 5c);[30,39] in this case the electron acceptor and electron donor iodine atoms are different. Crystal structures of I_2 (Fig. 5d), Br_2, Cl_2 and *p*-dibromobenzene (Fig. 5f)[40] give examples of amphoterism for the same halogen in the same molecule. The diiodine–methimazole complex, and other diiodine–secondary thioamide complexes (Fig. 5e), pertain to this last category where the same halogen atom both donates and accepts electrons.

It can be observed from Fig. 5 and detailed examinations of halogen contacts in crystals[40,41] that bases tend to approach the halogen approximately along the Hal–Hal or C–Hal bonds, whereas acids are usually attached nearly vertical to these bonds. These directional preferences have been explained[42] by an analysis of the electrostatic potential around halomethanes and the finding of positive potentials at the ends of chlorine, bromine and iodine, consistent with Lewis acidity, and of a negative ring around the halogen sites, indicating Lewis basicity. We have computed electrostatic potentials on the molecular surface of diiodine defined as the 0.002 au contour of the electronic density at the PM3 level of theory. We indeed find a positive potential at the ends of I_2 (V_{max} = +35 kcal mol^{-1}) and a negative ring around the iodine sides with surface minima of −8 kcal mol^{-1} at angles of 100° to the molecular axis. In the complex with methimazole, the side of S-bonded

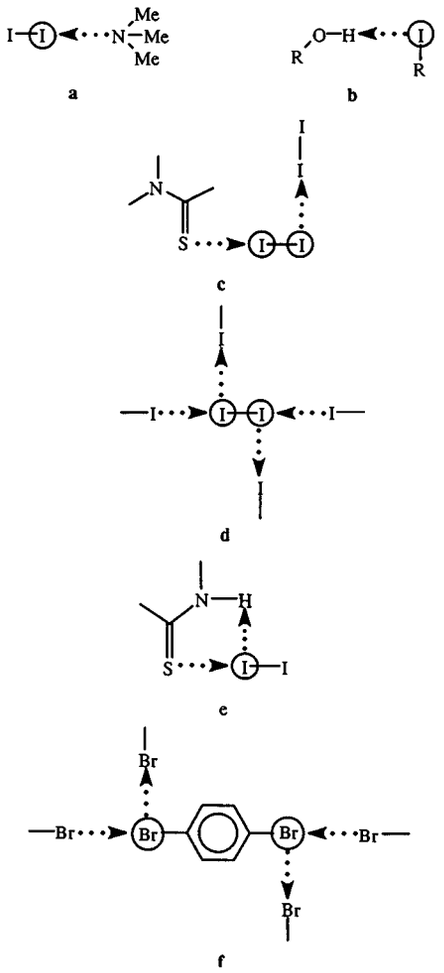
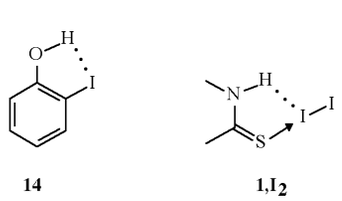


Fig. 5 Amphoteric behaviour of I and Br atoms. Arrows towards or away from halogens designate electron acceptance and donation, respectively. References for structures: (a) (d) (f) ref. 40; (b) postulated by putting the OH group in a lone-pair direction; (c) ref. 30; (e) PM3 molecular modelling of I_2–MMI.

iodine becomes still more negative ($V_{min} = -20$ kcal mol^{-1}). These values can be compared to V_{min} of axial iodocyclohexane (-21.3 kcal mol^{-1}) for which the formation enthalpy of the hydrogen-bonded complex with phenol (hydrogen bond donor similar in strength to cyclic thioureas)[43] is known[38a] to be -7.2 kJ mol^{-1}. In the same vein we remark on the similarity between *o*-iodophenol **14** and **1**–$\mathbf{I_2}$ (in both cases hydrogen is chelated



14 **1,I_2**

inside a five-membered ring) and estimate the hydrogen bond energy in **1**–$\mathbf{I_2}$ to be -6.9 kJ mol^{-1} from the value of **14**.[44]

Possible mechanisms of action of MMI, CBZ and PTU

The soft basicity (ability to complex I_2 and, by extension, I^+ and HOI, *vide infra*)[1] and the hard basicity (ability to complex hydrogen bond donors and, by extension, Fe^{3+} in the heme group of thyroid peroxidase)[1] are compared in Table 10 to their relative thyroid activity.[3] *In vivo* CBZ is rapidly and totally metabolised to MMI and the anti-thyroid action of CBZ can be ascribed entirely to MMI.[45–47] Our CBZ study[1] aimed only to give a rough estimation of the PTU basicity, unattainable for solubility reasons. From Table 10 data it is tempting to relate the

Table 10 Thyroid activity and basicity of MMI, CBZ and PTU

	Relative thyroid activity[a]	Soft basicity[b]	Hard basicity[c]
MMI	1	4.56[d]	2.11[e]
CBZ	1	3.15[f]	~1.32[f]
PTU	0.1	3.15[g]	~1.32[g]

[a] Ref. 3. [b] Log (formation constant of I_2 complexes). [c] Log (formation constant of *p*-fluorophenol complexes). [d] This work. [e] Ref. 13. [f] Ref. 1. [g] Roughly estimated from CBZ.[1]

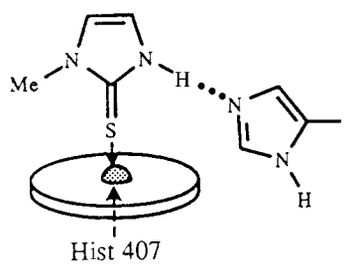
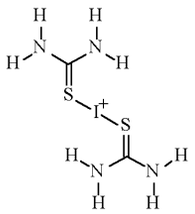


Fig. 6 Possible coordination of MMI to the TPO heme [ball and disk represent iron(III) and protoporphyrin, respectively]

higher MMI activity to its higher basicity. Possible acid–base chemistry of the anti-thyroid drugs MMI and PTU is described below.

Most studies[48] show that anti-thyroid drugs function as specific inhibitors of thyroid peroxidase (TPO). Since the activation of TPO–Fe(III) is carried out by coordination of H_2O_2 to iron,[49] TPO inactivation may occur through a competitive coordination of the drug to iron, assisted by hydrogen bonding with a histidine residue of the TPO protein (Fig. 6). Indeed iron–sulfur coordinations are frequent in metallo-enzymes[50] and hydrogen bonding of heme ligands with a distal histidine appears common in peroxidases.[51] MMI might compete more successfully than PTU with H_2O_2 if we consider the respective hydrogen-bond (hard) basicity pK_{HB} values of these ligands: 2.11 (MMI), ~1.32 (PTU), ~1.21 (H_2O_2, from organic peroxides[52]). The strong NH hydrogen-bond acidity of MMI[43] might validate a hydrogen bond-assisted linkup with TPO. Interestingly, while primary and secondary thioureas can inhibit lactoperoxidase (a TPO model) this is not the case for tetramethylthiourea,[8] which does not have hydrogen-bonding donor properties.

Acid–base chemistry also concerns the soft iodinated Lewis acids I_2 and/or I^+[53] and/or HOI which are produced[54–56] during the oxidation of iodide ions taken up by the thyroid. They are all potential electrophilic agents in the aromatic iodination of tyrosine residues of thyroglobulin. They can all be trapped by the strong soft bases PTU and, still more, by MMI, and be diverted from the hormone biosynthesis pathway.[8,57] We have largely documented the MMI diiodine basicity: MMI functions as a diiodine sponge, still more efficiently at the polar surfaces of the apical membrane of thryocytes where hormonosynthesis takes place.[3] We are not aware of data on the Lewis acidity of HOI but the greater electronegativity of OH compared with halogens certainly makes HOI a stronger iodinated Lewis acid than I_2 and even interhalogens. Still more acidic are I^+ cations: their binding energy to Lewis bases amounts at least to 274 kJ mol^{-1}[53] and are the largest for sulfur bases,[53] whereas the formation enthalpies of diiodine–thiourea complexes do not exceed 42 kJ mol^{-1}.[6] Numerous 2 thiourea: 1 I^+ complexes have been crystallised (*e.g.* **15**)[58] but in an aqueous medium the reaction of I_2 with thiourea gives the dication disulfide **16**.[59] Molecular I_2–thioamide complexes can evolve to give ionic complexes like **15** and then an oxidation product.[60] Actually the MMI disulfide **17**, the product of electrochemical oxidation of



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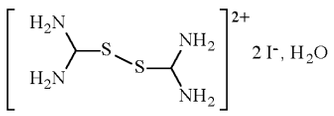

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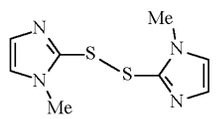

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MMI,[61] is the earliest MMI metabolite detected in an *in vitro* incubation system containing MMI, TPO, I^- and H_2O_2.[48f]

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