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Charge transfer complexes of drugs with iodine investigation by UV/visible spectroscopy

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Summary

Inspection of the chemical structure of various drugs suggests that they might interfere with thyroid metabolism by complexing molecular iodine in the thyroid gland. Spectroscopic analysis shows that such compounds form charge transfer complexes with iodine in a 1 : 1 stoichiometry. Strong donor–acceptor interactions were indicated by the high values of formation constant K_c for the iodine/drug complexes.

Introduction

Recent work in this laboratory has demonstrated strong interactions between synthetic antithyroid drugs (SAT) and molecular iodine. The charge transfer complexes formed have been shown to inhibit synthesis of thyroid hormones (Raby and Buxeraud, 1980; Buxeraud et al., 1985). A correlation was established between the antithyroid activity of the agent and the value of K_c for its complex with iodine. This relationship suggested that any strong electron donor would possess antithyroid activity. We investigated this possibility for a large number of molecules of pharmacological importance.

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Materials and Methods

Compounds

Iodine was bisublimed (Merck suprapur 4763), and was used without further purification. It was stored in the dark in a desiccator containing P_2O_5. The other compounds were commercially available. Since they were often in the form of the salt (hydrochloride or tartrate), the free bases were liberated in order to prepare solutions in organic solvents. The free bases were purified by HPLC. Carbon tetrachloride, chloroform and methylene dichloride were spectroscopic grade (Merck Uvasol), and were used without further purification.

Apparatus

The spectra were recorded on a double-beam Perkin-Elmer 554 UV/visible spectrophotometer equipped with a Peltier effect thermostated sam-

ple-holder. The temperature of the sample cells was regulated to $\pm 0.1°C$. The quartz sample cells had an optical path length of 1 cm.

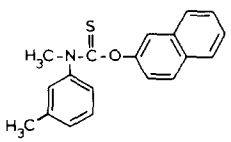
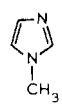
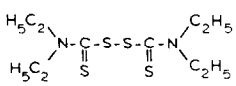
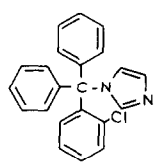
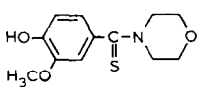
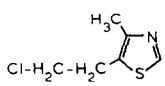
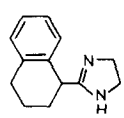
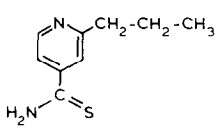
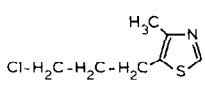
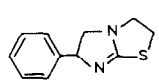
The chromatographic apparatus consisted of a Waters model 150 pump, U6K injector and model 440 detector connected to an Omniscribe model D 5000 chart recorder. A semi-preparative column was used (Bondapak C18, 7.8 mm diameter 3 cm long).

Procedure

The solutions of donor and acceptor were prepared just before use by dilution of stock solutions made up by accurate weighing.

TABLE 1

Structures of the drugs studied: molecules similar to synthetic antithyroid agents (SAT)

MOLECULES WITH AN NCS GROUP	MOLECULES DERIVATED OF THIAZOLE	MOLECULES DERIVATED OF IMIDAZOLE
 TOLNAFTATE	 THIAZOLE	 IMIDAZOLE  N-CH_3 IMIDAZOLE
 DISULFIRAM	 4-METHYL THIAZOLE	 CLOTRIMAZOLE
 VANITIOLIDE	 CLOMETHIAZOLE	 TETRAHYDROZOLINE
 PROTHIONAMIDE	 CLOPROTHIAZOLE	 LEVAMISOLE

The reactions were carried out directly in the sample cells by mixing 1.5 ml of the donor solution with 1.5 ml of the acceptor solution. The spectra were then recorded immediately. Measurements were carried out at different time intervals in order to study the stability of the complexes formed.

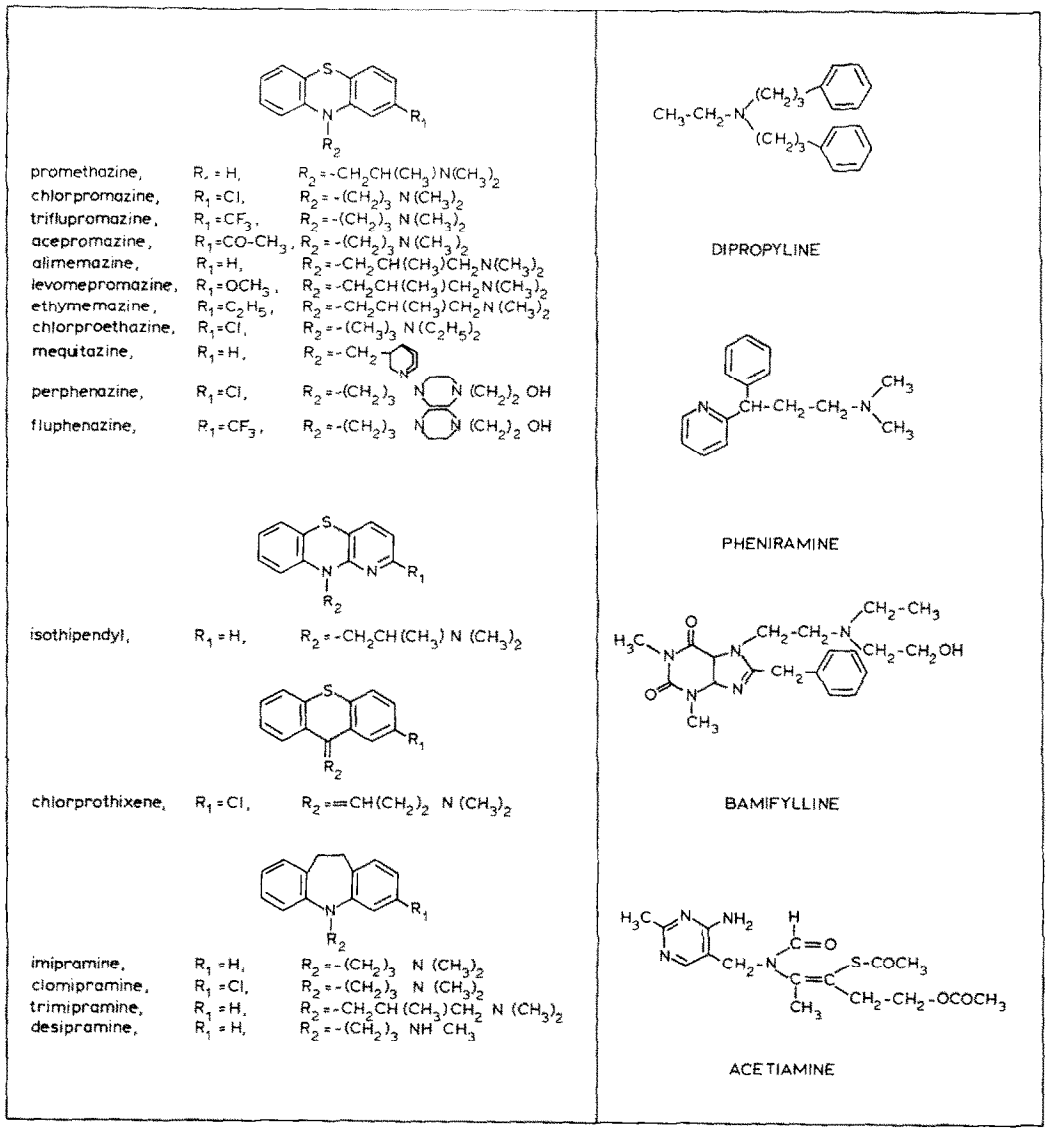
The thermodynamic parameters were evaluated by measuring the absorbance of a series of solutions as a function of temperature.

Results

Initially we investigated drugs of similar structure to SAT agents. These compounds possessed

TABLE 2

Structures of the drugs studied: molecules with a tertiary amino group



an NCS group (disulfiram, vanitiolide, etc.) or were derivatives of thiazole (clomethiazole, cloprothiazole, etc.) or imidazole (clotrimazol, levamisole, etc.). In the latter cases, measurements were also made on the parent compounds (thiazole and imidazole) in order to examine the effects of the substituents (Table 1).

Given the electron donor character of amino groups (Nagakura, 1958), we also investigated drugs containing electron-donating amino groups. They included compounds derived from phenothiazine and its isosters (promethazine, chlorpromazine, etc.), molecules derived from iminobenzyl (imipramine, etc.), from propylamine (pheniramine) and two other unrelated drugs (dipropyline and acetiamine). Table 2 lists the various compounds studied.

Visible region

Carbon tetrachloride was chosen as solvent due to its non-polar nature. Where the compounds under investigation were only poorly soluble in this solvent, we employed mixtures of chloroform and carbon tetrachloride, Unreliable results were obtained with chloroform alone. Methylene dichloride was only used for prothionamide.

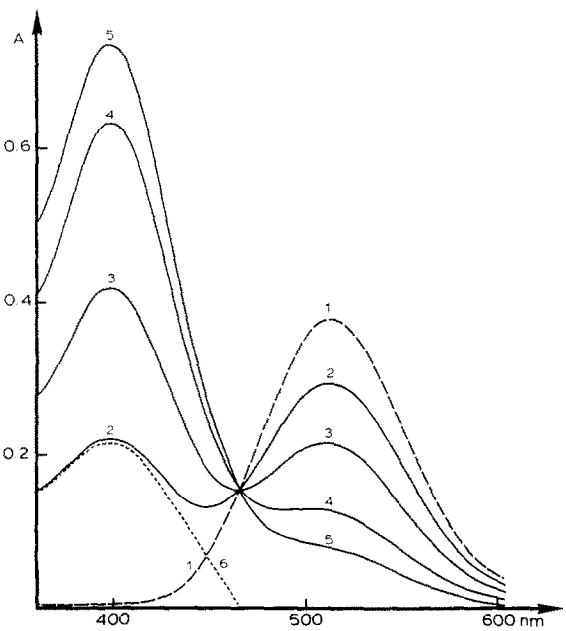


Fig. 1. Visible absorption spectra of desipramine–iodine complex in solution in CCl_4 (t = 20 °C). The concentration (M) of iodine is fixed at 4.209×10^{-4}. The concentrations (M) of desipramine are: (1) 0; (2) 0.200×10^{-3}; (3) 0.401×10^{-3}; (4) 0.802×10^{-3}; (5) 1.336×10^{-3}; (6) visible band calculated for complex in solution (2).

Addition of a solution of iodine to the donor solution leads to a hypsochromic shift of the iodine absorption band (515 nm). These "blue shifted bands" can be attributed to complex formation with iodine (Fig. 1). The intensity of the new band was found to increase with increasing donor concentration (at fixed iodine concentration). The curves obtained crossed at a single isobestic point, which for the desipramine–iodine complex was observed at 465 nm (Fig. 1). The absorption peak of the complex was evaluated by placing a solution of iodine in the reference beam. The native donor molecules do not absorb light at these wavelengths. Only vanitiolide and prothionamide showed some absorption at these wavelengths. For these two drugs, the absorption due to the complex was obtained by subtracting the absorption due to iodine from that due to the native drug.

For donors that do not absorb at the wavelengths used, the formation constants (K_c) of the complexes were calculated using Lang's method (Lang, 1962, 1968; Absil et al., 1984), based on the following equation:

$$|A_0||D_0| = 1/\epsilon_c(|D_0| + |A_0| - d_c/\epsilon_c) + 1/K_C\epsilon_c \quad (1)$$

where $|A_0|$ and $|D_0|$ are initial concentrations of acceptor and donor, respectively, ϵ_c is the molar extinction coefficient and K_c is the formation constant of the complex, and d_c is the absorbance of the complex itself. The value d_c is derived from the following equation:

$$d_c = d_s - d_{A_0} \quad (2)$$

where d_s is the measured optical density and d_{A_0} is the optical density of the free iodine.

The value of ϵ_c is required in order to solve Eqn. 1. This was computed iteratively using a least-squares method. The plot of $|A_0||D_0|/d_c$ against $|A_0| + |D_0| - d_c/\epsilon_c$ gives a straight line

of slope $1/\epsilon_c$ and intercept $1/K_c\epsilon_c$ (Fig. 2).

For a donor that absorbs at the wavelengths used, the method of Rose and Drago is applicable (Rose and Drago, 1959; Drago and Rose, 1959), based on the following equation:

$$K_c^{-1} = \frac{d_s - d_{A_0}}{\epsilon_c - \epsilon_a} - |A_0| - |D_0| + \frac{|A_0||D_0|(\epsilon_c - \epsilon_a)}{d_s - d_{A_0}} \quad (3)$$

ϵ_a is the molar extinction coefficient of the acceptor. This equation can be solved graphically, although this is tedious. Rearrangement of Eqn. 3 gives (Absil, 1984);

$$|A_0||D_0| = \frac{1}{\epsilon_c - \epsilon_a} \cdot ||D_0| + |A_0| - \frac{d_c}{\epsilon_c - \epsilon_a}| + 1/K_c(\epsilon_c - \epsilon_a) \quad (4)$$

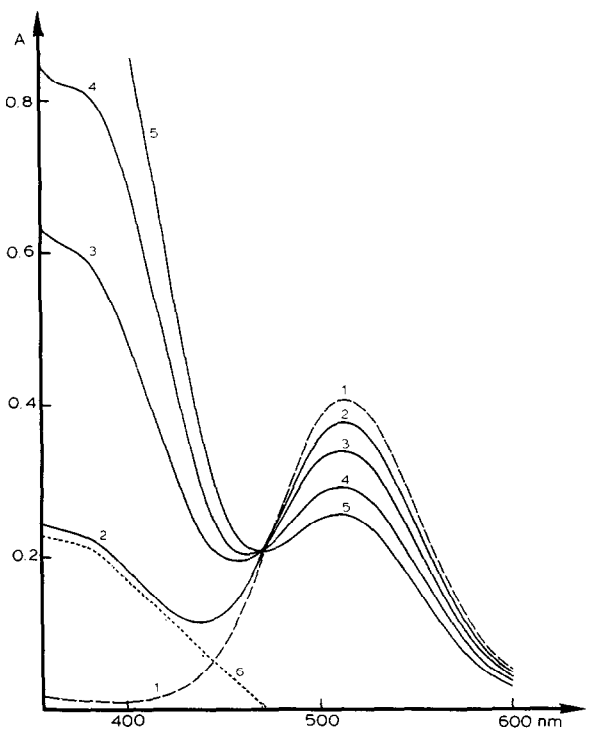


Fig. 2. Visible absorption spectra of acepromazine–iodine complex in solution in CCl_4 (t = 20°C). The concentration (M) of iodine is fixed at 4.45×10^{-4}. The concentrations (M) of desipramine are: (1) 0; (2) 0.766×10^{-4}; (3) 1.916×10^{-4}; (4) 2.879×10^{-4}; (5) 3.832×10^{-4}; (6) visible band calculated for complex in solution(2).

TABLE 3

Formation constants for complexes with iodine. Determined using Lang's method at 20°C in carbon tetrachloride

	K_c ($l \cdot mol^{-1}$)
Tolnaftate	57
Disulfiram	297
Vanitiolide	653 [1]
Prothionamide	–
Thiazole	10
4-methyl thiazole	22
Clomethiazole	25
Cloprothiazole	31
Imidazole	–
N-methylimidazole	426
	163 [2]
Clotrimazole	499
Tetrahydrozoline	308
Levamisole	841 [2]
Dipropyline	1715
Promethazine	4259 [a]
Chlorpromazine	3168
Triflupromazine	2803
Alimemazine	788
Acepromazine	–
Levomepromazine	738
Ethymemazine	731
Chlorproethazine	2507
Mequitazine	–
Perphenazine	1074
Fluphenazine	1115
Isothipendyl	2683
Chlorprothixene	3401
Imipramine	4907 [b]
Clomipramine	4545 [b]
Trimipramine	1003
Desipramine	2987
Pheniramine	–
Bamifylline	57 [1,c]
Acetiamine	216

[1] K_c determined using Rose and Drago's (1959) method.
[2] Studied in $CHCl_3/CCl_4$ mixture.
[a] K_c determined at 17°C.
[b] K_c determined at 22°C.
[c] K_c determined at 25°C.

This equation resembles Eqn. 1, since ϵ_a is zero for non-absorbing donors. This formulation of Rose and Drago's equation can be solved by a least-squares method.

Table 3 shows the values of K_c for the iodine complexes. They were calculated for temperatures ranging from 17 to 25°C. Most determinations were carried out at 20°C. The thermodynamic studies showed that over this temperature range the values of K_c only altered by about 20%. No order of magnitude change in K_c is therefore observed over this temperature range.

K_c values could not be measured for some of the complexes. In some cases, the complexes were not sufficiently stable for measurement at ambient temperature. The almost immediate appearance of I_3^- ions was detected by the characteristic peaks at 360 nm (Fig. 2) and 290 nm. This was the case for prothionamide, imidazole, acepromazine and oxomemazine. For pheniramine and mequitazine, complexes of 2:1 stoichiometry were detected. Both these compounds possess two electron-donating sites. For pheniramine, they correspond to the propylamine nitrogen and the nitrogen atom in the pyridine ring. For mequitazine, the nitrogen atom in the quinuclidine ring might not be sufficiently active to function as an electron donor, but the 10 *N*-atom on the phenothiazine ring could be involved (Table 2). K_c values cannot be calculated for complexes with 2:1 stoichiometry using the equations described above, which are only valid for 1:1 complexes.

The effect of solvent can be seen in the case of *N*-methylimidazole. More complex was formed in CCl_4 than in a mixture of CCl_4 and $CHCl_3$ (Table 3). This was used as a reference for interpretation of the results for bamifylline and levamisole which were not very soluble in CCl_4. A mixture of CCl_4 and $CHCl_3$ was therefore employed for these two drugs. It is probable that the K_c values for these two compounds would have been higher in pure CCl_4.

Thermodynamic parameters were determined for the stable complexes. The plot of $R \cdot \ln(K_c)$ against $1/T$ gives a straight line of slope $\Delta H°$ and intercept $\Delta S°$ (Fig. 3). Table 4 shows the various measured thermodynamic parameters. Recording the spectra of the "blue shifted bands" at

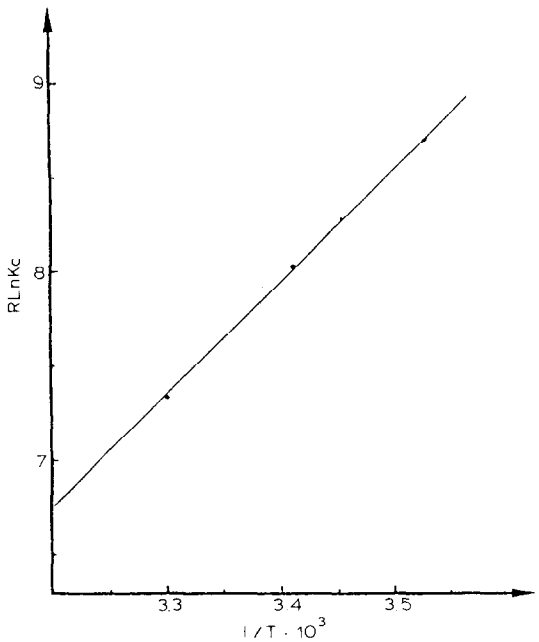


Fig. 3. Plot of $R \cdot \ln(K_c)$ against $1/T$ for the tolnaftate–iodine complex. The linear regression equation is: $y = 5.8x - 11.79$ ($z = 0.999$).

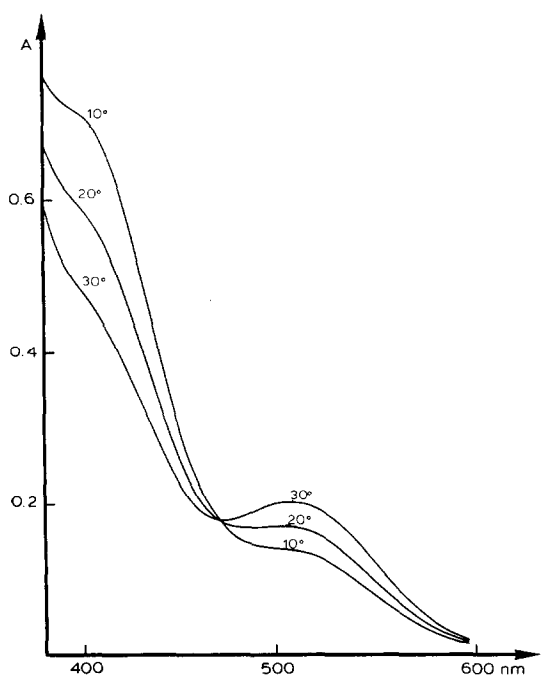


Fig. 4. Effect of temperature on the iodine complex with triflupromazine in CCl_4. The concentrations of iodine and triflupromazine are: 4.58×10^{-4} M, and 3.02×10^{-4} M, respectively.

TABLE 4

Thermodynamic parameters ± S.D. for several complexes in carbon tetrachloride

Complexes	$\Delta H°$ (kcal · mol^{-1})	$\Delta S°$ (cal · mol^{-1} · °K^{-1})	$\Delta G°_{293K}$ (kcal · mol^{-1})
Tolnaftate–iodide	5.80 ± 0.12	11.79 ± 0.49	2.35 ± 0.01
Disulfiram–iodide	6.96 ± 0.30	12.48 ± 1.04	3.32 ± 0.01
Thiazole–iodide	5.39 ± 0.16	13.72 ± 0.55	1.36 ± 0.02
4-methylthiazole–iodide	6.81 ± 0.14	17.21 ± 0.56	1.79 ± 0.02
Clomethiazole–iodide	7.08 ± 0.14	17.76 ± 0.50	1.87 ± 0.005
Cloprothiazole–iodide	6.68 ± 0.17	15.99 ± 0.57	2.00 ± 0.01
N-methyl imidazole–iodide	8.63 ± 0.74	17.3 ± 2.50	3.47 ± 0.02
Clotrimazole–iodide	10.95 ± 0.51	25.06 ± 1.89	3.62 ± 0.04
Chlorpromazine–iodide	11.17 ± 0.06	22.10 ± 0.22	4.70 ± 0.008
Trifluprazine–iodide	10.11 ± 0.21	18.64 ± 0.75	4.63 ± 0.02

different temperatures showed that the intensity of the absorption fell rapidly with increasing temperature (Fig. 4).

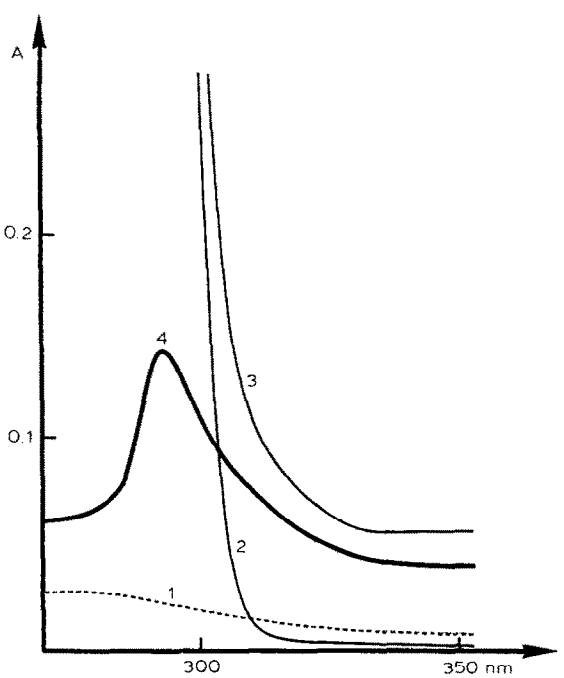


Fig. 5. UV spectra of bamifylline–iodine complex in $CCl_4/CHCl_3$ ($t = 25°C$). The concentrations (M) are: (1) I_2 3.730×10^{-4}; (2) bamifylline 2.330×10^{-4}; (3) I_2 3.730×10^{-4}; and bamifylline 2.330×10^{-4}; (4) calculated charge transfer band for complex.

TABLE 5

Absorption peaks for charge transfer bands (CTB) for various donor – acceptor complexes

	CTB λ_{max} (nm)
Tolnaftate	338
Disulfiram	310
Vanitiolide	330
Prothionamide	–
Thiazole	263
4-methyl thiazole	268
Clomethiazole	276
Cloprothiazole	278
Imidazole	253
N-methylimidazole	255
Clotrimazole	275
Tetrahydrozoline	258
Levamisole	256
Dipropyline	284
Promethazine	278–280
Chlorpromazine	264
Trifluprazine	272
Alimemazine	259
Acepromazine	266
Levomepromazine	279
Ethymemazine	264
Chlorprocthazine	260
Mequitazine	–
Perphenazine	275
Fluphenazine	275
Isothipendyl	268
Chlorprothixene	258
Imipramine	272
Clomipramine	266
Trimipramine	275
Desipramine	258
Pheniramine	–
Bamifylline	294
Acetiamine	258

UV region

The donor molecules at the concentrations used in this study (10^{-5}–10^{-6} M) absorb in the ultraviolet. The formation of the donor–acceptor complex leads to the appearance of a new absorption band in the near ultraviolet. This new band, called a charge transfer band (CTB), is characteristic for each complex. The peak is derived by placing in the reference beam a solution of donor at the same concentration as that in the complex. The absorption due to iodine must then be subtracted mathematically (Fig. 5). The CTBs are masked to some extent both by the absorbances of the donor and acceptor molecules themselves and by the presence of I_3^- ions. The CTBs are thus derived by extrapolation. Table 5 shows the peak values of the CTBs for the various systems studied.

Discussion

The drugs studied here were found to form *n–o* type charge transfer complexes with iodine. 1 : 1 stoichiometry was observed for most of the complexes. It was assumed from the presence of a single isobestic point and the linearity of the experimental points (Fig. 2). For some of the complexes, the stoichiometry was checked using the method of continuous variations described by Job (Absil, 1984; Job, 1928).

Previous work in this laboratory suggested that a given molecule would have antithyroid activity if the K_c value for the iodine complex was above a threshold of 100 $l \cdot mol^{-1}$, with a direct relationship between K_c and activity above this value. This is the value found for the complex KSCN–iodine at 20°C. It should be remembered that KSCN was used at one time as an antithyroid agent (Buxeraud et al., 1984, 1985). In addition, the K_c value for mercapto-2-thiazoline, which was also used for a long time as an antithyroid agent, was found to be around 2500 $l \cdot mol^{-1}$ (Buxeraud et al., 1984, 1985). From the results presented in Table 3, it can be seen that, apart from tolnaftate, and thiazole and its derivatives, all the other drug complexes had K_c values well above 100 $l \cdot mol^{-1}$. The complexes of phenothiazines (promethazine, chlorpromazine, triflupromazine, chlorproethazine, isothipendyl, chlorprothixene) and of imipramines, especially imipramine ($K_c = 4907$ $l \cdot mol^{-1}$) and clomipramine ($K_c = 4545$ $l \cdot mol^{-1}$) all had values close to or above 2500 $l \cdot mol^{-1}$.

It would appear, therefore, that the high capacity of these compounds to complex iodine could lead one to suspect that they would interfere with thyroid metabolism.

A few clinical studies on the effects of these agents on thyroid function have been reported. For example, Gwinup and Rapp (1975) and Wenzel (1981) have shown a significant fall in serum thyroxine after long-term treatment with phenothiazines, although no mechanism of action was proposed. In addition, the manufacturer's documentation on tetrahydrozoline and bamifylline has pointed out that thyroid dysfunction is a contra-indication for prescription of these drugs. Although no mechanism of action has been proposed. These considerations would suggest that these agents do in fact interact with the thyroid.

In conclusion, we can point out that the chemical structure of certain drugs suggests that they would have an effect on the thyroid. The value of the formation constants can be compared to known anti-thyroid agents such as mercapto-2-thiazoline ($K_c = 2500$ $l \cdot mol^{-1}$), or methimizole which is the only anti-thyroid drug presently available ($K_c =$ 23 000 $l \cdot mol^{-1}$; Buxeraud et al., 1985).

Our technique would therefore be able to determine rapidly whether long-term treatment with a given drug could be suspected to lead to an inhibition of thyroid function.

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