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Thermodynamic Studies of the Charge–Transfer Interactions of Chloranilic Acid with Moclobemide and Promethazine Hydrochloride

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Spectrophotometric absorption studies gave evidence for the formation of strongly bonded charge–transfer complexes between moclobemide and promethazine hydrochloride with chloranilic acid in non-aqueous media comprising chloroform and 1,4-dioxane. The transitions involved were detected at wavelengths longer than those of the single pure substances in the visible region. Equilibrium constants from the Scott equation could be measured together with other thermodynamic parameters and molar absorptivities at different temperatures. Theoretical arguments are presented as to the spontaneity of these interactions.

Key words charge–transfer complex; chloranilic acid; moclobemide; promethazine hydrochloride; spectrophotometric absorption study; thermodynamic study

π -Acceptors are known to interact with a wide range of electron-donating compounds with a consequent formation of charge–transfer complexes. Chloranilic acid and other π -acceptors have been variously utilized in the spectrophotometric assay and analysis of many drug substances.^{1–5} Studies utilizing π -acceptors as spray (locating) reagents on TLC plates for the qualitative detection of some electron-donating drugs have been reported.^{6–10} Earlier studies^{11,12} have demonstrated that chloranilic acid formed intensely purple-colored charge–transfer complexes with moclobemide and promethazine hydrochloride. Such complex formation formed a basis for the spectrophotometric determination of the two drugs in pure samples and in their various dosage forms.

So far, the literature has not documented any interaction of chloranilic with moclobemide and promethazine hydrochloride in the light of their thermodynamics. The present study dwells on the thermodynamics of the charge–transfer interactions of chloranilic acid with moclobemide and promethazine hydrochloride. The association constants, molar absorptivities, standard free energy changes (ΔG°), standard enthalpy and entropy changes (ΔH°) and (ΔS°) of the formed complexes were all highlighted. These thermodynamic parameters could serve as valuable indices in the rapid quality assessment of the drugs under study since some of these parameters are concentration dependent.

MATERIALS AND METHODS

Materials and Reagents Aurorix[®] tablets (Roche); promethazine hydrochloride powder (A.B. Knight Pharmaceuticals); chloranilic acid (Riedel de Haen); 1,4-dioxane and chloroform (May and Baker) were used. Other reagent solvents were of analytical grade and used as such. All laboratory reagents were freshly prepared.

Preparation of Standard Solutions Moclobemide: Ten Aurorix[®] tablets were placed on a clean, dry glass mortar and pulverized to a fine powder. An amount equivalent to 1 g of the moclobemide was quantitatively transferred into a 100 ml flask with the aid of chloroform. The flask was shaken for 30 min to completely dissolve the drug, then the mixture was filtered to remove the excipients. The filtrate was poured into a

glass dish and exposed at room temperature to drive off the chloroform. Recrystallization of the residue yielded 97.3% moclobemide from the methanol–water medium. A standard solution of moclobemide was formed by redissolving 0.514 g of moclobemide in 50 ml of chloroform to provide a 3.83×10^{-2} M standard solution.

Promethazine: An amount of the salt equivalent to 0.614 g of promethazine base was accurately weighed in an analytical balance (Sauter) and dissolved in about 15 ml of water in a 250 ml separatory funnel. The solution was made alkaline with 3 ml of 2 M sodium hydroxide and shaken successively for 2 min with 15 ml and three 10 ml portions of chloroform, each extract being washed with the same 15 ml of water in another separate funnel. The washed extracts were pooled and passed through 2 g of anhydrous sodium sulphate supported on a filter paper in a small funnel, and then into a 50 ml volumetric flask; the volume was completed with chloroform to provide a 3.83×10^{-2} M standard solution of promethazine.

Absorption Spectra A solution of chloranilic acid (3.0×10^{-3} M) was made in 1,4-dioxane, and its wavelength of maximum absorption was determined using a digital Pye Unicam double beam Uv-Vis spectrophotometer (SP8-100). Color was developed by mixing 2 ml of chloranilic acid with 2 ml of 3.83×10^{-2} M moclobemide, and the wavelength of maximum absorption for the resulting solution was determined. A similar procedure was repeated using 2 ml of 3.83×10^{-2} M promethazine, and the wavelength of maximum absorption was determined for the resulting complex.

Association Constant and Free Energy Change Serial volumes of 0.1 to 0.6 ml of 3.83×10^{-2} M moclobemide solution in 0.1 ml steps were transferred to different test tubes. The solutions were diluted to 3 ml with chloroform, and 2 ml of a 3.0×10^{-2} M solution of chloranilic acid in dioxane was added. The contents were mixed (by gentle shaking) and left at room temperature (27 °C) for 30 min before analysis at 526 nm. Further analysis of the reaction mixtures was done by subjecting them to temperatures of 50, 70 and 90 °C in a thermostated water bath.

The same procedure as described above was repeated using a 3.83×10^{-2} M solution of promethazine. The reaction mixtures in this case were left at room temperature for 60

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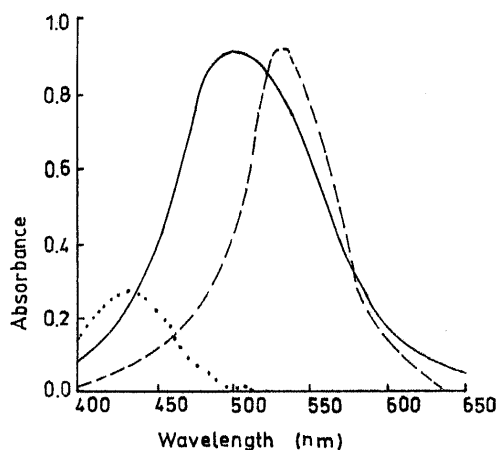


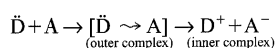
Fig. 1. Absorption Spectra of Chloranilic Acid (····); Moclobemide-Chloranilic Acid Complex (---); and Promethazine-Chloranilic Acid Complex (—)

Chloranilic acid: 5.0×10^{-3} M; moclobemide: 3.0×10^{-3} M; promethazine: 3.52×10^{-3} M.

min before analysis at 500 nm.

RESULTS AND DISCUSSION

The formation of complexes between the electron donors (moclobemide and promethazine) and the electron acceptor (chloranilic acid) was detected by observing the shift in the visible spectrum of the mixture toward longer wavelengths (bathochromic shifts) when the chloranilic acid solution in 1,4-dioxane was used as a reference (Fig. 1). Apart from the bathochromic shifts exhibited by the mixtures of the reacting substances relative to solutions containing single pure substances, the instantaneous change of the yellowish-pink color of chloranilic acid in dioxane to purple upon reaction with either of the drugs studied is sufficient indication of charge-transfer complex formation. It is discernible from Fig. 1 that the chloranilic acid-moclobemide reaction mixture showed an intense band at 526 nm, while a strong absorption maximum was exhibited by the chloranilic acid-promethazine reaction mixture at 500 nm. The appearance of these bands is attributed to charge-transfer transitions from the n -donors, promethazine and moclobemide, to the π -acceptor, chloranilic acid, with a consequent formation of the latter's anion radical according to the following scheme:



Earlier reports^{11,12} indicated that the interaction between chloranilic and moclobemide required no less than 30 min to come to completion. Promethazine, however, required no less than 60 min for complete complexation with chloranilic acid. Of interest in this study is the fact that a 1:1 electron-donor-acceptor (EDA) interaction has been reported for the interaction of chloranilic acid with moclobemide and promethazine.^{11,12}

Based on a 1:1 complex, the association constants of moclobemide and promethazine complexes were calculated from the following single mathematical model:

$$A + D = AD \quad (1)$$

and by the application of the Scott equation¹³ which is a

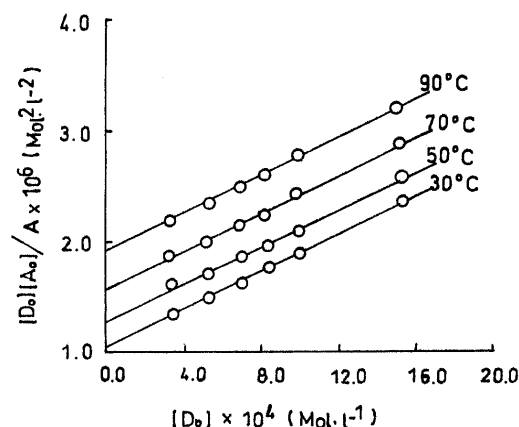


Fig. 2. Plots of $[D_0][A_0]/A$ versus $[D_0]$ for Moclobemide-Chloranilic Acid Complex at Different Temperatures

Moclobemide: 3.83×10^{-2} M; chloranilic acid: 3.0×10^{-3} M. The curves have about the same intercepts as that of 30°C; they were separated to avoid crowding.

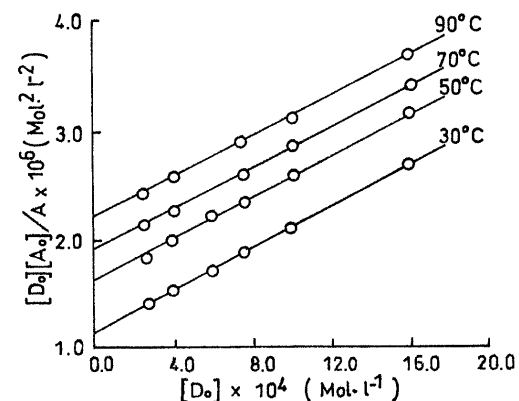


Fig. 3. Plots of $[D_0][A_0]/A$ versus $[D_0]$ for Promethazine-Chloranilic Acid Complex at Different Temperatures

Promethazine: 3.83×10^{-2} M; Chloranilic Acid: 3.0×10^{-3} M. The curves have about the same intercepts as that of 30°C; they were separated to avoid crowding.

modification of the Benesi-Hildebrand equation¹⁴) thus:

$$\frac{[D_0][A_0]}{A_\lambda^{AD}} = \frac{[D_0]}{\epsilon_\lambda^{AD}} + \frac{1}{K_c^{AD} \epsilon_\lambda^{AD}} \quad (2)$$

where $[D_0]$ and $[A_0]$ are the initial concentrations of the reactant species, A_λ^{AD} is the absorbance of the complex at the wavelength λ , ϵ_λ^{AD} is the molar absorptivity, and K_c^{AD} is the association constant.

The values of ϵ_λ^{AD} and K_c^{AD} can be obtained graphically from the slope and intercept of a plot of $[D_0][A_0]/A_\lambda^{AD}$ versus $[D_0]$, with $[A_0]$ kept constant. To minimize experimental errors, the slopes and intercepts were determined by the method of least squares.¹⁵ Plots of Eq. 2 for moclobemide-chloranilic acid and promethazine-chloranilic acid complexes are presented in Figs 2 and 3, respectively. The intercepts calculated varied slightly with temperature for the complexes studied.

Various thermodynamic parameters for the two interactions were calculated from the following well-known equation:

$$\text{Log } K_c^{AD} = -\frac{\Delta H^\circ}{2.303RT} + \text{constant} \quad (3)$$

Therefore, a plot $\log K_c^{AD}$ versus the reciprocal of the ab-

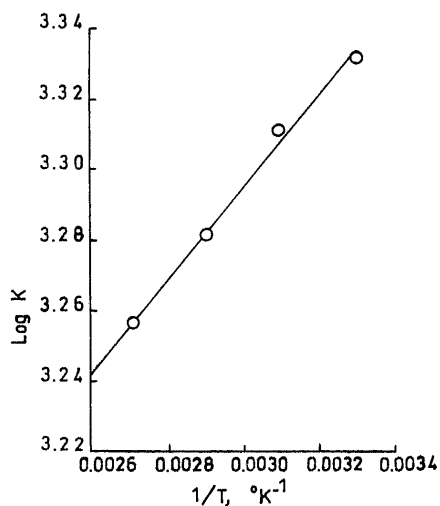


Fig. 4. Log K of the Moclobemide-Chloranilic Acid Interaction versus $1/T$

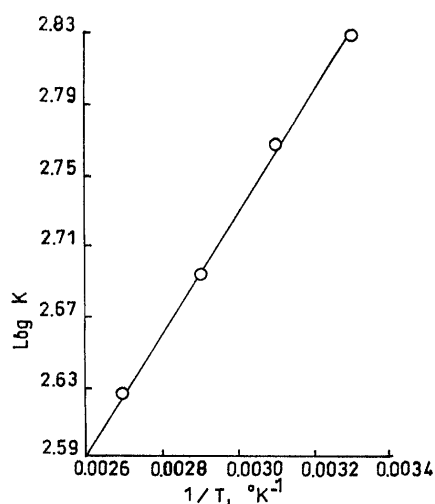


Fig. 5. Log K of the Promethazine-Chloranilic Acid Interaction versus $1/T$

solute temperature, $1/T$, should give a linear slope of $-\Delta H^\circ/2.303R$ if the standard enthalpy change of the reaction, ΔH° , does not depend on the temperature; R is the gas constant. The Gibb's free energy change of a reaction, ΔG° , can be related to changes in the standard enthalpy, entropy, ΔS° , and association constant according to the following equations:

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \quad (4)$$

$$\Delta G^\circ = -RT \ln K_c^{AD} \quad (5)$$

Representative plots of Eq. 3 are shown in Figs 4 and 5. The slopes and intercepts were also calculated by a least squares method. The thermodynamic parameters from these equations are presented in Table 1. The molar absorptivities were found to be independent of temperature for both complexes. Therefore, the absorptivities presented in Table 1 represent essentially an average estimated from working at different temperatures.

The association constants were generally high and were discovered to decrease slightly with an increase in temperature. It is deducible from Table 1 that the formed complexes

Table 1. Association Constant (K), Standard Free Energy (ΔG°), Standard Enthalpy (ΔH°), and Standard Entropy (ΔS°) Changes Associated with the Interaction of Chloranilic Acid with Moclobemide and Promethazine in Aqueous Media at Different Temperatures

Temperature (°C)	K, M^{-1}	ΔG° (kcal/mol)	ΔH° (kcal/mol)	ΔS° (cal/deg/mol)
Moclobemide-chloranilic acid				
30	2146.35	-4.62		13.321
50	2031.23	-4.89		13.33
70	1901.85	-5.15	-0.584	13.30
90	1795.49	-5.41		13.28
		$\lambda=526 \text{ nm};$	$\epsilon=625.77$	
Promethazine-chloranilic acid				
30	657.15	-3.91		7.83
50	573.70	-4.08		7.87
70	492.90	-4.23	-1.535	7.85
90	406.84	-4.34		7.71
		$\lambda=500 \text{ nm};$	$\epsilon=1515.55$	

are highly thermostable, hence the high values of the association constant even at high temperatures. Because of these high values of the association constants, ΔG° values of both interactions were negative and high even though the ΔH° values were relatively small. Another characteristic feature of the chloranilic acid complexes with moclobamide and promethazine was a high positive entropy change which can account for the fact that ΔG° was high and negative even though the heat of formation of the complexes was relatively small.

A negative free energy change ($-\Delta G^\circ$) and a positive entropy change are indicative of a spontaneous reaction.¹⁶⁾ The interactions of chloranilic acid with moclobemide and promethazine occur spontaneously, and negative ΔH values, as are evident in Table 1, are themselves proof of spontaneous reactions. Andrews and Keefer¹⁷⁾ have, in earlier studies, demonstrated that ΔH° and ΔS° generally become more negative as the stability constant for molecular complexation increases. As the binding between donor and acceptor becomes stronger, ΔH° would be expected to have higher negative values. High negative ΔH° and association constant values indicate strong bonding between chloranilic acid and the studied drugs as well as a high stability of the resultant charge-transfer complexes.

The high stability of these complexes is an added advantage, especially in the quantitative analyses of the two drugs via charge-transfer complex formation, since the reactant mixtures containing chloranilic acid and the drugs can be analysed even after 24 h storage in the dark. The choice of dioxane as the solvent in this study was based on its low dielectric constant, and the stable color formation obtained may confirm that it did not interfere with or shield the charge-transfer process. In all cases, very stable complexes were formed, but the chloranilic acid complex with moclobemide was comparatively more stable than its complex with promethazine hydrochloride. It is most likely that moclobemide has a lower ionization potential than promethazine, judging from its higher stability constant with chloranilic acid.

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