African Journal of Pure and Applied Chemistry Vol. 5(8), pp. 255-264, August 2011
Available online at http://www.academicjournals.org/AJPAC
ISSN 1996 - 0840 ©2011 Academic Journals

Full Length Research Paper

Spectrophotometric and thermodynamic studies of the charge transfer complexation of nitroimidazoles with chloranilic acid following metal hydride reduction

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Accepted 24 June, 2011

The spectrophotometric and thermodynamic properties of the charge-transfer (CT) complexation formed between reduced nitroimidazoles and chloranilic acid has been carried out. The possibility of room temperature reduction of metronidazole and tinidazole *via* hydride transfer using $LiBH_4$ and $NaBH_4$ was examined and the physicochemical properties of the resulting complex of the reduced nitroimidazoles with chloranilic acid were studied. The energy changes accompanying the formation of the CT band were studied over four temperature ranges of 30, 50, 60 and 80°C. The formation constants and molar absorptivities over these temperature ranges were obtained using the Benesi-Hildebrand plot. Other physicochemical parameters such as energy of transition, transition dipole, oscillator frequency and ionization energies and thermodynamic properties were estimated and related to the stability of the formed charge-transfer band. Reduction of nitroimidazoles with metal hydrides was completed at room temperature within 10 min with the formation of purple-coloured solution with chloranilic acid (CAA). The transition energies were of the order of 2.303 eV with ionization energy of 6.054 eV for the complexes. Variation existed in the oscillator frequency and transition dipole of the formed complexes with higher values obtained for MZ-CAA (metronidazole- chloranilic acid) complex. The Gibbs energy and entropy varied with the temperature and room temperature values favoured formation of stable complexes. The superiority of the metal hydride reduction was clearly evident from well defined physicochemical properties of the CT band and this is the first assessment of the utilization of the room temperature metal hydride reduction of nitroimidazoles.

Key words: Nitroimidazoles, metal-hydride reduction, physico-chemical studies, thermodynamic studies.

INTRODUCTION

Nitro derivatives of five-membered heterocyles are of considerable interest. Some are biologically active with anti-inflammatory or vasodilator activity (Katrizky et al., 2005). The 5-nitroimidazoles are used as antiamoebic, antiprotozoal and antibacterial agents. Two important members of this chemical class are metronidazole and tinidazole. The discovery of the anti-trichomonal properties of metronidazole revolutionised the treatment of disease. Chemically, metronidazole is 2-methyl-5-nitroimidazole-1-ethanol and tinidazole is 1 – (2 – ethyl – sulphonyl ethyl)-2-methyl-5-nitroimidazole (Gennaro, 1993). The biological activity of nitroimidazoles is dependent upon the nitro group reduction due to the formation of active intermediate species (Knox et al., 1981) that interact with DNA to produce biochemical damage. Although, the amoebicidal properties of metronidazole were studied, it was not clinically tested until some years later. The most important derivatives contain the 5-nitroimidazole nucleus with substituents at the N-1 position of the heterocyclic aromatic ring (Zuman and Fijalek, 1990). Subsequent clinical tests have established metronidazole as the drug of choice in the treatment of all forms of amoebiasis in humans (Khambatta, 1968). Variation of the structure of metronidazole, principally to improve trichomonacidal activity and metabolic stability, led to the discovery of tinidazole. Tinidazole is active against *Entamoeba histolytica in vitro,* cecal amoebiasis in rats, and hepatic amoebiasis in hamsters. Clinical tests have established the value of tinidazole in the treatment of intestinal and

hepatic amoebiasis in humans (Khambatta, 1968). Tinidazole has about the same or slightly greater efficacy than metronidazole in the treatment of trichomoniasis and in giardiasis, it has been found to be effective against strains resistant to metronidazole (Gennaro, 1993). The biological activity of nitroimidazoles is dependent upon the nitro group reduction process due to the formation of active intermediate species (Knox, 1981; Edwards et al., 1986; Declerck and De Ranter, 1986; Declerck and De Ranter, 1987; Tocher and Edwards, 1984) that interact with DNA to produce biochemical damage.

Several methods have been reported for the determination of metronidazole and or tinidazole in bulk and dosage forms or in biological fluids. Majority of the procedures involve the reduction of nitro groups to the amino group prior to analysis. Some of the previously reported reducing agents and conditions are; Zn/HCl (Ahmed and Onah, 2003), Zn/HCl at elevated temperature (Rehman et al., 2005; Sastry et al., 1988) and Pd-C and formic acid (Dinesh et al., 2004). In our previous report (Adegoke et al., 2010), we established for the first time the possibility of room temperature reduction of nitroimidazoles using metal hydrides since majority of the previously adopted reduction systems are carried out at elevated temperatures. A new spectrophotometric method based on charge-transfer complexation of the reduced nitroimidazoles with chloranilic acid was then developed. The method was successfully applied to the determination of metronidazole and tinidazole in dosage forms and it compared favourably with pharmacopoeial methods.

In this paper, the spectrophotometric and thermodynamic studies of the formed CT complex are presented and thereby establishing the potential of room temperature hydride transfer reduction process.

EXPERIMENTAL

Materials and reagents

Metronidazole and tinidazole chemical reference substances (Sigma, USA). All reagents and solvents used were of analytical grade and include; methanol, ethyl acetate, ethanol, sulphuric acid, chloroform, acetone, 1,4-dioxan, hydrochloric acid, $LiBH_4$, $NaBH_4$, Pd-C, Zinc dust, acetic. Distilled water, glacial acetic acids, acetonitrile, chloranilic acid was obtained from Sigma – Aldrich, USA.

Equipment

A UV/VIS spectrophotometer (Unicam aurora, Pye Unicam, UK) Analytical balance H80 (Mettler, UK), Ultrasonic bath (Langford Electronics, UK), Vortex mixer (Griffins and George Ltd; Great Britain).

Preparation of stock solutions

Standard solutions of pure reference metronidazole and tinidazole (1200 µg ml^{-1}, corresponding to 7×10^{-3} and 4.9×10^{-3} mol L^{-1}, respectively) were prepared in 1,4-dioxan.

A 0.025 g quantity of chloranilic acid (CAA) powder was weighed into a clean 25 ml volumetric flask and acetonitrile (5 ml) was added. This was then shaken until it had dissolved appreciably. The solution was then made up to 25 ml mark with acetonitrile to make 0.1% w/v chloranilic acid solution.

General procedure for the reduction of the nitroimidazoles

A general approach to determine the best reducing agent for the nitroimidazoles was adopted by reducing the Metronidazole (MZ) and tinidazole (TZ) in 1,4-dioxan using the reduction systems; Zn/HCl in ethanol at 90°C, Palladium-Carbon/glacial acetic acid, $LiBH_4$/glacial acetic acid and $NaBH_4$/glacial acetic acid at room temperature. The optimum time required for the reduction process to go to completion was determined through the formation of purple colour with chloranilic acid, which represents the conversion of the nitro group to the amine. The effect of elevated temperature on the purple colour produced was studied by incubating the reaction vessels at 80°C and monitoring the colour changes.

In each case, a 0.025 g quantity of metronidazole powder was weighed into 7.5 ml hot ethanol with 2 ml 5 M HCl solution and 0.25 mg zinc dust in a clean beaker. The mixture was heated in a water bath at 90 ± 5°C for 15 min. The residue was cooled, filtered and washed with ethanol into a 25 ml flask. The solution was then made up to 25 ml mark with ethanol to make 0.1% w/v metronidazole stock solution (Rehman et al., 2005). The same procedure was repeated for TZ using 0.03 g quantity of tinidazole powder to give 0.12% w/v TZ stock solution. Four other reducing agents were used for the preparation of reduced metronidazole and tinidazole namely; glacial acetic acid and 0.25 mg Pd – C (room temperature) (Dinesh et al., 2004), glacial acetic acid and 0.25 mg $LiBH_4$ (room temperature), glacial acetic acid and 0.25 mg $NaBH_4$ (room temperature) and glacial acetic acid and 0.25 mg zinc dust (room temperature). The reduction procedures were quantitatively monitored by TLC and UV-VIS spectrophotometer.

Optimization of reaction conditions

The various reaction conditions such as optimum temperature required for the formation of charge transfer complexation between reduced nitroimidazoles and CAA was studied alongside optimum time and stoichiometric ratio as previously reported (Adegoke et al., 2010).

Validation studies

Using the optimized procedures, calibrations graphs were prepared as previously reported as follows; six tubes containing varying volumes of reduced metronidazole (MZ) stock solution, (0, 0.025, 0.05, 0.1, 0.15 and 2.0 ml) with respective concentrations (0, 5, 10, 20, 30 and 40 µg/ml) were prepared. 0.5 ml of the CAA was added to each of these tubes. These were allowed to stand for 5 min after which respective volumes of 1, 4-dioxan/Acetonitrile (6:4) mixture was added to make up to 5 ml reaction mixture. The absorbance readings of each of the mixtures were then recorded at 520 nm. For reduced tinidazole (TZ) stock solution (0, 0.02, 0.04, 0.08, 0.13, 0.17 and 0.33 ml) with respective concentrations (0, 4.8, 9.6, 19.2, 31.2, 40.8 and 79.2 µg/ml) were prepared. Sample work-up was repeated as for MZ. The absorbance readings of each of the mixtures were then recorded at 520 nm. These processes were repeated three times and on each occasion freshly prepared reduced metronidazole and tinidazole (TZ) stock solution was used. The average absorbance reading was obtained from the determinations, and used to generate the calibration curves.

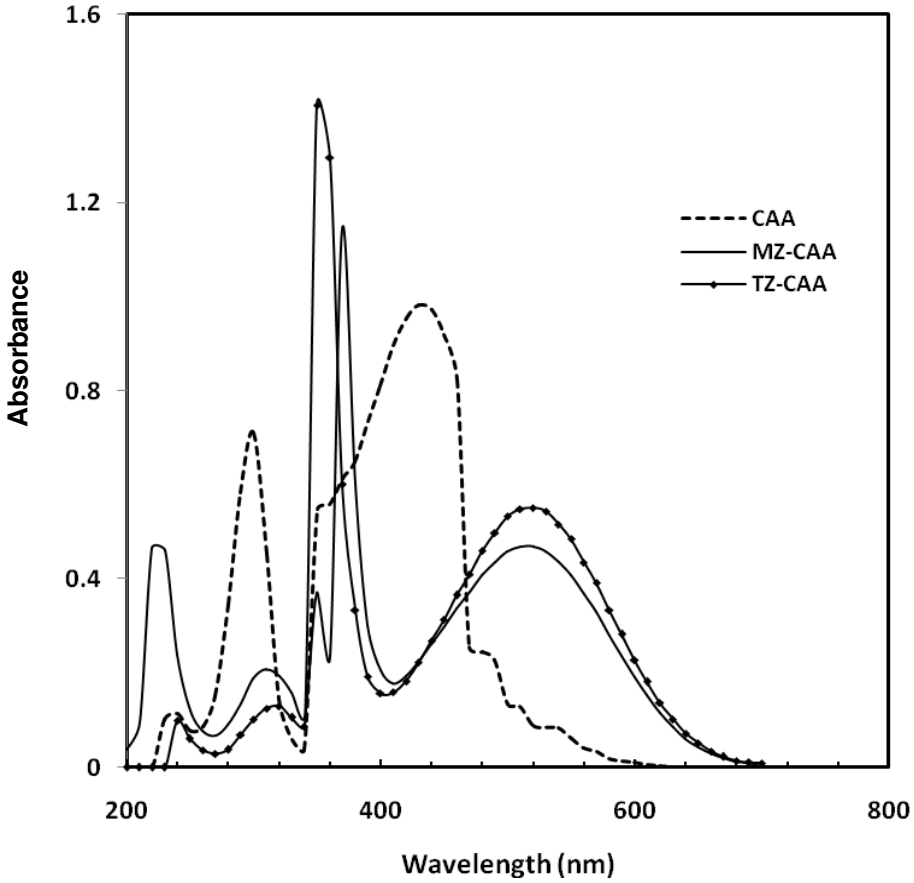


Figure 1. Absorption of spectra of the charge transfer complexation between metronidazole and tinidazole overlaid on chloranilic acid.

Estimation of molar absorptivity and formation constants

The Benesi-Hildebrand plot (Benesi and Hildebrand, 1949) was constructed from the calibration graphs to estimate the molar absorptivities and formation constants of the CT complexes formed between the CAA and the nitroimidazoles. The effects of temperature change on these parameters were studied by recording the absorbance of the charge transfer (CT) band at elevated temperatures and calculating the molar absorptivities and formation constants from the Benesi-Hildebrand equation.

Physicochemical parameterization of charge transfer complex

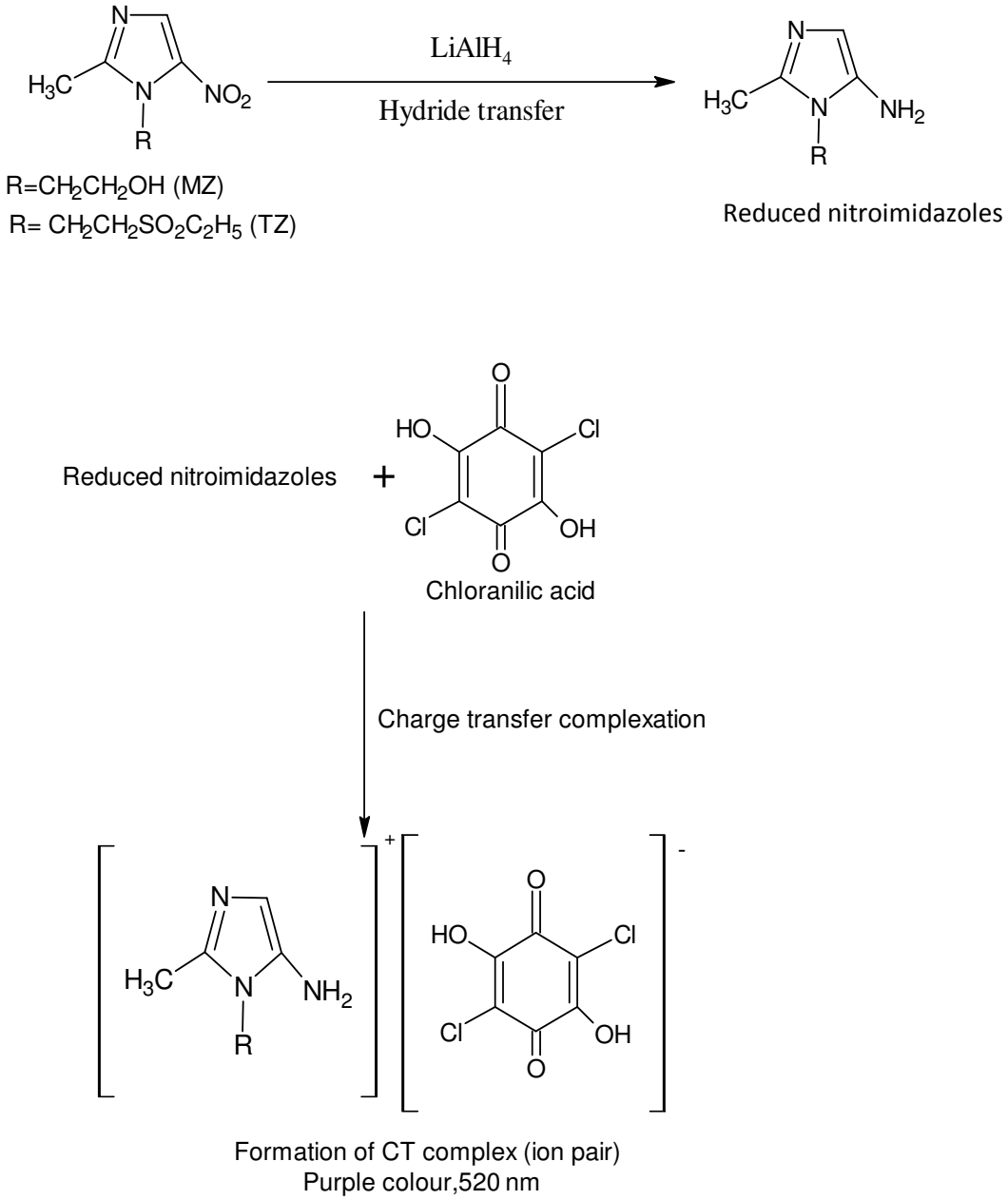
Some physicochemical properties of the charge transfer (CT) bands were estimated such as molar transition energy, oscillator strength, transition dipole, resonance energy and the ionization potential of the donor species; in order to establish the stability or otherwise of the formed complex between the reduced nitroimidazoles and CAA.

Thermodynamic studies

The free energy change, enthalpy of formation and the entropy associated with the formation of the new CT complex between CAA and nitroimidazoles reduced with metal hydrides were estimated from the data obtained at different temperature levels consisting of 30, 50, 60 and 80°C.

RESULTS AND DISCUSSION

The reduced forms of metronidazole and tinidazole formed immediate purple color with chloranilic acid. This is an evidence of the formation of a charger-transfer (CT) complex (Adegoke et al., 2011). Chloranilic acid is a well known π-acceptor and the reduced drugs containing amino functional groups serve as *n*-donors. Chloranilic acid has been used for the spectrophotometric determination of drugs containing n-electron donors such as nitrogen and oxygen (Mahrous et al., 1986; Zakhari et al., 1986; Okide and Udoh, 1998; Adikwu et al., 1999; Basavaiah and Charan, 2002). This molecular complex consists of constituents held together by weak secondary valence forces of the donor-acceptor type or hydrogen bonds. This secondary valence force is not a clearly defined bond but rather as an overall attraction between two aromatic molecules. Important factor in the formation of molecular complexes by this compound is presence of steric factors which hinders this process (Alfred et al., 1993). The absorption spectra of chloranilic acid and the complexes produced with the reduced nitroimidazoles are presented in Figure 1 for MZ and TZ complexes. The MZ complex exhibited pronounced peaks at 220, 310,



Scheme 1. Formation of charge-transfer complexation between reduced nitroimidazoles and chloranilic acid.

370 and a new low energy band at 520 nm. This new low-energy band which represents a bathochromic shift relative to CAA and reduced MZ was selected as the analytical wavelength. For TZ complex however, minor peaks were observed at 240 and 310 nm while the major peaks were at 350 and 520 nm. The slight differences in the intensity of the peaks points to the differences existing in the structure of the two nitroimidazoles. Since both metronidazole and tinidazole are 5-nitroimidazoles and both contain substituents at the 1-position (1-ethanol group in MZ and 1-ethyl-sulphonyl-ethyl in TZ) and the 5-methyl (ethyl in TZ) group the only substituent difference is the presence of ethyl sulphonyl group in TZ at1-position replaced by 1-ethanol group MZ. This may be responsible for the observed slight difference in their absorption spectra. However, as slight as the difference is, the high energy bands observed in MZ-CAA complex became completely minor peaks in TZ-CAA complex absorption spectrum showing that the sulphonyl-ethyl group has a deactivating influence on the 5-nitroimidazole skeleton. The reaction occurring leading to the formation of the new CT band is presented in Scheme 1. The formation of a radical anion in such molecular interactions has been established by

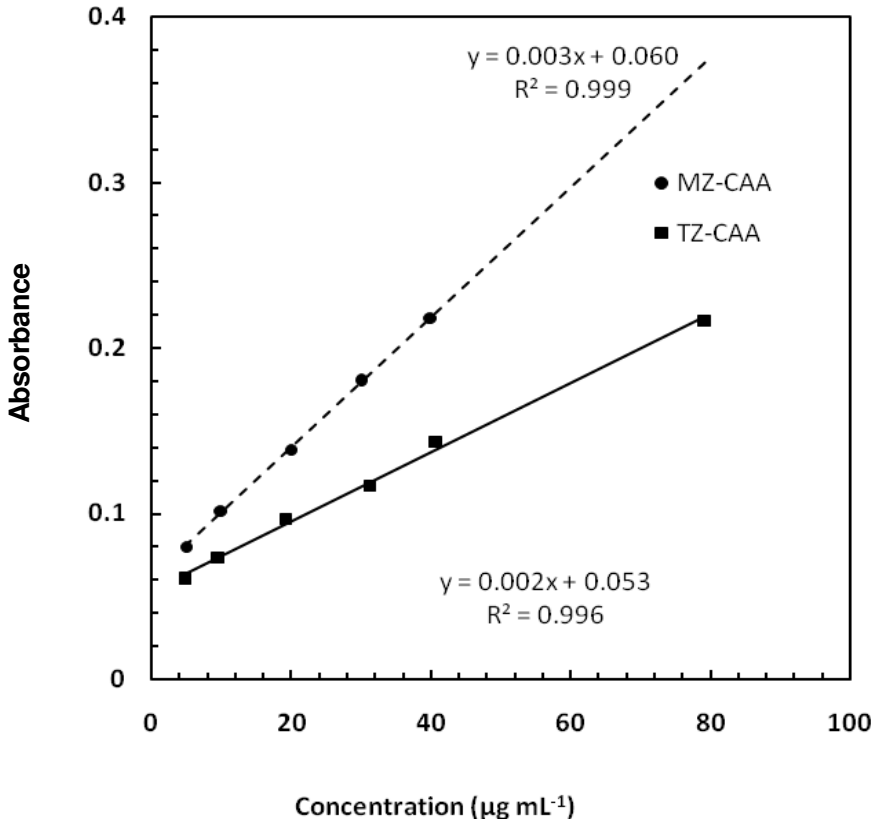


Figure 2. Calibration curves for the charge transfer complexes.

electron-spin resonance measurements (Abdel-Salam et al., 1985). The low energy band resulting from the CT complex formation represents a wavelength that is significantly higher than some of the previously reported procedures, offering the advantage of simple colorimetric analysis of these nitroimidazoles. The new band has been used for the spectrophotometric determination of the nitroimidazoles in dosage forms as previously reported (Adegoke et al., 2010).

Optimization reactions

The room temperature reduction process was adopted for the eventual determination of the nitroimidazoles as it yielded coloured derivatives that were stable and peak characteristics that were prominent and consistent. Optimization of reduction time revealed that reduction was completed within 10 min using the metal hydrides and was also found to be convenient since room temperatures were adopted. Intense and immediate purple colour was obtained when Pd-C, $LiBH_4$ and $NaBH_4$ were used as reducing agents in glacial acetic acid. The inability of Zn in ethanol to effectively reduce the compounds and then generating the purple-coloured complex with CAA might be due to interaction of Zn with CAA preventing it from being available for charge-transfer reaction. Due to the homogenous nature of $LiBH_4$, it was adopted as the reducing agent for both MZ and TZ, as this will not require filtration unlike Pd-C and Zinc reducing systems. The use of metal hydride reduction for the nitroimidazoles was the first reported procedure and convenient utilization of reducing agents. Many other reduction processes are usually carried out at elevated temperatures. The reduction of metronidazole has been reported to be a complex process involving 6 electrons for complete reduction of the nitro group to the amine derivative *via* hydroxylamine intermediate (La-Scalea et al., 1999). The purple colours produced with CAA however became slightly discharged at elevated temperatures. This is typical of most CT complexes as increase in temperature destroys the intermolecular binding forces of attraction between ion pairs.

Optimal difference in absorptivities were obtained when a 6:4 ratio of acetonitrile to 1,4-dioxan was used as solvents for quenching of the reaction.

Validation studies

The calibration curves prepared using the optimized procedures are presented in Figure 2 for both the MZ and TZ complexes. Excellent calibration data were obtained for the average determinations of the calibration curves

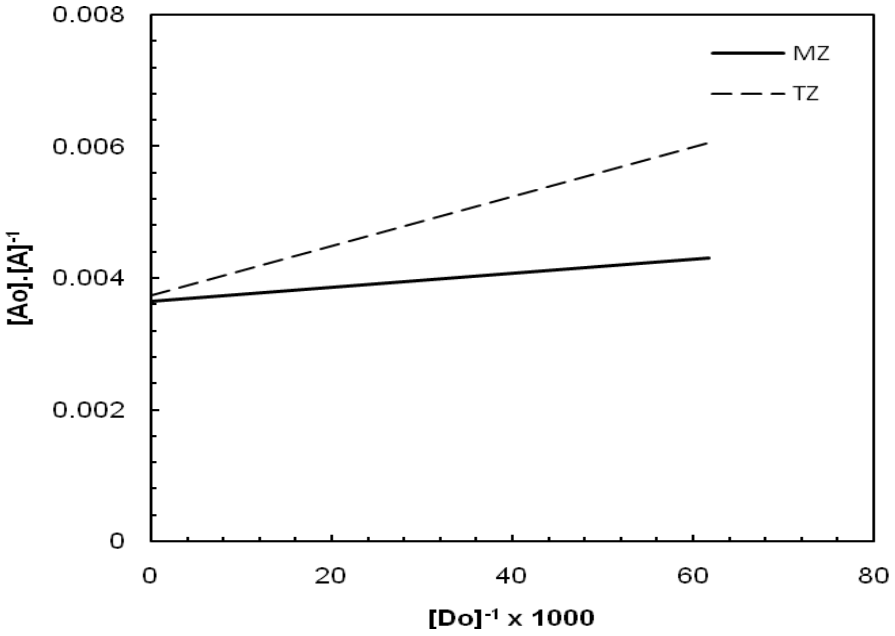


Figure 3. Benesi-Hildebrand plot for the charge transfer complexation.

Table 1. Evaluation of molar absorptivities and formation constants as a function of temperature.

Temperature (°C)	Molar absorptivity (ε) (L Mol^{-1} Cm^{-1})		Formation constant (K)	
	MZ	TZ	MZ	TZ
30	1.312×10^3	4.2986×10^3	5.578×10^9	5.9314×10^9
50	5.478×10^2	6.256×10^2	1.4904×10^9	1.8107×10^9
60	5.136×10^2	5.9345×10^2	1.3973×10^9	1.7177×10^9
80	4.794×10^2	5.6872×10^2	1.3041×10^9	1.646×10^9

constructed on each of three successive days. For metronidazole complex, the linear regression line equation is Y= 0.003 X + 0.060 with a coefficient of determination of 0.999 while for the tinidazole complex, Y = 0.002 X + 0.053 (r^2 = 0.996). For equimolar concentration of MZ and TZ with respect to CAA, higher absorptivities were observed for MZ complex relative to that of TZ complex confirming once again the improved colour formation of MZ to TZ complex due probably to differences in the functional groups attached to the two nitroimidazoles as noted for the absorption spectra earlier.

Estimation of molar absorptivity and formation constants

The absorbance values obtained in the calibration curve plot were plotted as a function of ratio of the molar concentration of the donor: acceptor ($[D]_0$: $[A]_0$) according molar absorptivities and formation constants were observed for the studied complexes at room temperature to the Benesi-Hildebrand equation (Benesi and Hildebrand, 1949).

$$\left(\frac{[A]_0}{A} = \frac{1}{K_{CT}\varepsilon_{CT}} \cdot \frac{1}{[D]_0} + \frac{1}{\varepsilon_{CT}}\right) \quad (1)$$

where $[A]_0$ is the initial concentration of the acceptor (CAA), A is the absorbance of the charge transfer band, $[D]_0$ is the initial concentration of the donor (nitroimidazoles), K_{CT} is the formation constant of the new charge transfer band and ε_{CT} is the molar absorptivity.

A plot of $[A]_0$ /A against $1/[D]_0$ will yield intercept as $1/\varepsilon$ and the slope as $1/K\varepsilon$ from where the formation constant and the molar absorptivity are obtained. The concentration of the acceptor was kept greater than the donor and fixed so that a wide concentration range could be adopted. The Benesi-Hildebrand plot is presented in Figure 3. The estimated molar absorptivities and formation constants as a function of temperature are presented in Table 1. As evident from the results, highest relative to the values determined at higher temperature levels. Marginal differences were however observed for

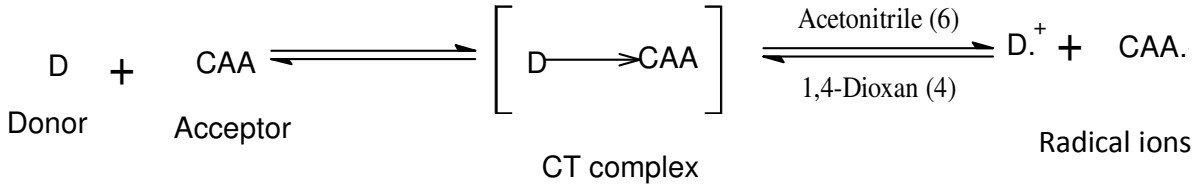


Figure 4. Donor-acceptor mechanism in charge-transfer process.

these parameters at temperatures of 50, 60 and 80˚C, though a gradual decline in the parameters were obtained. Although, the molar absorptivities is supposed to be independent of temperature, empirically this has been found not to hold true. This observation was also observed in the study of the CT complexation of CAA with pyrimethamine and Sulphadoxine (Onah and Odeiani, 2002). The plausible reason for the decline of molar absorptivities and formation constants as temperature increased may be due to the decreasing absorbance values of the formed CT band with elevated temperature. Since the formation of a charge transfer complex is an association of some type, and probably an association existing in equilibrium (Figure 4), any factor that will promote dissociation of the complex will lead to reduced absorptivity.

Temperature is one of such factors that can lead to breakdown of the formed complex especially if such formation is associated with an exothermic change and this will lead to the equilibrium shifting towards the free donor and acceptor species which do not have significant absorbance values at the 520 nm used as analytical wavelength. Thus expectedly, the complexes were determined at room temperature.

Physicochemical parameters for the charge transfer complexes

In order to characterize the formation of the complexes between the reduced nitroimidazoles and the charge acceptor, CAA, some physicochemical parameters were estimated to explain the propensity of the formation of the complexes.

The oscillator strength (*f*) is a dimensionless quantity used to express the transition probability of the CT band and the transition dipole moment (μ_{EN}) of the CT complex (Tsubomura and Lang, 1961). Both parameters are obtained from Equations 2 and 3, respectively.

$$f = 4.32 \times 10^{-9} [\varepsilon \Delta v_{1/2}] \quad (2)$$

$$\mu_{EN} = 0.0958 \left[\frac{\varepsilon_{CT} \Delta v_{1/2}}{\Delta v}\right]^{1/2} \quad (3)$$

where $\Delta v_{1/2}$ is the half-width, that is, the width of the band at the half the maximum absorption, and Δv ≈wavenumber at the absorption maximum. The oscillator strength, *f* and the transition dipole moment obtained are 5.67 and 1.86 for MZ and TZ complexes and 0.786 and 0.450 Debye respectively for MZ and TZ complexes.

Another physicochemical parameter calculated was the transition energy of the complex which is obtained from the expression hv_{CT} where *h* is Planck's constant and v_{CT} is the wavenumber of the absorption peak of the CT complex. The transition energy was found to be 2.303 eV, since both complexes absorbed maximally at 520 nm in the visible region which was used as the analytical wavelength.

The ionization potential, I_D, of the donor in the charge transfer complex is calculated using the empirical equation derived by Aloisi and Pigantro (1973) (Equation 4).

$$I_{D\,(ev)} = 5.76 + 1.53x10^{-4} v_{CT} \quad (4)$$

where v_{CT} is the wavenumber of the CT band in cm^{-1}. I_D was found to be 6.054 eV.

The resonance energy of the complex (R_N) in the ground state is obtained from the theoretical equation derived by Brieglab (1961) given in Equation 5.

$$\varepsilon_{CT} = 7.7 \times 10^4 / [hv_{CT}]/R_N - 3.5 \quad (5)$$

where ε_{CT} is the molar absorptivity of the complex at the maximum of the CT absorption, hv_{CT} is the transition energy of the complex .

The resonance energy was calculated as 3.703 and 1.261 eV respectively for MZ and TZ.

The dissociation energy (*W*) of the formed CT complex between reduced nitroimidazoles and CAA was calculated from the transition energy(hv_{CT}), ionization potential of the donor (I_D) and the electron affinity of CAA (E_A = 1.1) using the relationship (McConnel et al., 1953) in Equation 6.

$$hv_{CT} = I_D - E_A - W \quad (6)$$

The dissociation energy was found to be 2.651 eV.

The various physicochemical parameter obtained are summarised in Table 2. Some observable trends are clearly evident from these physicochemical parameters.

Table 2. Physicochemical parameters for the formation of CT-complex between nitroimidazoles and chloranilic acid.

CAA complex	CT λ_{max} (nm)	hv_{CT} (eV)	f	μ_{EN} (Debye)	R_N (eV)	I_D (eV)	W (eV)
MZ	520	2.303	5.67	0.786	3.703	6.054	2.651
TZ	520	2.303	1.86	0.450	1.261	6.054	2.651

The values obtained points to the good stability of the complex formed between CAA as acceptor and reduced nitroimidazoles as donors. The ionization potential of the donor gave a high value of 6.054 eV showing reduced nitroimidazoles as good *n*-electron donors. This is not surprising as nitrogen atom whether as a primary, secondary or tertiary amino group happen to be one of the best electron donors in charge transfer complexation reactions and most of the previously reported procedures involving CAA have been successfully carried out when the donor functional group contains nitrogen. The transition energy is about two times less than this ionization energy of reduced nitroimidazoles, hence, the energy is readily surmounted and the complex is produced readily. I_D was also found to be higher than the dissociation energy, W. Thus, the spontaneous decomposition of the CT complex will be minimal especially at room temperature where these values were obtained from.

The relatively high dissociation energy also implies that decomposition of the complex will require an externally applied energy which was noticed with increasing temperature. Likewise, the high values of the oscillator frequency and the resonance energy point to the good stability observed for the complexes. Indeed, the complexes were stable for days in the laboratory environment. The transition dipole moment having a high value suggests the existence of a good ion pair which was readily solvated and stabilized by the acetonitrile/1,4-dioxan as solvent mixture. The transition dipole and the oscillator frequency of the MZ-CAA complex were higher than the respective values for the TZ-CAA complex. This once again points to the higher stabilization impartation by the activating groups in metronidazole relative to the mildly deactivating influence of sulphonyl group in TZ. This stabilization effect is further demonstrated in the resonance energy obtained for MZ-CAA complex which is about two times higher than that observed for TZ-CAA complex.

Thermodynamic considerations of the CT complexation

The thermodynamic functions, standard free energy change (ΔG^0) the enthalpy change (ΔH) and the entropy change (ΔS) were obtained from the well established Equations 7, 8 and 9 respectively.

$$-\Delta G^0 = 2.303RT\log K_{CT} \quad (7)$$

$$Log\ K = -\frac{\Delta H}{2.303}\left(\frac{1}{T}\right) + Constant \quad (8)$$

$$-\Delta G^0 = \Delta H - T\Delta S \quad (9)$$

The enthalpy of the CT formation was obtained by plotting the Log of formation constant against the reciprocal of absolute temperature. The plots for MZ and TZ complexes are presented in Figure 5. The various thermodynamic parameters obtained are presented in Table 3. The standard free energy gave a negative value pointing to the exothermic nature of the complex formation. This thus explains why higher temperature values led to decrease in the absorbance of the complex. The Gibbs free energy became increasing higher with increase in temperature denoting that it becomes difficult to generate the complex at higher temperatures. Since it is established that the formation of the complex occurs through an exothermic process, higher temperature will prevent the spontaneity of the charge transfer complexation. Hence, lower absorptivities and lower formation constants were also obtained as temperature increased. The high Gibbs free energy obtained even at room temperature however attests to the ease of formation of the complex. Generally, slightly higher free energy values were obtained for the TZ complex confirming once again the ease of formation of the MZ-CAA complex by virtue of activating substituents. Though relatively small, the enthalpy change also points to the possibilities of ease of formation of the CT complexes. The enthalpy of formation for the MZ complex is higher than that of the TZ complex pointing to the relative ease of the formation of the MZ-CAA complex. The entropy also gave relatively high values with the value reducing as temperature increased. A gradual decline in the entropy with temperature increase was observed for both systems implying a lower degree of randomness as a function of temperature and lower tendencies of forming stable complexes. All the thermodynamic parameters estimated however suggest that the complexes are relatively stable at room temperature compared to the elevated temperatures and demonstrated the suitability of metal hydride-reduction for the nitroimidazoles.

Conclusion

The formation of stable complexes when the nitroimidazoles were reduced by metal hydride as evident from the formation constants, transition and thermodynamic energy changes points to the suitability of

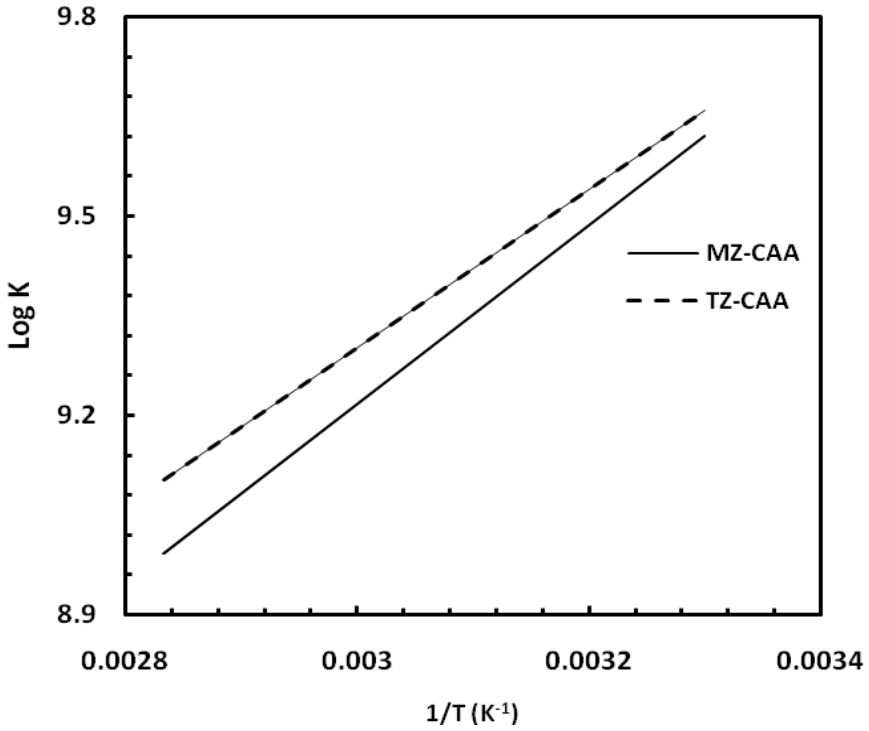


Figure 5. Plot of Log K of MZ and TZ complexes as a function of 1/T (K^{-1}).

this reduction system for routine analysis. Further extension to other reducible groups will be investigated later.

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