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ON THE FORMATION OF CHARGE TRANSFER COMPLEXES BETWEEN NEUROLEPTIC DRUGS AND CHLORANIL

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Abstract—The interaction of thirty neuroleptic drugs with chloranil in 50% acetone–ethanol mixture has been studied spectrophotometrically. The features of the resulting complex have been characterized. The kinetics of the formation of the complex have been studied in the range of 120–300 K. A relative parameter for the donor strength of the drugs involved could be deduced from the results. The electron donating properties of these compounds are compared with their pharmacological activity.

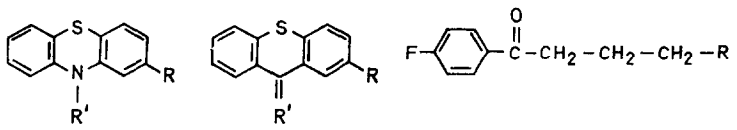
SUPPORT for the assumption that charge transfer complex formation process plays a vital role, especially in the pharmacological activity of drugs,[1–3] appears to be provided by the neuroleptic drugs (major tranquillizers) and particularly the phenothiazine since these appear to be good electron donors and various workers have noted the low ionization potentials of these compounds. Pullman,[4] deduced these values by calculations of the highest-occupied molecular orbital of phenothiazine and of chlorpromazine. Orloff and Fitts[5] and Lyons and Mackie[6] later confirmed these results. Also, pharmacologically, the neuroleptic drugs probably act in the brain neurons without any degradation during their progression in the human body.[7] Consequently, it is possible that interactions with biological receptors are a specific property of those molecules.

We paid particular attention to the study of these derivatives in order to determine whether the pharmacological action involves a charge transfer complex or not. With this object, the absorption spectrophotometry was used principally at low temperatures. At first this method is applied systematically through a large temperature range to study the charge transfer spectra and to determine the kinetics of interactions.

In a previous communication,[8] the first results relating to interactions in solution between chloranil and a large range of neuroleptic drugs (major tranquilizers) were given. The basic aim of this report is to give the results as a whole, and to deduce from them a relative parameter for the donor strength of the studied compounds. It may then be possible to compare quantitatively the electron donating properties with pharmacological activity of these neuroleptic drugs.

EXPERIMENTAL

In those solutions studied, chloranil was taken as electron acceptor, and electron donors, some compounds with neuroleptic activity were chosen (i.e. significant derivatives of three different molecules, phenothiazine, butyrophenone and thioxanthene). To these a few substances with butyrophenone related structure were also included. In Fig. 1 the three rings are represented.



phenothiazine thioxanthene butyrophenone

FIG. 1. The three rings of the neuroleptic drugs studied in this work.

An acetone–ethanol (1:1) mixture was used as solvent. This mixture freezes as a rigid gel and spectrophotometric measurements may be continued below freezing temperature. Absorption spectra were recorded on a Cary-14 spectrophotometer with British Oxygen Company low temperature equipment in the range of 120–300 K, using an optical cell of path length (0·210 $\pm$ 0·006 mm).

Neuroleptic drugs were supplied by Janssens Pharmaceutica and the Specia Co. Chloranil and solvents were obtained from Merck.

RESULTS AND DISCUSSION

When a chloranil solution (5.10^{-3} or 10^{-2} M) and a solution of neuroleptic drugs (5.10^{-2} or 10^{-1} M), are mixed (Table 1), in most cases a new absorption band appears in the spectrum. Figure 2 shows the absorption spectra of a promazine–chloranil mixture. The behaviour of the absorption bands is almost the same for all spectra that were studied.

The presence of a system of two bands is noted, of which the maxima are lying at about 420 and 445 nm. Their shape and situation are characteristic of the bands of the chloranil radical-ion. These are well known and described by various authors.[9,10] In this experiment, they appear in the spectrum, whether at room temperature or at a lower temperature when the sample is cooled. When the temperature is lowered a characteristic feature of these bands appears, their intensity increases, reaching a maximum and then fades away.

Moreover, the appearance of a new absorption band, having all the characteristics of a charge transfer band, is noted in the temperature range of 190–240 K. Its λ_{max} is lying at (685 $\pm$ 15 mm). It is difficult to give the exact value of λ_{max} for this band because of its broad nature. It appears at a temperature where the bands of chloranil-ion are reaching their maximum intensity. If cooling is carried on, the intensity of this charge transfer band increases as the bands of chloranil ion decreases in intensity.

This phenomenon is quite reversible when the temperature is varied in the opposite direction, i.e. from 120–300 K. As we have stated, the nature of the spectra is almost the same in all cases, whatever the nature of the donor; apart from this, the maximum of the charge transfer band is on the same wavelength in all the spectra. The only difference between the mixtures lies in the intensity of the bands at a given temperature. Among the 30 studied donors (i.e. 16 phenothiazine, 1 thioxanthene, 10 butyrophenone derivatives and 3 compounds with butyrophenone related structure) only 4, phenothiazines (cf. Table 1) did not produce any change in their spectrum when mixed with a chloranil solution, whatever the temperature.

When the absorbance of these new absorption bands is plotted against the temperature, a similar curve is obtained for each compound considered. Figure 3 is an example

TABLE 1. ΔH° VALUES FOR THE FORMATION OF THE CHLORANIL RADICAL-ION IN NEUROLEPTIC DRUG-CHLORANIL SOLUTIONS

Compounds	$-\Delta H^\circ$ (kcal/mole)
Phenothiazines	
Acepromazine	4·56 ± 0·24
Alimenazine	5·08 ± 0·92
Aminopromazine	5·52 ± 0·48
Chlorpromazine	5·12 ± 0·26
Dixyrazine	4·78 ± 0·46
Fluphenazine	—
Levomepromazine	3·42 ± 0·28
Mepazine	0·30 ± 0·09
Perphenazine	0·72 ± 0·06
Prochlorperazine	—
Promazine	5·96 ± 0·20
Propericiazine	0·52 ± 0·06
Thiethylperazine	0·66 ± 0·09
Thioproperazine	—
Thioridazine	—
Triflupromazine	4·12 ± 0·16
Thioxanthene	
Chlorprothixene	0·19 ± 0·05
Butyrophenones	
Aceperone	0·37 ± 0·07
Benperidol	1·82 ± 0·12
Clofluperidol	3·98 ± 0·44
Droperidol	0·96 ± 0·06
Fluanisone	0·31 ± 0·07
Haloperidol	5·16 ± 0·45
Moperone	5·30 ± 0·68
Spiroperidol	0·69 ± 0·11
Triperidol	5·78 ± 0·78
Others	
Fluspirilene	1·17 ± 0·11
Isopirilene	1·26 ± 0·09
Pimozide	1·43 ± 0·03

of fluanisone taken as a donor. The temperatures are plotted as abscissae and the absorbance of two bands (λ_{max} = 445 and 685 nm) as ordinates.

Another aspect to this work, the presence of chloranil radical-ion in these mixtures, was confirmed by electron paramagnetic resonance.

The simultaneous appearance, in the absorption spectrum, of a donor–acceptor mixture in solution, a charge transfer band and some characteristic bands of the acceptor ion, was observed, as previously reported by Foster and Thomson[11] and was explained in various ways.[11,12] The charge transfer band was assigned more particularly to an outer complex between donor and acceptor, while the chloranil ion appeared by dissociation of an inner complex. We ourselves had taken up[8] this interpretation for the appearing of the charge transfer band. A careful study has shown[13,14] that

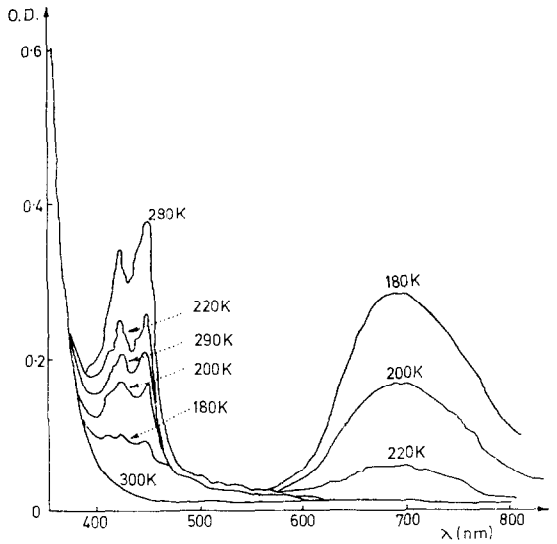


FIG. 2. Absorption spectra at various temperatures of promazine 0·1 M-chloranil 0·01 M mixture in 1:1 acetone–ethanol.

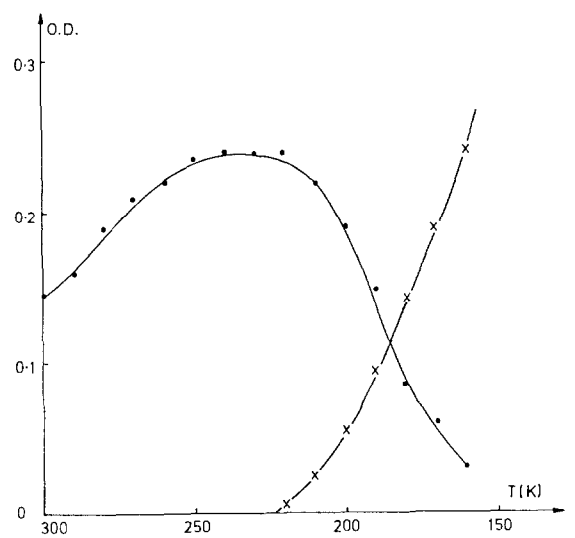


FIG. 3. Variation with temperature of the optical density of the maximum of the chloranil ion band (●——●) and of the charge transfer band (×——×) appearing in the spectrum of fluanisone 0·08 M-chloranil 0·01 M mixture in 1:1 acetone–ethanol.

the appearance of new band in the spectra that we have just described, may be explained as follows: the band system (λ_{max}= 420 and 445 nm) is compatible with the formation of chloranil ion from chloranil (CHL) and some neuroleptic drug (N) according to a chemical equation as (1).

$$CHL + N \rightleftharpoons (CHL^- \,.\, N^+) \rightleftharpoons CHL^- + N^+ \quad (1)$$

With regard to the charge transfer band it is compatible with the formation of a charge transfer complex between formed chloranil ion and solvent (S) according to an equilibrium as (2). Of course, the two equilibria (1) and (2) are displaced to the right when temperature is lowered.

$$CHL^- + S \rightleftharpoons (CHL^- \,.\, S) \quad (2)$$

The characteristics of the spectra described were used to calculate the formation constants of chloranil ion (1). At some temperatures, because the formed chloranil ion is involved in the complex with solvent, the second equilibrium had to be taken into account in the calculations. Optical densities of the charge transfer band and of the chloranil ion bands were used to determine, by the Beer–Lambert law, the concentrations involved in the expression of the formation constants. The equilibrium constant K were calculated as previously described,[13,14] in the temperature range of 120–300 K. The change of these constants with temperature is almost the same in all cases. When the logarithm of K is plotted against the reciprocal of temperature a linear relation is obtained. In Fig. 4, 1 nK is plotted against 1/T for chloranil–promazine complex. For the donor strength of the considered compounds we have a choice of K (or $\Delta F°$, depending only on K) or of $\Delta H°$ (or $\Delta S°$ which generally is varying linearly with $\Delta H°$; it is the case here). According to Mulliken and Person,[12] the term "stability of the complex" (or "strength of the donor or acceptor") usually refers to the magnitude of K; however the enthalpy of formation $\Delta H°$ is more closely related to the stabilization by the charge transfer forces and the concepts of strength based on the theory. Moreover Foster[15] shows, in the case of some trinitrobenzene-donors complexes, that the enthalpy of formation of the complexes is related to the ionization potential of the donors, having a similar structure.

$\Delta H°$ was used to give the donor strength of neuroleptic drugs, especially as the enthalpy constant was determined over a large temperature range; except for a factor the enthalpy is the angular coefficient of the straight line 1 nK = f(1/T), as in Fig. 4. The determination of $\Delta H°$ for each neuroleptic drug studied, provides a relative scale of the donor strengths of these compounds. In Table 1 the various neuroleptic drugs are listed and the results are given for their donor strength. The donor strength was compared with the pharmacological activity using the method of Dresse,[7] based on the behaviour of self-stimulation of the rats carrying an implanted electrode in the brain (lateral hypothalmus).

In Fig. 5 and Table 2 are given the donor strength and the dose of the drug which reduce the activity of self-stimulation of the rat in the above conditions. Activity ranged from 0·01 mg/kg for spiroperidol to 40 mg/kg for aceperone.

Figure 5 fails to show any correlation, i.e. the three phenothiazine derivatives requiring a weak dose (fluphenazine: 0·08 mg/kg; thioproperazine: 0·25 mg/kg; prochlorperazine: 0·73 mg/kg) do not exhibit any absorption band resulting from a charge transfer. On the other hand the three derivatives requiring a larger dose for

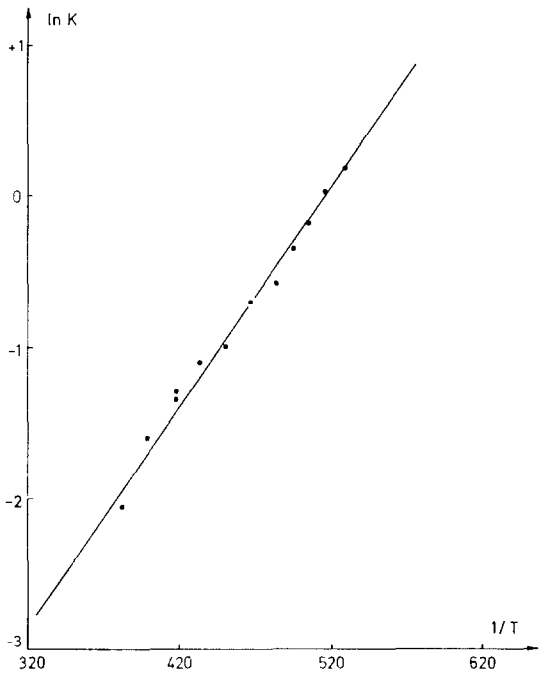


FIG. 4. Plot of 1 nK against 1/T for the promazine–chloranil system.

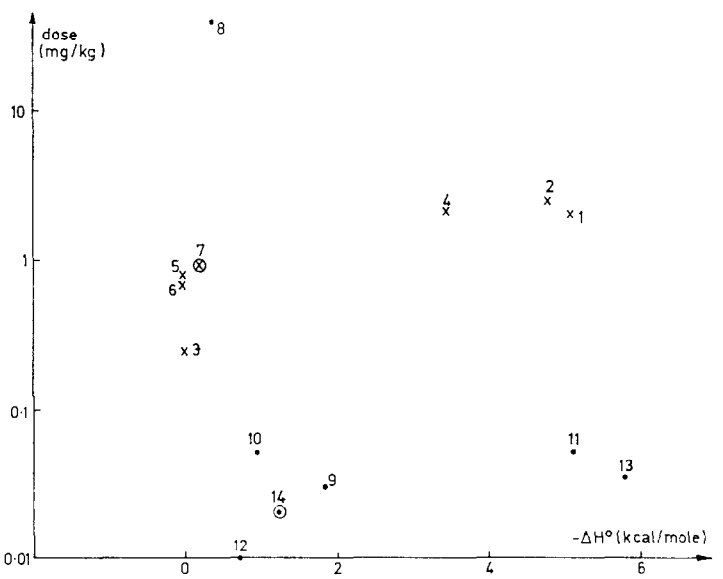


FIG. 5. Variation of neuroleptic activity with electron donor strength.

TABLE 2. NEUROLEPTIC DRUGS STUDIED BY DRESSE[7] AND IN THIS WORK; DOSE OF EACH DRUG 50 PER CENT REDUCING THE BEHAVIOUR OF SELF-STIMULATOIN OF THE RATS AND ENTHALPY OF FORMATION OF THE CHLORANIL ION IN EACH CHLORANIL-DRUG SOLUTION

Compounds	Dose mg/kg	$-\Delta H°$ kcal/mole
Phenothiazines		
Chlorpromazine	2·0	5·12
Dixyrazine	2·5	4·78
Fluphenazine	0·08	0*
Levomepromazine	2·14	3·42
Prochlorperazine	0·73	0*
Thioproperazine	0·25	0*
Thioxanthene		
Chlorprothixene	0·95	0·19
Butyrophenones		
Aceperone	42·000	0·37
Benperidol	0·030	1·82
Droperidol	0·052	0·96
Haloperidol	0·052	5·16
Spiroperidol	0·010	0·69
Triperidol	0·035	5·78
Others		
Isospirilene	0·020	1·26

* Zero value is corresponding to the absence of absorption bands from charge transfer complexes.

the same pharmacological activity (chlorpromazine: 2·0 mg/kg; levomepromazine: 2·14 mg/kg; dixyrazine: 2·5 mg/kg) do exhibit an important $\Delta H°$ (5·12, 3·42 and 4·78 kcal/mole respectively). Among the butyrophenone derivatives, aceperone which is requiring a very large dose (42 mg/kg) has a little value of $\Delta H°$ (0·37 kcal/mole) but with regard to the other molecules of this family very different enthalpies (from 0·69 to 5·78 kcal/mole) are corresponding to relatively similar doses (from 0·010–0·053 mg/kg).

CONCLUSION

From the results no correlation was seen between donor strength and pharmacological activity of the neuroleptic drugs. But before concluding that there is total absence of charge transfer interaction at the activity site some other electron acceptors ought to be investigated.

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