SPECTROSCOPIC ANALYSIS OF IODINATED MOLECULAR COMPLEXES OF THIAZOLE AND THIAZOLINE DERIVATIVES

Jean-François Lagorce, Jacques Buxeraud*, Anne-Catherine Jambut-Absil and Claude Raby

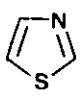
Laboratoire de Chimie Organique et de Chimie Thérapeutique, Faculté de Pharmacie, 2, rue du Docteur Marcland, 87025 Limoges Cedex, France

Abstract - Molecular interactions between iodine and the heterocyclic compounds, thiazole, 4-methylthiazole, clomethiazole, cloprothiazole, 2-methyl-2-thiazoline and 2-thiazoline-2-thiol were studied by uv/vis spectroscopy. These molecules were found to form charge transfer complexes with iodine of the n-σ type in a 1:1 stoichiometry. Formation constants of the iodinated complexes of thiazole, 4-methylthiazole, clothiazole and cloprothiazole ranged from 10 M^{-1} to 30 M^{-1} . The much higher values found for 2-methyl-2-thiazoline and 2-thiazoline-2-thiol indicated a strong donor-acceptor interaction. Only the latter two derivatives have an action on the thyroid gland, and might, therefore, be suitable starting compounds for the synthesis of new antithyroid agents.

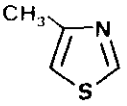
The present study represents an extension of previous work on the interactions of iodine with imidazole derivatives [1] to derivatives of thiazole and thiazoline. As for imidazole, thiazole is a heterocyclic compound whose basic structure forms part of numerous drugs. In the course of a systematic investigation of molecular interactions between iodine and drugs, we determine in this paper the spectral parameters and the formation constants of the iodine complexes of a number of relatively simple molecules based on the thiazole or thiazoline structure : thiazole, 4-methylthiazole, clomethiazole, cloprothiazole, 2-methyl-2-thiazoline and 2-thiazoline-2-thiol. The principle objective was to evaluate potential antithyroid activity in order to find new heterocyclic compounds with strong electron donor properties, which could be employed as antithyroid agents.

EXPERIMENTAL

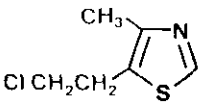
Iodine was bisublimed (Merck Suprapur), and was kept in the dark in a desiccator containing P_2O_5. The donors, thiazole (I), 4-methylthiazole(II), clomethiazole (III), cloprothiazole (IV), 2-methyl-2-thiazoline (V) and 2-thiazoline-2-thiol (VI) are commercially available compounds which were carefully purified by preparative hplc.



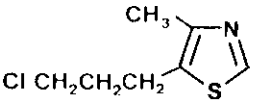
(I)



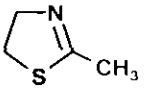
(II)



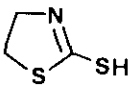
(III)



(IV)



(V)



(VI)

(I) thiazole
(II) 4-methylthiazole
(III) 5-(2-chloroethyl)-4-methylthiazole or clomethiazole
(IV) 5-(3-chloropropyl)-4-methyl thiazole or cloprothiazole
(V) 2-methyl-2-thiazoline
(VI) 2-thiazoline-2-thiol

The solvent was carbon tetrachloride of spectroscopic grade (Merck Uvasol), and was used without further purification. Its low water content (0.01%) did not interfere with the formation of the iodinated complexes.

Spectra were recorded on a Uvicon 930 double beam uv/vis spectrophotometer equipped with a Peltier effect sample holder (temperature regulated to $\pm$ 0.1°C). the Helma quartz sample cells had an optical path length of 10 mm. All glassware used in the experiments was carefully dried in a stream of dry nitrogen.

The solutions of iodine and the compounds I to VI were prepared by dilution of stock solutions made up by accurate weighing. The complexes were formed directly in the sample cuvettes by mixing 1.5 ml of solution of iodine in carbon tetrachloride with 1.5 ml of a solution of donor in the same solvent. The absorbances of the complex were recorded at various wavelengths close to the peak of the halogen complex, enabling calculation of the formation constants K_c of the iodinated complexes. For each complex, thermodynamic parameters were also calculated by measuring the absorbance of a series of solutions at temperatures from 5°C to 40°C.

RESULTS

Visible region

At concentrations ranging from 10^{-2} to 10^{-4}M, none of the donors absorbed significantly in the region of the absorption bands of the iodinated complexes.

The addition of a solution of iodine to the donors led to an alteration of the visible band of iodine (515 nm), which shifted to shorter wavelengths (hypsochromic shift). This is illustrated for the 2-methyl-2-thiazoline -iodine complex in Figure 1. The new bands of the halogenated complexes all crossed at a single isosbestic point.

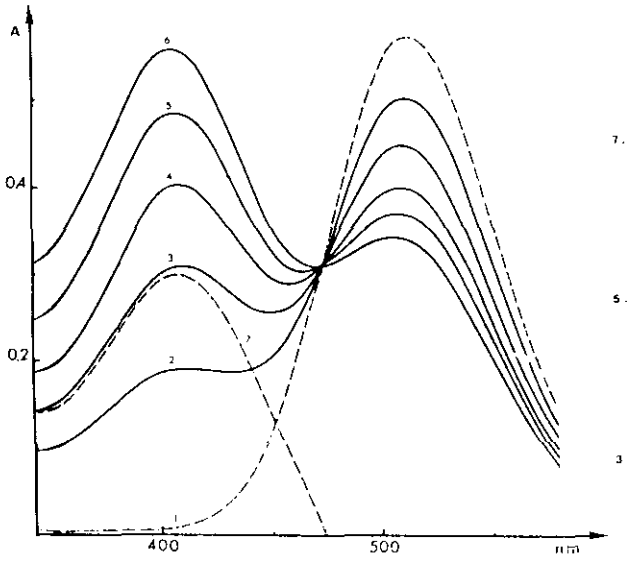


Figure 1 : Visible absorption spectra of 2-methyl-2-thiazoline-iodine complex (solvent, carbon tetrachloride, temperature 20 ± 0,1°C). Key : (1) $5.906.10^{-4}$M iodine ; (2) $5.906.10^{-4}$M iodine and $3.607.10^{-4}$M 2-methyl-2-thiazoline (3) $5.906.10^{-4}$M iodine and $6.721.10^{-4}$M 2-methyl-2-thiazoline ; (4) $5.906.10^{-4}$M iodine and $1.008.10^{-3}$M 2-methyl-2-thiazoline ; (5) $5.906.10^{-4}$M iodine and $1.344.10^{-3}$M 2-methyl-2-thiazoline ; (6) $5.906.10^{-4}$M iodine and $1.680.10^{-3}$M 2-methyl-2-thiazoline ; (7) absorption curve of complex obtained for solution 3 by placing a $5.906.10^{-4}$M iodine solution in the reference beam.

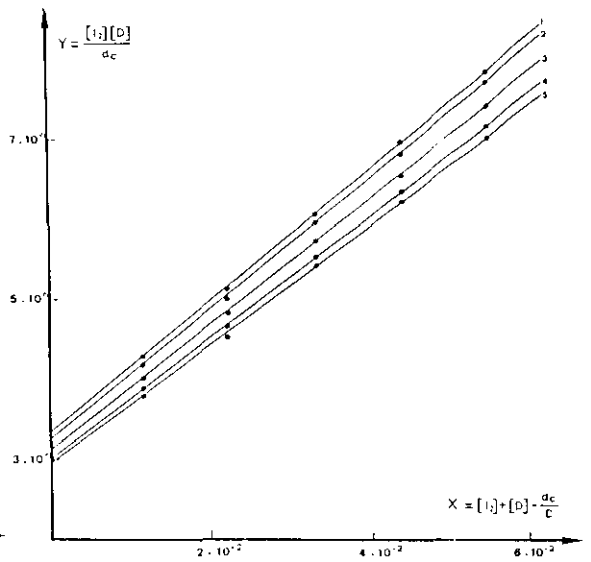


Figure 2 : Graphic representation of Lang equation obtained for the clomethiazole-iodine complex.
Lines 1,2,3,4 and 5 were obtained at 440 410, 435, 430 and 420 nm, respectively. The linear regression equations are :
(1) $Y = 8.31\times10^{-4} X + 3.32\times10^{-5}$ ($r = 0.999$).
(2) $Y = 8.12\times10^{-4} X + 3.25\times10^{-5}$ ($r = 0.999$).
(3) $Y = 7.80\times10^{-4} X + 3.14\times10^{-5}$ ($r = 0.998$).
(4) $Y = 7.57\times10^{-4} X + 3.01\times10^{-5}$ ($r = 0.999$).
(5) $Y = 7.48\times10^{-4} X + 2.96\times10^{-5}$ ($r = 0.999$).

For each complex, 1:1 stoichiometry was confirmed by mathematical analysis of the πg-σu orbital transition of iodine, analysis of the absorbances, the experimental points to a linear regression equation (Figure 2). Further calculations using the Liptay method[2] also confirmed the presence of a single complex.

The determination of the formation constants K_c of the iodinated complexes and the molar extinction coefficients ϵ_c were derived from the following equation which has been discussed in a previous publication[3] and which has been previously describ by T. Kubota.

$$[Ao][Do]/d_c = \left[[Ao] + [Do] - d_c/\epsilon_c\right] 1/\epsilon_c + 1/K_c\epsilon_c$$

The formation constants K_c and the molar extinction coefficients ϵ_c of the various donor-acceptor complexes are listed in Table I, and the thermodynamic parameters are given in Table II. The complex with 2-methyl-2-thiazoline was too unstable to allow calculation of thermodynamic parameters.

Table I : Formation constants (K_c) and molar extinction coefficients (ϵ_c) for iodine complexes in solution in carbon tetrachloride[a]

Donors	λ (nm)	ϵ [b] ($l.M^{-1}.cm^{-1}$)	K_c [b] (M^{-1})	Mean K_c
thiazole[c]	420	1352	9.89	
	425	1373	10.07	
	430	1359	10.40	10.25±0.2
	435	1345	10.31	
	440	1281	10.60	
4-methylthiazole[d]	425	1653	20.45	
	430	1585	21.26	21.55±0.9
	435	1498	21.89	
	440	1389	22.59	
clomethiazole[e]	410	1231	24.96	
	415	1305	24.84	
	420	1337	24.84	
	425	1343	25.32	25.01±0.19
	430	1321	25.17	
	435	1283	24.83	
	440	1203	25.07	
cloprothiazole[f]	410	1326	29.79	
	415	1386	29.97	
	420	1390	31.16	
	425	1391	30.94	30.80±0.67
	430	1339	31.67	
	435	1293	31.08	
	440	1213	31.01	
2-methyl-	400	1485	1094	
	405	1510	1148	
2-thiazoline[g]	410	1521	1181	1200± 86
	415	1474	1290	
	420	1450	1286	
2-thiazoline-	425	2939	2616	
	430	3042	2327	
2-thiol[h]	435	2743	2616	2527±118
	440	2659	2532	
	445	2414	2544	

a temperature 20 ± 0.1°C

b Values were calculated from absorption data in the visible region.

c 5 different thiazole-I_2 solutions ; $[I_2]$ 3.904×10^{-4} M ; [thiazole] varied from 3.75×10^{-2} to 3×10^{-1} M.

d 4 different 4-methyl thiazole-I_2 solutions ; $[I_2]$ 3.73×10^{-4} M ; [4-methylthiazole] varied from 2.6×10^{-2} to 1.3×10^{-1} M.

e 5 different clomethiazole-I_2 solutions ; $[I_2]$ 4.58×10^{-4} M ; [clomethiazole] varied from 1.09×10^{-2} to 5.47×10^{-2} M.

f 5 different cloprothiazole-I_2 solutions ; $[I_2]$ 4.58×10^{-4} M ; [cloprothiazole] varied from 0.76×10^{-2} to 3.78×10^{-2} M.

g 5 different 2-methyl-2-thiazoline-I_2 solutions ; $[I_2]$ 5.91×10^{-4} M ; [2-methyl-2-thiazoline] varied from 0.336×10^{-3} to 1.680×10^{-3} M.

h 5 different 2-thiazoline-2-thiol-I_2 solutions ; $[I_2]$ 5.78×10^{-5} M ; [2-thiazoline-2-thiol] varied from 1.16×10^{-4} to 4.64×10^{-4} M.

Table II : Thermodynamic parameters obtained for the iodine complexes

Donors	$\Delta H°$ kcal mol^{-1}	$\Delta S°$ cal $mol^{-1}K^{-1}$	$\Delta G°_{293}$ kcal mol^{-1}
thiazole[a]	5.39 ± 0.16	13.72 ± 0.55	1.36 ± 0.02
4-methylthiazole[b]	6.81 ± 0.14	17.21 ± 0.56	1.79 ± 0.02
clomethiazole[c]	7.08 ± 0.14	17.76 ± 0.50	1.87 ± 0.005
cloprothiazole[d]	6.68 ± 0.17	15.99 ± 0.57	2.00 ± 0.01
2-thiazoline-2-thiol[e]	10.87 ± 1.44	21.54 ± 5.02	4.57 ± 0.03

a $[I_2]$ 3.904×10^{-4} M ; [thiazole] varied from 3.75×10^{-2} to 3×10^{-1}M

b $[I_2]$ 3.74×10^{-4}M ; [4-methylthiazole] varied from 2.6×10^{-2} to 1.3×10^{-1}M

c $[I_2]$ 4.58×10^{-4} M ; [clomethiazole] varied from 1.09×10^{-2} to 5.47×10^{-2}M

d $[I_2]$ 4.58×10^{-4} M ; [cloprothiazole] varied from 0.76×10^{-2} to 3.78×10^{-2}M

e $[I_2]$ 5.78×10^{-5} M ; [2-thiazoline-2-thiol] varied from 1.16×10^{-4} to 4.64×10^{-4}M

Ultraviolet region

All the donors displayed strong absorption (Table III), whereas iodine had weak absorption in the uv region.

Table III : Molar extinction coefficients of donors obtained in the ultraviolet region[a]

Donors	λmax (nm)	log ϵ max
thiazole	257.5	3.86
4-methylthiazole	258	3.14
clomethiazole	256.4	3.42
cloprothiazole	256.4	3.42
2-methyl-2-thiazoline	259.5	3.48
2-thiazoline-2-thiol	283 256	4.18 3.96

a solvent : carbon tetrachloride ; temperature : 20 ± 0.1°C

The high values of the molar extinction coefficients of the complexes in this spectral region allowed much lower donor concentrations than those required for the visible spectra. The iodinated complexes had quite different spectral characteristics, and a typical spectrum of the iodine-2-methyl-2-thiazoline complex is shown in Figure 3. By subtracting the absorbances due to free iodine and free donor, curve 4, corresponding to the absorbance of the complex was

obtained. This charge transfer complex had a peak at 266.5 nm. The uv spectral parameters are listed in Table IV.

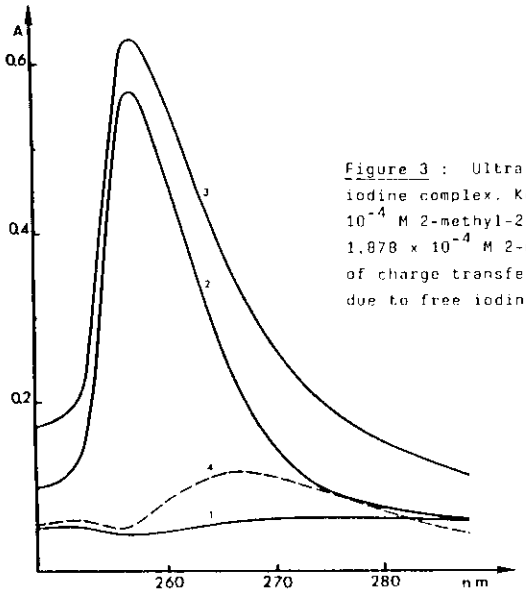


Figure 3 : Ultraviolet spectra of the 2-methyl-2-thiazoline-iodine complex. Key : (1) 6.281 x 10^{-4} M iodine ; (2) 1.878 x 10^{-4} M 2-methyl-2-thiazoline ; (3) 6.281 x 10^{-4} M iodine and 1.878 x 10^{-4} M 2-methyl-2-thiazoline ; (4) Graphical extrapolation of charge transfer band obtained by subtracting the absorbances due to free iodine and free 2-methyl-2-thiazoline.

Table IV : Absorption peaks for charge transfer bands (CTB) for the various donor -acceptor complexes. (solvent : CCl_4; temperature 20 ± 0.1°C.)

Complexes	λ max of CTB (nm)
thiazole-I_2	263
4-methyl-thiazole-I_2	268
clomethiazole-I_2	276
cloprothiazole-I_2	278
2-methyl-2-thiazoline-I_2	266.5
2-thiazoline-2-thiol-I_2	310

CONCLUSION-DISCUSSION

The spectroscopic data demonstrated the n-σ nature of the charge transfer complex between iodine and the derivatives of thiazole and thiazoline. These complexes all had a 1:1 stoichiometry. The results indicated a moderate molecular interaction of iodine with the thiazole derivates and a strong interaction with the thiazoline derivatives.

For the thiazole series, the value of K_c was higher for the derivatives with alkyl substituents on the thiazole ring. The introduction of a methyl group at position 4 doubled the value of K_c (10.25 M^{-1} for thiazole and 21.55 M^{-1} for 4-methylthiazole). A further substituent on position 5 such as a 2-chloroethyl or chloropropyl group only slightly increased the K_c value (25.01 M^{-1} for clomethiazole and 30.8 M^{-1} for cloprothiazole). Partial hydrogenation of the thiazoline nucleus led to a marked increase in the K_c value of the iodinated complex due to elimination of the aromatic character of the molecule. Thus for the two derivatives of thiazoline, the values of K_c were 1200 M^{-1} for 2-methyl-2-thiazoline and 2527 M^{-1} for 2-thiazoline-2-thiol. The replacement of the methyl group on 2-methyl-2-thiazoline by a SH group doubled the K_c value.

Previous work in our laboratory[3,5-7] has shown that a given compound can be expected to have antithyroid activity if its formation constant, K_c, of the iodinated complex is at least 100 M^{-1} and that the antithyroid activity increases with increasing values of K_c. For methimazole which is the strongest antithyroid agen known, we found a K_c value of 23194 M^{-1}. The derivatives of thiazole tested in this study all had K_c values above 100 M^{-1}, and due to their strong affinity for iodine might be excepted to interfere with thyroid metabolism.

Two main points should be noted :
- the results indicated that thiazoline substituted with a SH group in position 2 could serve as a starting point for the synthesis of new antithyroid agents.
- the strong molecular interaction between iodine and the derivatives of thiazoline suggest that drugs based on this nucleus might have antithyroid activity.

ACKNOWLEDGMENTS

We thank F. Claude for her technical assistance and J. Bouillaguet for her secretarial assistance.

REFERENCES

1. A.C. Jambut-Absil, J. Buxeraud, C. Moesch, J.F. Lagorce, and C. Raby, **Heterocycles**, 1986, 24, 1955.

2. W. von Liptay, **Z. Electrochem**, 1965, 65, 375.

3. J. Buxeraud, A.C. Absil, and C. Raby, **J. Am. Pharm. Sciences**, 1984, 73, 1687.

4. T. Kubota, **J. Am. Chem. Soc.**, 1965, 87, 458.

5. C. Raby and J. Buxeraud, **Eur. J. Med. Chem.**, 1980, 15, 425.

6. J. Buxeraud, A.C. Absil, J. Claude, C. Raby, G. Catanzano, and C. Beck, **Eur. J. Med. Chem.**, 1985, 20, 43.

7. A.C. Absil, J. Buxeraud, and C. Raby, **Can. J. Chem.**, 1984, 62, 1807.

Received, 13th March, 1989