GLOBAL JOURNAL OF PURE AND APPLIED SCIENCES VOL. 10, NO. 1, JANUARY 2004: 147-153
COPYRIGHT(C) BACHUDO SCIENCE CO. LTD. PRINTED IN NIGERIA. ISSN 1118- 0579

THERMODYNAMIC STUDIES ON THE CHARGE-TRANSFER COMPLEX BETWEEN AMITRIPTYLINE AND CHLORANILIC ACID

JOHNSON OGODA ONAH

(Received 31 March, 2003; Revision accepted 28 May, 2003)

ABSTRACT

Spectrophotometric technique was employed to investigate thermodynamic parameters associated with the interaction between amitriptyline and chloranilic acid in non-aqueous medium. The molecular complex produced a purple colour with absorption maximum at 520 nm and was stable over 9 h. The equilibrium constant, K_e^{AD}, at 298°K and 333°K were generally low, i.e. 0.2304 and 0.3896 respectively; there was slight increases as the temperature was elevated. The enthalpy change (ΔH) and entropy change (ΔS) of interaction were respectively –1.21 ± RSD 0.96% KJ mol^{-1} and –0.029 ± RSD 0.026% KJ mol^{-1}. The apparent free energy change (ΔG) was similarly low, i.e. –3.6378 KJ mol^{-1} at 298°K and –2.6102 KJ mol^{-1} at 333°K. A gradual decrease in ΔG was similarly observed as the temperature was increased suggesting that the complexation was exothermic. Comparison of the K_e^{AD} values with literature data indicate that these values are lower by a factor of 10^3 while ΔG decreased by a factor of between 5 and 6. These values clearly indicate the influence of stereochemistry of amitriptyline on the complexation reaction. The molar absorbtivity and Sandell's sensitivity for the complex were 4666 l mol^{-1} cm^{-1} and18 ng/ml respectively.

KEY WORDS: Amitriptyline , chloranilic acid, thermodynamic parameters

INTRODUCTION

Organic functional groups with nonbonding electrons are candidates for charge-transfer (CT) complexes with molecules having π-antibonding orbitals. Typical π- acceptors include chloranil (Belal et al. 1986; Onah, 1995), chloranilic acid (Saleh and Askal, 1991; Abdel-Gawad, 1997 Adikwu et al. 1998; Onah and Odeiani, 2002) tetracyanoethylene(Ibrahim et al. 1986), trinitrobenzene (Foster, 1969) and even maleic anhydride (Foster, 1969). Several synthetic and quantitative reports involving pharmaceutical (Agarwal and El Sayed, 1981;Rizk et al. 1981) and other nitrogenous compounds (Agarwal and El Sayed, 1981; Muralikrishna et al. 1984; Ibrahim, 1997) have been presented in the literature. Although CT complexes may be considered as molecular complexes their formation and stability have several limitations. For pharmaceutical analysis there is no direct evidence of the existence of the complex other than the colour formation. Secondly, isomeric or termolecular complexes may form depending upon the polar or polarizing nature of solvents employed and even solvation of π-donor and/or π-acceptor molecules may affect the absorption maximum of the complex. Our studies involving different kinds of non-polar solvents and different functional groups (Unpublished) have demonstrated that these limitations didn't constitute a significant deviation from the theoretical predictions. CT complexes continues to be of scientific importance because information gained from the molecular interaction may help to explain interactions in biological systems.

Spectrophotometric studies on CT complexes of benzanilides with π-acceptors have been reported (Mourad, 1988), substituted benzanilides acts as an electron donor and the nature of electronic interaction is either π-π* or n-π* depending on the substituent group present.

No report has been cited in the literature involving the analysis of AMT with π-acceptor like chloranilic acid. Many of our previous studies were carried out on compounds containing primary amino functions as π- donors. AMT is a molecule with a secondary ammonium function in addition to π- delocalized bonding electrons, therefore the present study was aimed to investigate the thermodynamic parameters like equilibrium constant (K_e), enthalpy (ΔH) and entropy (ΔS) changes in relation to the stability of the complexes. These information will subsequently form a basis for the development of a quantitative technique for analysis of drugs.

Amitriptyline (AMT) hydrochloride [3-(10,11-dihydro-5H-dibenzo [a,d] cyclohept-5-ylidene)-propyldimethylammonium chloride], is a tricyclic antidepressant drug of the family of dibenzocycloheptadiene derivative and is a

JOHNSON OGODA ONAH, Department of Pharmaceutical Chemistry, University of Jos, Jos, Nigeria.

Table 1. Thermodynamic changes determined from the complexation between AMT and CA at different temperatures.

Temp. °K	K_c	ΔG KJ/mole	ΔH KJ/mole	ΔS KJ/mole
298	0.2304	-3.6376		
303	0.2613	-3.3815		
313	0.2063	-3.1082	-1.21± RSD 0.96%	-0.0291± RSD 0.026%
323	0.3572	-2.765		
333	0.3896	-2.6102		

Molar absorptivity (ε) = 4666 l mol^{-1} cm^{-1}

frequently used and misused drug (Baeck et al. 2000). AMT is primarily used in the management of depression especially of endogenous origin (British National Formulary, 2000). It is also used, albeit temporarily, in alleviating enuresis in children and adolescents (British National Formulary, 2000). Various analytical protocols have been developed for AMT and other tricyclic antidepressant drugs (Greenway and Dolman, 1999; Karpinska and Suszynska, 2001; Zhao and Olesik, 2001; Veraart and Brinkman, 2001; Macherey-Nagel, 2001).

EXPERIMENTAL

Material and method

Amitriptyline powder (99.5% pure); Chloranilic acid (Riedel de Haem,) was recrystallized from acetone. Chloroform (AnalaR:BDH) was redistilled and dried with anhydrous sodium sulphate. 1,4-Dioxan (May & Baker) was used without further purification. All other reagents were of analytical grade.

Determination of absorption maximum for the CT complex

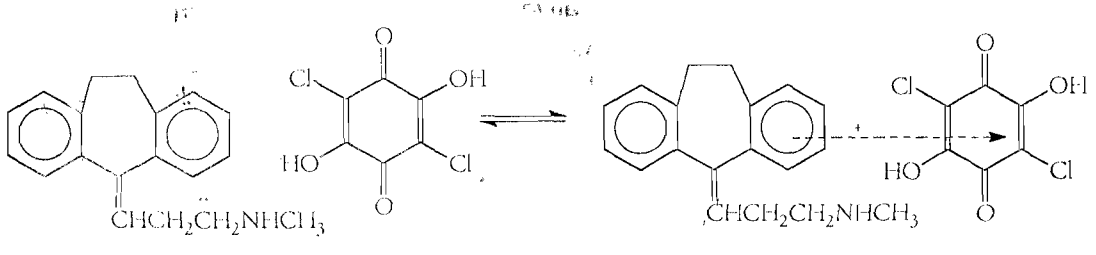
Amitriptyline and chloranilic acid solutions (0.1 % each) were prepared in 1,4-dioxan and mixed in equal proportions and allowed to stand in the dark for between 15 and 20 minutes for equilibrium to be established before it was scanned on a spectrophotometer (Jenway, Model 6400) through the entire visible spectrum.

Determination of Molar absorptivity of the CT complex

Stock solutions of amitriptyline and chloranilic acid equivalent to 1.911 x 10^{-2} M (6.0 mg/ml) and 5.01 x 10^{-3} M (1.047mg/ml) were prepared respectively. Measured volumes of 1.0, 2.0, 3.0, 4.0 and 5.0 ml amitriptyline were transferred into different 10 ml volumetric flasks and 1.0 ml of chloranilic acid added to each flask; the volumes were made-up to mark by adding dioxan. Five replicate preparations were arranged and the contents mixed thoroughly before absorbances were measured after 20 minutes. The stability of the colour was monitored for 9 h at regular intervals of 1 h. The mean values of the absorbances were computed and plotted against the corresponding concentrations. The curves were regressed by the method of least squares (Bauer, 1971). The slope represents the molar absorptivity. Sandell's sensitivity coefficient was similarly calculated.

Stoichiometric relationship between amitriptyline and chloranilic acid CT complex.

The stock solutions of amitriptyline (1.911 x 10^{-2} M) and chloranilic acid (5.01 x 10^{-3} M) were mixed in the following ratios: 1:9, 2:8, 3:7 to 9:1. Again the complexes were allowed to stand for 20 minutes before their absorbances were measured at the absorption maximum. The Job's continuous variation plot was constructed.



AMT CA CT- complex

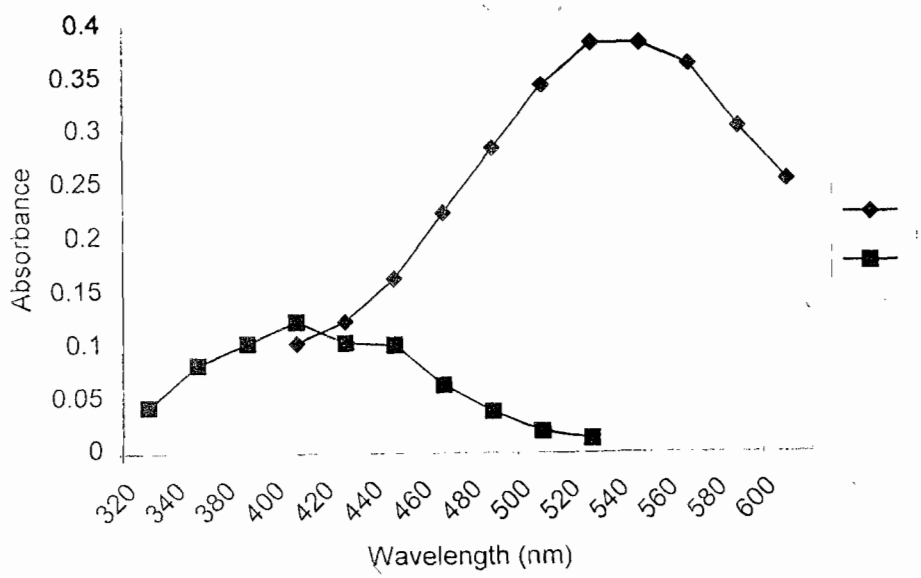


Fig. 1: Determination of absorption maxima for CA and amitriptyline-chloranilic acid complex. CA (◆) and AMT-CA complex ( ).

Optimization of analytical technique

The sensitivity of the spectrophotometer was established first by standard method. The limit of detection and quantitation were determined by dilution method. Different concentrations of amitriptyline were prepared and absorbances mesaured after complexing with a constant concentration of chloranilic acid; the precision, accuracy, linearity were also determined. Optimum concentration of chloranilic acid and amitriptyline was achieved by keeping the concentration of one constant and varying the other and vice-versa; the concentrations were further varied simultaneously. From the results, the optimum concentration that gave the best reproducibility was selected for the analysis.

Determination of equilibrium constant and free energy change

The free energy changes of the interaction between chloranilic acid and amitriptyline and the associated equilibrium constant were determined by the method reported earlier (Adikwu et al. 1998; Onah and Odeiani, 2002). Essentially, measured amounts of pure amitriptyline (1.911 x 10^{-2} M to 11.466 x 10^{-2} M) equivalent to 1.0, 2.0 3.0 to 6.0 ml were accurately transferred into volumetric flasks and 1.0 ml chloranilic acid (5.01

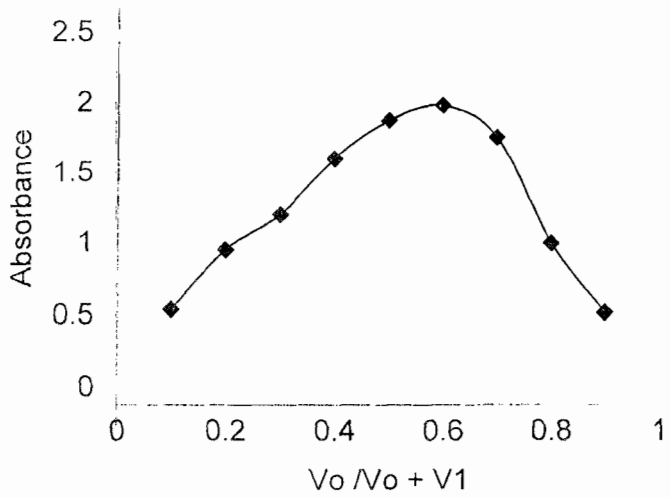


Fig. 2: Determination of stoichiometric relationship between AMT and CA complex (Job's continuous variation plot).

x 10^{-3} M) added to each flask. The volumes were brought up to mark and absorbance measured at 520 nm. The procedure was repeated at temperatures of 30°, 40°, 50° and 60 ° C employing a thermostated water bath. Each of the measurement was repeated five times.

RESULT AND DISCUSSION

The maximum absorption was found for chloranilic acid (CA) solution at 420 nm. On the addition of amitriptyline (AMT) the absorption maximum shifted to 520 nm (Fig. 1). The purple colour which developed rapidly stabilized after 15 minutes when kept in the dark. The coloured charge-transfer complex (AMT-CA) monitored over a period of 9 h, showed no change in absorbance, supporting stability. It was found suitable for the analysis under the experimental condition. The optimization of the analytical procedure followed the standard protocols; the choice of chloroform and 1,4-dioxan solvents was because of their low dielectric constant unlike acetonitrile and ethyl acetate and the fact that their interaction with CA under the conditions employed was not significant.

The limit of detection of the coloured complex and of quantitation were 5 ng/ ml and 15 ng/ml respectively. The CT complex obeys Beer-Lambert law over a wide range of concentrations suggesting that solvation, isomeric and termolecular complexes were also not formed. The linearity test developed in the optimization and calibration steps satisfied the following model equation:

$$A_{520} = 0.00215 + 2.143 \times 10^{-4}x$$

where A_{520} is absorbance at 520 nm; x is the concentration of the analyte in moles per litre, the correlation coefficient was 0.99. The relative standard deviation of the intercept and slope were 0.0036 % and 0.0012 % respectively when five (5) replicate determinations was carried out. The precision of this analytical technique gave an average relative standard deviation of 0.84. The molar absorptivity of the complex was 4666 l mol^{-1} cm^{-1} with Sandell's sensitivity calculated to be 18 ng/ ml.

The Job's continuous variation plot (Fig.2) shows the 1:1 stoichiometric relationship confirming that isomeric or termolecular complexes were not present. Beer/Lambert plots between 1.0 mg and 20.0 mg/ml were linear. The preponderance of stoichiometric values reported in the literature between π-donors and π-acceptors, particularly with chloranilic acid have been 1:1 (Rizk et al. 1981; Adikwu and Ofokansi, 1997; Onah and Odeiani, 2002). Because of this we proceeded to investigate the equilibrium constant for the complexation applying the method reported earlier (Adikwu et al. 1998).

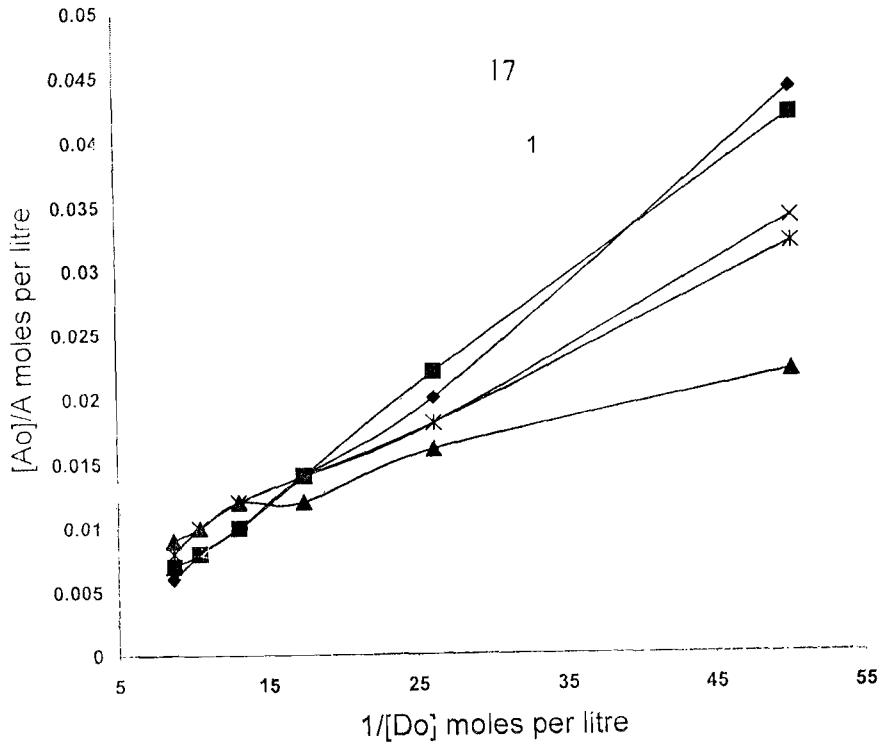


Fig.3: Plot of $[A_o]$ / A against 1 / $[D_o]$ for AMT-CA complex at different temperatures (S_1 = 25 °C; S_2 = 30 °C; S_3 = 40 °C; S_4 = 50 °C and S_5 = 60 °C). $[D_o]$ = 1.911 x 10^{-2} M to 11.466 x 10^{-2} M and $[A_o]$ = 5.01 x 10^{-3} M; A = absorbance.

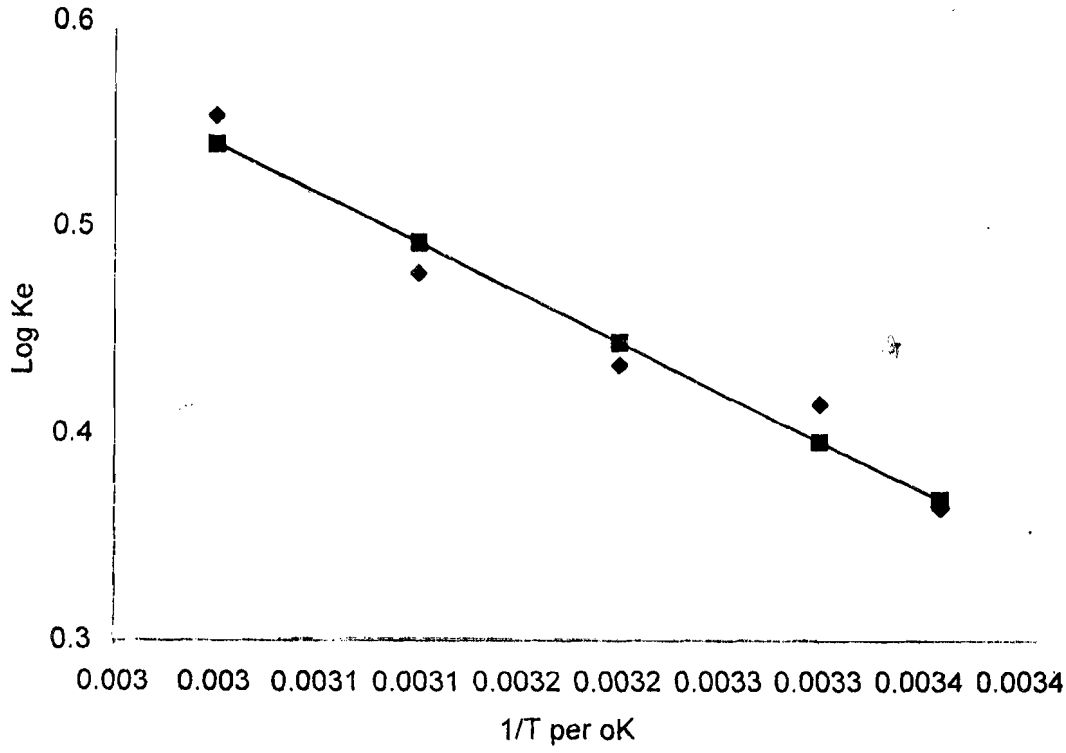


Fig.4: Determination of enthalpy through plot of Log K_e^{AD} against 1 / T K^{-1}. The line curve represents the regressed data.

The interaction between π-donor (AMT) and π-acceptor (CA) has been formulated as follows (Foster, 1969).

$D + A \leftrightarrow D:A$ (1)

from which the equilibrium constant K_e^{DA} can be computed by adapting the Benesi-Hildebrand equation summarized as follows:

$$[A_o]/A = 1/K_e^{DA}.\varepsilon_\lambda^{DA}.[D_o] + 1/\varepsilon_\lambda^{DA} \quad (2)$$

where $[D_o]$ and $[A_o]$ are the initial concentrations of the donor and acceptor molecules; A is the absorbance of AMT-CA at λ_m ; ε_λ^{DA} is the molar absorptivity and K_e^{DA} is the equilibrium constant of the complexation. The fundamental requirement for the application of Benesi-Hildebrand equation is that $[A_o]$ must be kept constant and low by several factors of $[D_o]$ so that K_e^{DA} can be extrapolated to infinite dilution.

The plot of $[A_o]$ / A against 1 / $[D_o]$ gave a linear curve from which K_e^{DA} and ε_λ^{DA} were computed from the slope and intercept respectively. Graphical illustrations of this interaction at different temperatures employing equation (2) are represented in figure 3. Linearity test on the data generated satisfied the following model equation:

$$A_{520} = 0.000216 + 0.000788x$$

with a correlation coefficient of 0.97. The precision associated with the intercept and slope were 1.06 x 10^{-4} % and 5.52 x 10^{-4} % respectively. The intercept of the various plots at different temperatures displayed slight differences that might have arisen from the limitations inherent in the Benesi-Hildebrand model equation. We observed that the plots are closely packed because of the slight differences in equilibrium constant values, as a result of which the experimental points were omitted in the graph.

The thermodynamic energy changes such as the apparent Gibb's free energy (ΔG), enthalpy (ΔH) and entropy (ΔS) were calculated from the following familiar equations:

$$(\Delta G) = -2.303RT\log K_e \quad (3)$$

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

substitution of equation (3) into equation (4), we have

$$\log K_e = \Delta H/2.303\ RT - \Delta S/\ 2.303R \quad (5)$$

From equation (5) the plot of $\log K_e^{DA}$ against the reciprocal of temperature yielded ΔH from the slope (Fig.4), the entropy was calculated from the intercept. In a similar way, this plot was satisfied by the following regression equation

$$A_{520} = 1.52 - 0.635x$$

with a regression coefficient of 0.98. Table1 illustrate these computations which are averages from replicate observations.

The thermodynamic data calculated for the interaction between AMT and CA are relatively very low (by a factor of 10^3) when compared with the general observations reported in the literature (Foster, 1969; Adikwu et al. 1998;

Onah and Odeiani, 2002). A great majority of the earlier reports involve relatively small primary aromatic amines acting as electron donors so it is conceivable that the degree of interaction and consequently the stability between these small molecules depend principally upon their co-planarity. The greater the overlap between the orbital of the donor and acceptor molecules the greater would be the thermodynamic values of ΔG, ΔH and the lower the value of ΔS. From general principles, it is reasonable to assume that there is a direct relationship between stability and large and negative values of ΔG and ΔH. AMT is a large molecule and has a tertiary substitution at the possible donor site (amino group), suggesting a more complicated conformation and stereochemistry of the complex around the donor site. It is our suggestion that the low ΔG and ΔH values when compared directly with earlier reports (Adikwu et al. 1998; Onah and Odeiani, 2002) relate to the difficulty in establishing and maintaining strong orbital over-lap between the donor (AMT) and acceptor (CA) molecules. Of the many unpublished studies that we have carried out in our laboratory involving π-donors and π-acceptors, this is the first time that we experience the influence of stereochemistry at the donor site (propyldimethylamino group) and the associated values of ΔG and ΔH.

The influence of solvation phenomenon on the component molecules (Foster, 1969), possible interference due to donor and acceptor molecules on the absorption maximum of the complex (Foster, 1969), the formation of termolecular and isomeric complexes and the effect of temperature (Foster, 1969) are factors that determine the accuracy and reliability of experimental data (Onah and Odeiani, 2002). Since the stoichiometry in this study was 1: 1 and Beer-Lambert law was obeyed throughout these determinations, we assume that these limitations have been reduced to the barest minimum.

The traditional approach to determining thermodynamic parameters cannot be applied to π-donor / π-acceptor interactions because the associated energy changes which are usually very small cannot be measured with the desired level of accuracy and reproducibility.

CONCLUSION

This study reveals that electronic interaction, (i.e. π electron of donor transfers to antibonding π^*- orbital of the acceptor) is affected by conformation and stereochemistry. The low thermodynamic values obtained in this report are indicative of this relatively weak interaction. The result also shows that termolecular, isomeric, solvation and temperature variables did not influence the absorption behaviour of the complex as Beer-Lambert law was obeyed. The traditional techniques of determining thermodynamic parameters could not be applied in this instance because of very low heat changes evolved. The quantitative application of this charge-transfer complexation to drug analysis will be the subject of the next communication.

ACKNOWLEDGEMENT

The author wishes to express gratitude to the Department of Pharmaceutical Chemistry for material assistance and to CHAN Pharmaceutical Industry Jos, Nigeria for donating pure amitriptyline powder.

REFERENCE

Abdel-Gawad, F. M., 1997. Spectrophotometric determination of some pharmaceutical piperazine derivatives through charge-transfer and ion-pair complexation reactions. J. Pharm. Biomed. Anal. 15(11): 1679-1585.

Adikwu, M. U. and Ofokansi, K. C., 1997. Spectrophotometric determination of moclobemide by charge-transfer complexation. J. Pharm. Biomed. Anal. 16; 529-532.

Adikwu, M.U.; Ofokansi, K.C. and Attama, A.A.1998. Thermodynamic studies of the charge-transfer interactions of chloranilic acid with moclobemide and promethazine hydrochloride. Biol. Pharm. Bull 21; 1243-1246.

Agarwal, S. P. and El Sayed, M. A., 1981. Utility of π-acceptor in charge-transfer complexation of alkaloids: Chloranilic acid as spectrophotometric titrant in non-aqueous media. Analyst 106, 1157-1162.

Baeck, S.K.; Lim, M.A.; Park, S.Y.; Lee, J.S.; Lee, H.S. and Koo, K.S., 2000. Blood concentrations of amitriptyline and its metabolite in rats after acute oral administration od amitriptyline. J. Anal. Toxicol. 24 (4): 271-274

Bauer, E. L., 1971. Statistical Mannual for Chemists. Academic Press, London ,p61-70.

Belal, S. F., Al Kheir, A. A., Ayad, M. M. and Al Adl, S.A., 1986. Spectrophotometric determination of some pharmaceutical carbonyl compounds through oximation and subsequent charge-transfer complexation reactions. Analyst 111: 1039-1043.

British National Formulary (BNF), 1998. The Pharmaceutical press, London, p 154-156.

Foster, R., 1969. In Organic Charge-transfer complexes, Academic Press, London, p33-93

Greenway, G.M. and Dolman, S. J. L., 1999. Analysis of tricyclic antidepressants using electrogenerated chemiluminiscence. Analyst 124(5); 759-762.

Ibrahim, F.A.; Rizk, M.S. and Belal, S.F. 1986. Tetracyanoethylene in pharmaceutical analysis. Part I: A spectrophotometric method for the determination of some pharmaceutically important hydrazines and pyrazolone derivatives. Analyst 111: 1285-1287.

Ibrahim, A. M. A., 1997. Charge-transfer complexes (CTC) of naphthalene derivatives. I CTC of naphthalene, 1- and 2- naphthol with pi-acceptors and iodine. Can. J. Anal Sci. Spectrosc. 42(5): 146-152.

Karpinska, J. and Suszynska, J., 2001. The spectrophotometric simultaneous determination of amitriptyline and chlorpromazine hydrochloride in their binary mixtrues. J. Trace Microprobe tech. 19(3): 355-364.

Macherey Nagel 2001. Application Note, A-1888, 2 Feb., p 2.

Mourad, A. E., 1988. Carge-transfer complexes of benzanilides with π-acceptors. Spectrochim Acta, 44A: 53-56.

Onah, J. O., 1999. Thin-layer chromatographic detection of some common drugs by π-acceptor complexation. Acta Pharm. 49: 217-220.

Onah, J. O. and Odeiani, J. E., 2002. Physico-chemical studies on the charge-transfer complex formed between sulfadoxine and pyrimethamine with chloranilic acid. J. Pharm. Biomed. Anal. 29; 639-647.

Rizk, M. S., Watash, M. I. and Ibrahim, F. A., 1981. Spectrophotometric determination of piperazine via charge-transfer complexes. Analyst 106: 1163-1167.

Sale, G. A. and Askal, H. F., 1991. Spectrophotometric determination of some pharmaceutical amides through charge-transfer complexation reactions. J. Pharm. Biomed. Anal. 3: 219-224.

Veraart, J. R. and Brinkman, U.A.T., 2001. Dialysis-solid-phase extraction combined on-line with non-aqueous capillary electrophoresis for improved detectability of tricyclic antidepressants in biological samples. J. Chromatogr. 922 (1-2): 339-346.

Zhao, J. and Olesik, S.V., 2001. Reversed-phase separation of basic tricyclic antidepressants using buffered and fluoroform-enhanced fluidity mobile phases. J. Chromatogr. 923 (1-2): 107-117.