Chem. Pharm. Bull. 37(1) 151—154 (1989)

Spectroscopic Analysis of Charge Transfer Complex Formation between Neuroleptics and Iodine

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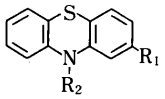
Molecular interactions between iodine and various neuroleptics were investigated by UV/Vis spectroscopy. Iodine was found to form charge transfer complexes in a 1 : 1 stoichiometry and of *n*-σ type with these molecules. The values of the formation constants K_c of these iodinated complexes indicate a strong donor–acceptor interaction. These drugs can therefore be expected to interfere with thyroid metabolism.

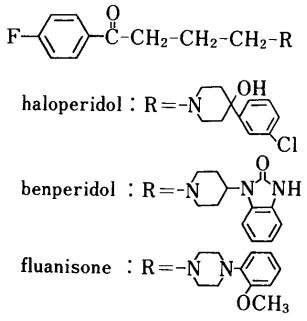
Keywords neuroleptic; charge transfer complex; iodine; formation constant; potential iatrogenic thyroïd dysfunction

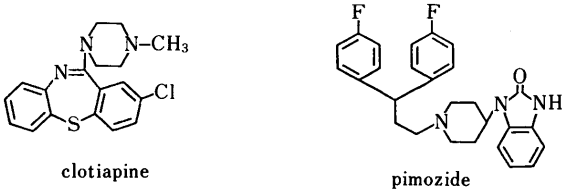
Strong molecular interactions between synthetic antithyroid agents (SAT) and iodine have been found to be due to the formation of charge transfer complexes. Formation of such complexes can inhibit thyroid hormone synthesis.[1,2]

In the course of a systematic investigation of potential thyrotoxicity of drugs not principally designed for action on the thyroid, many agents were found to form complexes with molecular iodine. This study presents the results of a spectroscopic analysis of the molecular interactions between various neuroleptic drugs and iodine. These molecules were chosen because their structures contain a tertiary amino-chain, Nagakura[3] and Yada *et al.*[4] showed that amines were capable of complexing molecular iodine.



chlorpromazine	$R_1=Cl$	$R_2=(CH_2)_3N(CH_3)_2$
acepromazine	$R_1=COCH_3$	$R_2=(CH_2)_3N(CH_3)_2$
triflupromazine	$R_1=CF_3$	$R_2=(CH_2)_3N(CH_3)_2$
levomepromazine	$R_1=OCH_3$	$R_2=CH_2CH(CH_3)CH_2N(CH_3)_2$
cyamemazine	$R_1=CN$	$R_2=CH_2CH(CH_3)CH_2N(CH_3)_2$
alimemazine	$R_1=H$	$R_2=CH_2CH(CH_3)CH_2N(CH_3)_2$
pipotiazine	$R_1=SO_2N(CH_3)_2$	$R_2=(CH_2)_3N$-$(CH_2)_2OH$
propericiazine	$R_1=C\equiv N$	$R_2=(CH_2)_3N$-OH
perimetazine	$R_1=OCH_3$	$R_2=CH_2CH(CH_3)CH_2N$-OH
perphenazine	$R_1=Cl$	$R_2=(CH_2)_3N$-$N(CH_2)_2OH$
fluphenazine	$R_1=CF_3$	$R_2=(CH_2)_3N$-$N(CH_2)_2OH$





clotiapine pimozide

Chart 1. Chemical Structures of the Neuroleptics Studied

Results

The neuroleptics used belong to different chemical classes of compounds, namely (Chart 1): phenothiazine derivatives (chlorpromazine, pipothiazine, *etc.*; derivatives of dibenzothiazepine (clotiapine); derivatives of butyrophenones and related compounds (haloperidol, benperidol, *etc.*).

Visible Region The solutions of iodine and donor were both made up in the same solvent. In most cases, carbon tetrachloride was used due to its apolar nature. However, in some cases due to solubility problems (*e.g.* pimozide[5]) a mixture of chloroform and carbon tetrachloride was used. Pure chloroform was only employed in the case of haloperidol.

At concentrations between 10^{-3} to 10^{-4} M·dm^{-3}, 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). The new absorption bands corresponding to the iodinated complexes all showed an isobestic point, which for the haloperidol–iodine complex was observed at 460 nm (Fig. 1). For each system, the absorption peak of the complex was measured by employing a solution of iodine for which the concentration was determined as a function of the quantity of free iodine. In other words, the calculation was performed using the absorption maximum of the visible band of iodine.

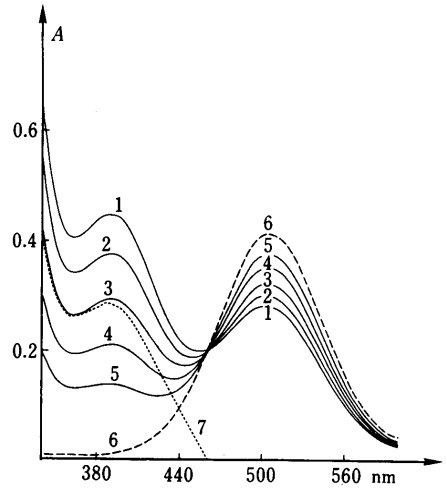


Fig. 1. Visible Absorption Spectrum of the Haloperidol–Iodine Complex in $CHCl_3$ at Ambient Temperature (*ca.* 20 °C)

The iodine concentration was fixed at 5.57×10^{-4} M. The concentrations of haloperidol (M) were: (1) 3.99×10^{-4}, (2) 3.19×10^{-4}, (3) 2.39×10^{-4}, (4) 1.60×10^{-4}, (5) 7.98×10^{-5}, (6) 0, (7) calculated visible band of complex for solution (3).

Formation constants, K_c of the drug–I_2 complexes were evaluated from the blue-shifted bands by the method of Lang[6-8] using the following equation:

$$[A_o][D_o]/d_c = 1/\varepsilon_c[[D_o]+[A_o]-d_c/\varepsilon_c]+1/K_c\varepsilon_c \quad (1)$$

where at the given wavelength $[A_o]$ and $[D_o]$ are initial concentrations of acceptor and donor, d_c is the absorbance of the complex, ε_c is the molar extinction coefficient of the complex, and K_c is the formation constant of the complex. The value of d_c was derived from:

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

where d_s is the optical density of the solution of the complex, d_{A_o} is the calculated optical density of the free iodine. In order to solve Eq. 1 by the least-squares method, the value of ε_c must be calculated. An iterative method using a computer program was employed. The graphical representation of the term $[A_o][D_o]/d_c$ as a function of $[A_o]+[D_o]-d_c/\varepsilon_c$ produces a straight line of slope $1/\varepsilon_c$ and intercept $1/K_c\varepsilon_c$ (Fig. 2).

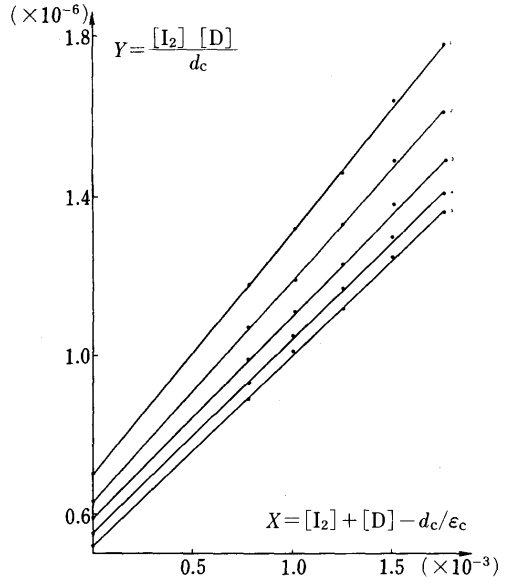


Fig. 2. Plot of Lang Equations for the Pimozide–Iodine Complex

The experiment was carried out in $CCl_4/CHCl_3$ at ambient temperature (*ca.* 20 °C). The regression lines are given by the following equations:
(1) 430 nm: $Y=6.17\times10^{-4}X+6.97\times10^{-7}$ ($r=0.999$)
(2) 425 nm: $Y=5.58\times10^{-4}X+6.33\times10^{-7}$ ($r=0.999$)
(3) 420 nm: $Y=5.18\times10^{-4}X+5.86\times10^{-7}$ ($r=0.999$)
(4) 415 nm: $Y=4.92\times10^{-4}X+5.54\times10^{-7}$ ($r=0.999$)
(5) 405 nm: $Y=4.80\times10^{-4}X+5.24\times10^{-7}$ ($r=0.999$)

TABLE I. Formation Constants K_c for the Drug–Iodine Complexes. Determination by the Method of Lang in Carbon Tetrachloride (*ca.* 20 °C)

	K_c ($l\cdot mol^{-1}$)		K_c ($l\cdot mol^{-1}$)
Chlorpromazine	3169	Perimetazine	n.a.[a]
Acepromazine	n.a.	Perphenazine	1074
Triflupromazine	2803	Fluphenazine	1115
Levomepromazine	741	Clotiapine	n.a.
Cyamemazine	n.a.[a]	Haloperidol	n.a.[b]
Alimemazine	788	Benperidol	503[a]
Pipotiazine	1179[a]	Fluanisone	n.a.
Propericiazine	n.a.[a]	Pimozide	889[a]

n.a.: not available. *a*) In a mixture of $CHCl_3$ and CCl_4. *b*) In $CHCl_3$.

The formation constants K_c and the molar extinction coefficients of the various donor–acceptor systems are shown in Table I. They were all determined at ambient temperature (*ca.* 20 °C). In some cases, formation constants could not be determined due to the instability of the complexes. This instability was indicated by the almost immediate production of I_3^- ions which are detected from their absorbances at 360 nm (Fig. 3) and 290 nm. This phenomenon was observed in all cases where formation constants could not be determined (acepromazine–iodine, clotiapine–iodine, perimetazine–iodine, *etc.*).

Thermodynamic analysis was only possible for the chlorpromazine–iodine and triflupromazine–iodine complexes (Table II).

To confirm that only one complex was formed, we carried out a matrix analysis as described by Liptay.[9] This

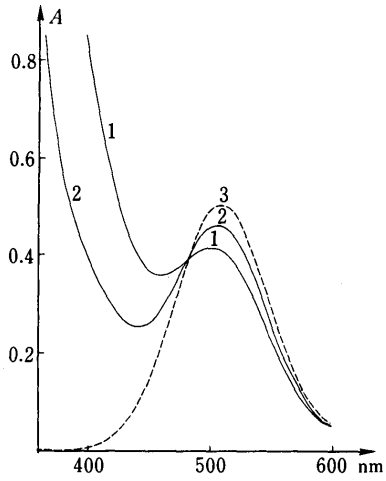


Fig. 3. Visible Absorption Spectra of the Perimetazine–Iodine Complex in $CCl_4/CHCl_3$ at Ambient Temperature (*ca.* 20 °C)

The iodine concentration was fixed at 5.74×10^{-4} M. The concentrations (M) of perimetazine are: (1) 1.02×10^{-3}, (2) 5.11×10^{-4}, (3) 0.

TABLE II. Thermodynamic Data on the Chlorpromazine–Iodine and Triflupromazine–Iodine Complexes

	Chlorpromazine–iodine	Triflupromazine–iodine
$-\Delta H$ kcal mol^{-1}	11.17±0.06	10.11±0.21
$-\Delta S^\circ$ kcal mol^{-1} K	22.10±0.22	18.64±0.75
$-\Delta G^\circ_{293K}$ kcal mol^{-1}	4.70±0.008	4.63±0.02

TABLE III. Liptay Matrix for the Clotiapine–Iodine Complex (*ca.* 20 °C)

λ (nm)	Sol. 1	Sol. 2	Sol. 3	Sol. 4	Sol. 5
1) Liptay matrix of corrected absorbances (A_{corr})[a]					
410	0.663	0.564	0.461	0.316	0.167
415	0.648	0.551	0.451	0.310	0.163
420	0.621	0.529	0.433	0.297	0.157
425	0.584	0.497	0.407	0.379	0.147
2) Values referred to 410 nm					
	1	1	1	1	1
	0.977	0.977	0.978	0.981	0.976
	0.937	0.938	0.939	0.940	0.940
	0.881	0.881	0.883	0.883	0.880

a) Concentrations (M) of components of the 5 solutions: $[I_2]$ fixed at 5.79×10^{-4}; [clotiapine] sol. $1=5.38\times10^{-4}$; sol. $2=4.30\times10^{-4}$; sol. $3=3.23\times10^{4}$; sol. $4=2.15\times10^{-4}$; sol. $5=1.08\times10^{-4}$.

was particularly important in cases where formation constants could not be determined. Examination of the chemical structures of the various drugs suggested that several groups could potentially bind with iodine. Table III shows the results of the matrix analysis at 410, 415, 420 and 425 nm for the clotiapine–iodine reaction. The absorbances of a series of solutions of the complex were recorded. The calculated absorbance of non-complexed iodine was subtracted from each value. Since the donor does not absorb in this region, only that due to free iodine needs to be taken into account.

$$A_{corr} = A_{obs} - \varepsilon_{I_2}[I_2] \quad (3)$$

A_{corr} is the corrected absorbance of the complex. A_{obs} is the absorbance of the donor–iodine mixture, and ε_{I_2} is the molar extinction coefficient of iodine, $[I_2]$ is the concentration of noncomplexed iodine. The corrected absorbance values for the different solutions at the different wavelengths are arranged in a matrix. The values are then referred to a single wavelength (410 nm, Table III). For a single complex all values should be identical (within the limits of experimental error). Similar results were obtained for the other donors, indicating the presence of a single complex with iodine.

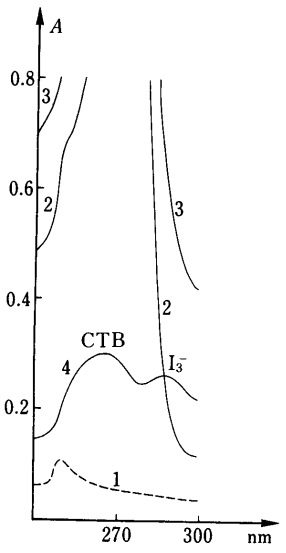


Fig. 4. UV Absorption Spectra of the Propericiazine–Iodine Complex in $CCl_4/CHCl_3$ at Ambient Temperature (*ca.* 20 °C)

The concentrations (M) were: (1) I_2 6.06×10^{-4}, (2) propericiazine 4.10×10^{-5}, (3) I_2 6.06×10^{-4} and propericiazine 4.10×10^{-5}, (4) calculated charge transfer band for the complex.

TABLE IV. Absorption Peaks of the Charge Transfer Bands (CTB) for the Neuroleptic–Iodine Complexes

	CTB λ_{max} (nm)		CTB λ_{max} (nm)
Chlorpromazine	264	Perimetazine	—
Acepromazine	266	Perphenazine	275
Triflupromazine	272	Fluphenazine	275
Levomepromazine	279	Clotiapine	—
Cyamemazine	—	Haloperidol	276
Alimemazine	259	Benperidol	276
Pipotiazine	264	Fluanisone	275
Propericiazine	264	Pimozide	274

Ultraviolet (UV) Region In the near-UV region, mixtures of the donor and acceptor gave rise to an absorption band that was more intense than the sum of those of the two components. The new band is referred to as a charge transfer band (CTB), with a characteristic peak for each particular complex. This peak is observed by placing a solution of donor at the same concentration as that of the complex in the reference beam. The calculated absorbance due to the free iodine must also be subtracted from the final value. For the propericiazine–iodine complex this peak was observed at 264 nm (Fig. 4). Table IV shows the CTBs for all the systems studied.

The CTBs of cyamemazine–iodine, perimetazine–iodine, and clotiapine–iodine complexes could not be determined due to the presence of a high concentration of I_3^- ions which absorb at 290 nm.

Discussion

Spectroscopic analysis of the charge transfer complexes of these neuroleptic drugs with iodine demonstrated the *n*-6 nature of these complexes. From the existence of a single isobestic point, it was concluded that the complexes had a 1 : 1 stoichiometry.

As described by Mulliken,[10] and Popov and Deskin,[11] the formation of I_3^- ions is due to the transformation of an "outer complex" to an "inner complex" liberating I^- ions which react with free molecular iodine.

$$\text{donor} + I_2 = = = = \text{donor–}I_2 \text{ (outer complex)}$$

$$\text{donor–}I_2 = = = = \text{donor–}I^+I^-$$

$$\text{donor–}I^+I^- = = = = [\text{donor–}I]^+ + I^- \text{ (inner complex)}$$

$$I^- + I_2 - - - - I_3^-$$

Previous work from our laboratory[12] has demonstrated that antithyroid activity can be expected from molecules whose formation constant of the iodinated complex K_c exceeds $100\ l \cdot mol^{-1}$. This is the value obtained or the complex of KSCN with iodine. KSCN was previously employed as an antithyroid agent.[2,12] The formation constant for the complex with mercapto-2 thiazoline, another antithyroid agent, is around $2500\ l \cdot mol^{-1}$.[2,12] From the results shown in Table I it can be seen that several of the neuroleptics gave values above $2500\ l \cdot mol^{-1}$. A K_c of $3169 \pm 40\ l \cdot mol^{-1}$ was found for the complex of iodine with chlorpromazine.

The marked production of I_3^- ions also indicated strong donor–acceptor interactions for many of the complexes. It can be seen, therefore, that these neuroleptics are able to complex with molecular iodine. *In vivo*, this would tend to inhibit oxidation to I^+ ions and lead to a partial blockade of thyroid hormone synthesis. These drugs should therefore be considered as potentially thyrotoxic, especially in view of the long-term nature of treatment with neuroleptics.

Experimental

Iodine was from Merck (bisublimed Suprapur 4763). It was used without further purification, and was kept in the dark in a dessicator containing P_2O_5. The drugs employed were all commercially available compounds which were purified by high performance liquid chromatography (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.

Apparatus Spectra were recorded using a Kontron 860 double-beam UV/Vis spectrophotometer equipped with a Peltier effect thermostated sample holder (temperature regulated to ± 0.1 °C). The quartz sample cells with stoppers (Helma 110 QS) had an optical path length of 10 mm.

Method Solutions of iodine of around 10^{-4} M were made up freshly before use by accurate weighing. The solutions of the various donors were prepared by accurate dilution of stock solutions prepared gravimetrically. The reactions were carried out directly in the spectrophotometer sample cells, by mixing 1.5 ml of the donor solution with 1.5 ml of the solution of iodine. The absorbances of the solutions were recorded immediately at various wavelengths.

References

1) C. Raby and J. Buxeraud, *Eur. J. Med. Chem.*, **15**, 425 (1980).
2) J. Buxeraud, A. C. Absil, J. Claude, C. Raby, G. Catanzano, and C. Beck, *Eur. J. Med. Chem.*, **20**, 43 (1985).
3) S. Nagakura, *J. Am. Chem. Soc.*, **80**, 520 (1958).
4) H. Yada, J. Tanaka, and S. Nagakura, *Bull. Chem. Soc. Jpn.*, **33**, 1660 (1960).
5) F. Comby, Doctoral Thesis, Limoges University, Frace, **00**, 37 (1985).
6) R. P. Lang, *J. Am. Chem. Soc.*, **84**, 1185 (1962).
7) R. P. Lang, *J. Phys. Chem.*, **72**, 2129 (1968).
8) A. C. Absil, J. Buxeraud, and C. Raby, *Can. J. Chem.*, **62**, 1807 (1984).
9) W. Liptay, *Z. Elektrochem.*, **65**, 375 (1962).
10) R. S. Mulliken, *J. Phys. Chem.*, **56**, 801 (1952).
11) A. I. Popov and W. Deskin, *J. Am. Chem. Soc.*, **80**, 2976 (1958).
12) J. Buxeraud, A. C. Absil, and C. Raby, *J. Am. Pharm. Sci.*, **73**, 1687 (1984).