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SPECTROSCOPIC ANALYSIS OF IODINATED MOLECULAR COMPLEXES OF N-METHYL IMIDAZOLE AND OTHER IMIDAZOLE AND IMIDAZOLINE DERIVATIVES OF PHARMACOLOGICAL IMPORTANCE

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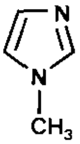
Abstract - Molecular interactions between iodine and heterocyclic molecules such as N-methylimidazole, methimazole, clotrimazole, levamisole and tetrahydrozoline were investigated by UV/Vis spectroscopy. Iodine was found to form charge transfer complexes with these molecules of 1:1 stoichiometry of the n-σ type. The values of the formation constants Kc of these iodinated complexes indicated a strong donor-acceptor interaction. These compounds can therefore be expected to have an action on thyroid metabolism.

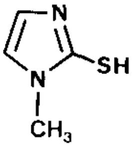
Nitrogenous heterocyclic compounds are known to form charge transfer complexes with iodine. A number of these heterocyclic complexes have been studied both qualitatively and quantitatively[1,2,3]. In the course of a general study of drug interactions with iodine, we investigated the interactions with iodine of various imidazole and imidazoline derivatives of pharmacological importance. We were particularly interested to determine the spectral parameters and the formation constants of these iodinated complexes. Based on a previously published structure-activity model, potential antithyroid activity of these derivatives can be predicted.

EXPERIMENTAL

Iodine was from Merck (bisublimed Suprapur) and was kept in the dark in a dessicator containing P_2O_5. The donor molecules N-methylimidazole (I), methimazole (II), clotrimazole (III), levamisole (IV) and tetrahydrozoline (V) were commercialy available compounds which we purified by HPLC. The solvents, carbon tetrachloride and chloroform, were from Merck (Uvasol for spectroscopy) and were used without further purification. Their very low water content (max. 0.01%) did not affect complex formation.



(I)



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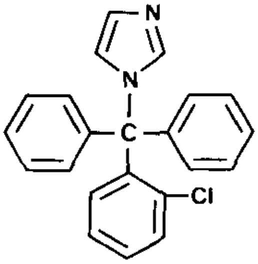

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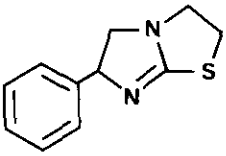

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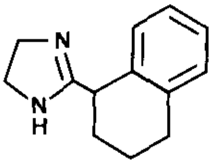


(V)

(I) N-methyl-imidazole

(II) 1-methyl-imidazole-2-thiol or methimazole

(III) 1-|(2-chlorophenyl)diphenylmethyl|-1H-imidazole or clotrimazole

(IV) 2,3,5,6-tetrahydro-6-phenylimidazo|2,1,b|thiazole or levamisole

(V) 4,5-dihydro-2-(1,2,3,4-tetrahydro-1 naphthalenyl)-1H-imidazole or tetrahydrozoline

Spectra were recorded using a Perkin-Elmer 554 double beam UV/Vis spectrophotometer equipped with a Peltier effect thermostated sample holder (temperature regulated to ± 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.

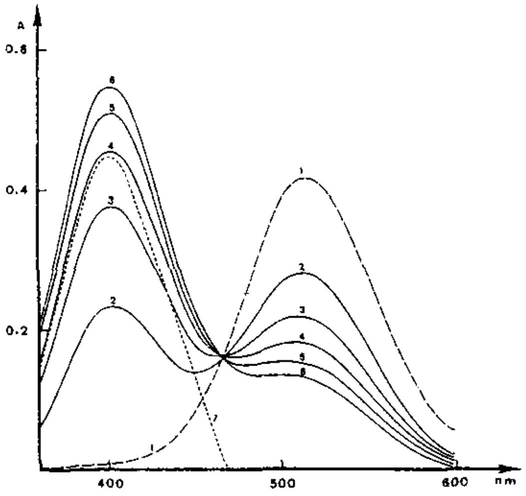
The donor-acceptor complexes could only be studied in dilute solution in which they are in equilibrium with the starting compounds. Their physical properties, especially their spectra differ from the starting compounds and we therefore used UV/Vis spectroscopy to study the reactions. Solutions of iodine and the various donors were prepared by accurate dilution of stock solutions prepared gravimetrically. The reactions were carried out directly in the spectrophotometer sample cells. The absorbances of the solutions were recorded immediately at various wavelengths close to the peak for the halogen complex. Molecules which were not very soluble in carbon tetrachloride and those whose complex was insoluble in this solvent were studied in a mixture of carbon tetrachloride and chloroform (1:1 v/v). The levamisole/iodine system was investigated in the solvent mixture. The N-methylimidazole/iodine system was studied in both pure carbon tetrachloride and the solvent mixture. All the other systems were investigated in pure carbon tetrachloride.

RESULTS

Visible region

At concentrations of 10^{-3} to 10^{-4} M, the donors were completely transparent to visible light. Addition of a solution of iodine shifts the 515 nm iodine band to shorter wavelengths (hypsochromic shift) (Fig.1). The new absorptions bands corresponding to the iodinated complexes were all found at the isobestic point. For each system, the absorption peak of the complex was measured by placing a solution of iodine at the same concentration as used for complex formation in the reference beam.

For each complex, 1:1 stoichiometry was confirmed by mathematical analysis of the πg-σu orbital transition of iodine, analysis of the absorbances, the presence of a single isobestic point, and the exact fit of the experimental points to a linear regression equation (Fig.2). Further analysis using the Liptay matrix method[3-6] also demonstrated the presence of a single complex.



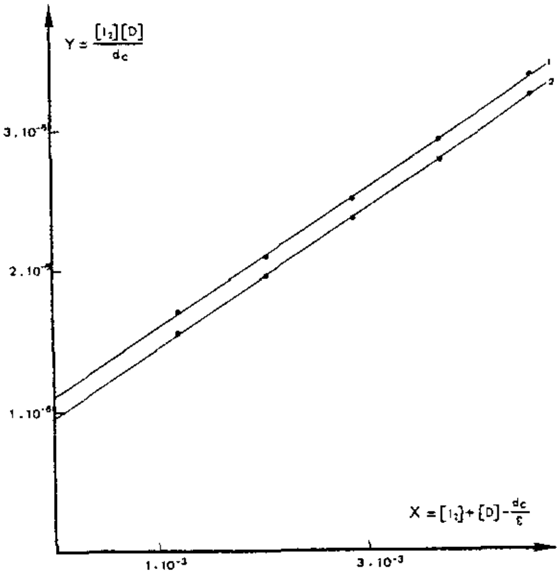


Figure 1: Visible spectra of clotrimazole-I_2 complex in CCl_4 at 20°C. The molar concentration of iodine is: 4.37×10^{-4}. The molar concentrations of clotrimazole are: (1) 0; (2) 0.88×10^{-3}; (3) 1.77×10^{-3}; (4) 2.66×10^{-3}; (5) 3.55×10^{-3}; (6) 4.44×10^{-3}; (7) visible band for complex in solution (4)

Figure 2: Plot of Lang equation for the clotrimazole-iodine complex at 20°C. The linear regression equations are:

(1) 390 nm $Y = 4.97 \times 10^{-4}X + 1.09 \times 10^{-6}$ $(Z = 0.999)$

(2) 400 nm $Y = 4.91 \times 10^{-4} X + 0.97 \times 10^{-6}$ $(Z = 0.999)$

Formation constants Kc and molar extinction coefficients ϵc were derived from equation (1):

$$Kc = \frac{|C|}{(|Ao| - |C|)(|Do| - |C|)} \qquad (1)$$

where $|C|$ is the concentration of complex, $|Ao|$ is the initial acceptor concentration and $|Do|$ the initial donor concentration. The term $|C|$ of equation (1) can be replaced by $dc/\epsilon c$ giving equation (2):

$$|Ao||Do|/dc = |Ao| + |Do| - dc/\epsilon c \quad 1/\epsilon c + 1/Kc\epsilon c \qquad (2)$$

where dc is the absorbance of the complex, ϵc is the molar extinction coefficient of the complex at the given wavelength and Kc is the formation constant of the complex. In order to solve equation (2) using a least squares fit the value of ϵc must be calculated. An iterative method using a computer was employed. The graphical representation of the term $|Ao||Do|/dc$ as a function of $|Ao| + |Do| - dc/\epsilon c$ produces a straight line of slope $1/\epsilon c$ and intercept $1/Kc\epsilon c$ (Fig.2). The formation constants Kc and the molar extinction coefficients of the various donor-acceptor systems are shown in tables I and II.

Table I - Formation constants (Kc) and Molar extinction coefficients (ϵc) for iodine complexes in solution in carbon tetrachloride [a]

Donor	λ (nm)	ϵc ($l.M^{-1}.cm^{-1}$) [f]	Kc ($l.M^{-1}$) [f]	Mean Kc
N-methylimidazole [b]	400	1,638	422	
	405	1,630	422	426 ± 7
	410	1,576	434	
Methimazole [c]	425	4,683	23,419	
	430	4,416	22,921	
	435	4,062	24,098	23,194 ± 667
	440	3,759	23,162	
	445	3,469	22,095	
	450	3,002	23,470	
Clotrimazole [d]	390	2,013	455	
	395	2,049	480	
	400	2,038	505	499 ± 32
	405	2,000	518	
	410	1,905	538	
Tetrahydrozoline [e]	375	17,680	270	
	385	20,510	248	308 ± 72
	395	12,961	410	
	405	14,697	302	

[a] 20 ± 0.1 °C

[b] 8 different N-methylimidazole-I_2 solutions; $|I_2|$ 3.72×10^{-4} M; |N-methylimidazole| varied from 0.52×10^{-3} to 7.5×10^{-3} M

[c] 4 different methimazole-I_2 solutions; $|I_2|$ $6.1\ 7 \times 10^{-5}$ M; |methimazole| varied from 4.69×10^{-5} to 1.88×10^{-4} M

[d] 5 different clotrimazole-I_2 solutions; $|I_2|$ 4.37×10^{-4} M; |clotrimazole| varied from 0.89×10^{-3} to 4.44×10^{-3} M

[e] 3 different tetrahydrozoline-I_2 solutions; $|I_2|$ 4.03×10^{-4} M; |tetrahydrozoline| varied from 0.56×10^{-4} to 1.69×10^{-3} M

[f] Values were calculated from absorption data in the visible region

Table II - Formation constants (Kc) and Molar extinction coefficients (ϵc) for iodine complexes in solution in carbon tetrachloride and chloroform [a]

Donor	λ (nm)	ϵc ($l.M^{-1}.cm^{-1}$) [d]	Kc ($l.M^{-1}$) [d]	Mean Kc
N-methylimidazole [b]	380	1,490	171	
	385	1,565	164	
	390	1,602	159	163 ± 4
	395	1,599	160	
	400	1,550	160	
Levamisole [c]	400	2,370	818	
	410	1,863	858	
	420	1,451	837	841 ± 17
	425	1,247	850	

a 20 ± 0.1 °C

b 4 different N-methylimidazole-I_2 solutions; $|I_2|$ 4.06 x 10^{-4} M; |N-methylimidazole| varied from 0.33 x 10^{-2} to 1.64 x 10^{-2} M

c 4 different levamisole-I_2 solutions; $|I_2|$ 4.067 x 10^{-4} M; |levamisole| varied from 0.38 x 10^{-3} to 1.27 x 10^{-3} M

d Values were calculated from absorption data in the visible region

UV region

All donors studied had a characteristic absorption in the UV region. The iodinated complexes have different spectral characteristics, and a typical spectrum of the iodine N-methylimidazole complex is shown in figure 3. By subtracting the absorbances due to free iodine and free donor, curve 4, corresponding to the complex was obtained. This charge transfer complex had a peak at 255 nm. Another absorption band between 290 and 300 nm could sometimes be observed, which is characteristic of I_3^- ions (Fig.4). Table III shows the UV spectral parameters.

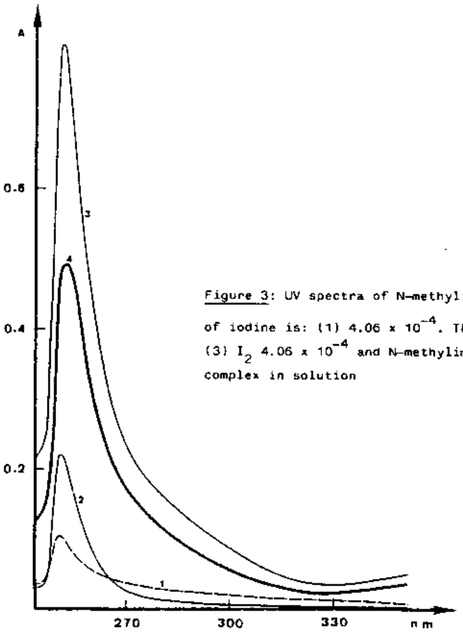


Figure 3: UV spectra of N-methylimidazole-I_2 complex in $CCl_4/CHCl_3$ at 20°C. The molar concentration of iodine is: (1) 4.06 x 10^{-4}. The molar concentrations of N-methylimidazole are: (2) 1.64 x 10^{-3}; (3) I_2 4.06 x 10^{-4} and N-methylimidazole 1.64 x 10^{-3}; (4) calculated charge transfer band for complex in solution

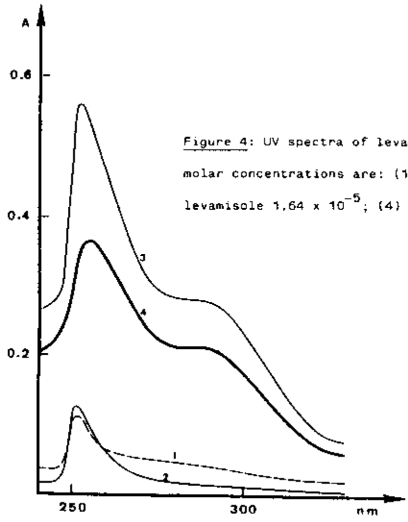


Figure 4: UV spectra of levamisole-I_2 complex in $CCl_4/CHCl_3$ at ambient temperature (≈ 20°C). The molar concentrations are: (1) I_2 4.06×10^{-4}; (2) levamisole 6.36×10^{-5}; (3) I_2 4.06×10^{-4} and levamisole 1.64×10^{-5}; (4) calculated absorption band for complex in solution.

Table III - Absorption peaks for charge transfer bands (CTB) for the various donor-acceptor complexes

Complexes	λ max of CTB
N-methylimidazole-I_2	260 [a]; 255 [b]
Methimazole-I_2	272 [a]
Clotrimazole-I_2	275 [a]
Tetrahydrozoline-I_2	258 [a]
Levamisole-I_2	256 [b]

a Results for complexes in carbon tetrachloride
b Results for complexes in carbon tetrachloride/chloroform

CONCLUSION

Spectroscopic analysis of the charge transfer complexes of these derivatives with iodine demonstrates the n-σ characters of these complexes. They have a 1:1 stoichiometry, and the results indicate strong donor-acceptor interaction. The reaction of complex formation is accompanied by the formation of I_3^- ions. The "outer complex" is transformed into an "inner complex" liberating I^- ions which react with molecular iodine.

$$\text{Donor} + I_2 \rightleftharpoons \text{Donor-}I_2 \quad \text{(outer complex)}$$
$$\text{Donor-}I_2 \rightleftharpoons \text{Donor-}I^+I^-$$
$$\text{Donor-}I^+I^- \rightleftharpoons |\text{Donor-}I|^+ + I^- \quad \text{(inner complex)}$$
$$I^- + I_2 \longrightarrow I_3^-$$

Previous work from our laboratory[4,5,7,8] has demonstrated that antithyroid activity can be expected from molecules whose formation constant of the iodinated complex Kc exceeds 100 $l.M^{-1}$. Above this value, antithyroid activity is directly related to the value of this constant. For methimazole, the strongest antithyroid agent, we found a value of 23,194 $l.M^{-1}$ for Kc. The other molecules tested, N-methylimidazole, clotrimazole, levamisole, and tetrahydrozoline also have values of Kc considerably above 100 $l.M^{-1}$, and can therefore be expected to interfere with thyroid metabolism. Furthermore, the values of Kc that we found agree with those from animal studies[9].

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