Study of Charge transfer complexes of chlorothiazide

Asmaa A. Ibrahim*, Farouk A. Adam³ and Ahmed M. Allam³

Chemistry Department, Faculty of Science, Aswan University, Aswan 81528, Egypt.

Received: 31/12/2020
Accepted: 4/2/2021

© Unit of Environmental Studies and Development, Aswan University

Abstract:
The CT-complexes of chlorothiazide (n-donor) with picric acid, 3, 5-dinitrobenzoic acid (pi-acceptor) and iodine (sigma-acceptor) were investigated at different temperatures and solvents. These complexes were investigated in polar solvents (methanol, acetonitrile) and nonpolar solvents (dichloromethane and chloroform). The structures of the CT-complexes were studied by 1HNMR, infrared spectra and elemental analyses. The donation method was occurred from the lone pair of electron of nitrogen atom in chlorothiazide to pi-acceptors (n→ π*) and to sigma-acceptor (n–σ). Scanning electronic microscopy (SEM) shows images of chlorothiazide with 3,5-dinitrobenzoic acid, indicates that the produced complex is crystalline with a rod-like shape as the major crystals shapes. The molecular composition of the charge transfers complexes was 1:1 ratio (donor: acceptor) which determined by spectrophotometric titration. The extinction coefficient, εCT, the formation constant, KCT, transition dipole moment (μ), the oscillator strength (f), resonance energy (RN), ionization potential IP and transition energy (ECT) values of the complex were calculated.

Keywords: Drug; acceptors; IR spectra; spectrophotometric titration

1- INTRODUCTION
Chlorothiazide is good diuretic agent. The pharmacology of the drug explains the mechanism of action and shortcomings of problems of kidney function and systemic arterial hypertension. The pKα of chlorothiazide are listed as 6.85 and 9.45 (Whitehead et al., 1961). Chlorothiazide determinate by ultra violet spectra, chromatography and electrochemically (Sunshine, 1963; Abdel-Moety et al., 1993; Cohen et al., 1962). Complexes of the chlorothiazide with transition metals were studied (Supuran, 1996). The CT- complex of hydrochlorothiazide and reserpine with iodine were determined (Abdine et al., 1978). The reaction of 2-aminothiazole with acceptors as 3, 5-dinitrosalicylic acid and 3, 5-dinitrobenzoic acid yield 1: 1 molar ratio (Mohamed et al., 2005). The formation of charge transfer complex of oxatamide as donor with 2, 3-dichloro-5, 6-dicyanobenzoquinone as acceptor was determined spectrophotometric at different temperatures and solvents (Pandeeswaran and Elango, 2006). Studies of complexes formed of colchicine with acceptors were determined in dichloromethane at 21°C (Arslan and Duymus, 2007).

Corresponding author*: E-mail address: doc_somaia@hotmail.com
Interaction between azelastine and pa-acceptors were synthesized to form charge transfer complexes. (Salama et al., 2011). The CT- complexes were given from the reactions of chloranilic acid and picric acid with the Sweeteners Saccharin (Naglah et al., 2015). Interaction of 3, 5-dimethylpyrazole with 2, 3-dichloro-5, 6-dicyano-p-benzoquinon were studied (Habeeb et al., 2015). The reaction between iodine and drugs (nortriptyline and imipramine) determined spectrophotometric at various temperatures insolvents as chloroform and dichloromethane (Hasani and Akbari, 2007). The interactions of aryl 2-azomethine dibenzothiophene with nitrobenzene compounds were determined. (El-Mossalamy et al., 2016). The reaction between iodine and drugs (nortriptyline and imipramine) determined spectrophotometric at various temperatures insolvents as chloroform and dichloromethane (Hasani and Akbari, 2007). The interactions of aryl 2-azomethine dibenzothiophene with nitrobenzene compounds were determined. (El-Mossalamy et al., 2016). The CT- complex of thymol with Bromocresol purple were studied by elemental analyses, UV-Vis and IR (Ibrahim et al., 2017). The CT – complexes of mebendazole with chloranilic acid (CA), 3,5-dinitrosalicylic acid, and picric acid were confirmed by analytical tools (Alghanmi and Alhazmi, 2019). In this article, spectrophotometric studies were used for the conformation of CT complexes formed between the chlorothiazide and acceptors at different temperatures and solvents. The formation constants and physical parameters were studied.

2- MATERIALS AND METHODS

2.1. Materials and reagents

Donor was obtained from Chemical Industries Development (Syed), Acceptors and solvents were obtained from Sigma-Aldrich Chemical Company. The structure of Chlorothiazide, 3,5-dinitrobenzoic acid and picric acid compounds are displayed in Scheme 1.

2.2. Instrumentals

Elemental analyses (Perkin-Elmer CHN 2400) were measured carbon, hydrogen, and nitrogen percent. The spectra of reactants and charge transfer complexes were obtained from a Jenway 6305 Spectrophotometer (range 200–600 nm).1HNMR data were recorded on Varian Spectrometer (200 MHZ). Scanning electron microscopy of CT-complex were used on SEM-Quanta FEG 250 instrument. Infrared spectra were obtained on Bruker FT-IR Spectrophotometer (4000–400 cm⁻¹).

2.3. Preparation of solid complex

Where adding solution of chlorothiazide (2957 mg, 1mmol) to solution of iodine (1269 mg, 1mmol), picric acid (229 mg, 1mmol) and 3,5-dinitrobenzoic acid (212 mg, 1mmol). The reaction mixtures were stirred for about 3 h, kept overnight where the yield precipitated. The yields were filtered, washed and left for 24 h to dry.

2.4. Photometric method

Photometric method was determined for the reactions of the drug and the acceptors. X=0.25, 0.50, 0.75, 1.00, 1.50, 2.0, 2.50 and 3.00 mL of acceptors solution (0.6×10⁻³ M) addition to 1.00 mL of donor (0.6×10⁻³ M) and complete by solvent in measuring flask 5. The photometric titration curve obtained by the draw of the maximum value of absorbance against to the Cd: Ca ratio (Skooge, 1985). KC and εCT value calculated by applied modified Benesi-Hildebrand equation (Benesi and Hildbrand, 1949).

2.5. Biological effect

All complexes were tested with bacterial strains (Staphylococcus aureus and Escherichia coli) and fungal strains (Penicillium corylophilum, Alternaria alternate and Fusarium verticillioides).
Scheme 1. The structure donor and acceptors (chlorothiazide (CH), picric acid (PA), 3,5-dinitrobenzoic acid (DNB)).

3- RESULTS AND DISCUSSIONS

3.1. Elemental analyses

In Table (1), the values of Elemental analyses were consistent with the photometric data of donor: acceptor (1:1 ratio). So that, the proposed molecular were formulated as CH-DNB, CH-PA, and CH-I2 (Scheme 2).

![Chemical structures](image1)

Scheme 2. Proposed molecular structure of CT complexes

| Compound          | MP, °C | Elemental analysis | color  | Yield, % |
|-------------------|--------|--------------------|--------|----------|
|                   |        | C (found)          | H (found) | N (found) |        |
|                   |        | Cal.               | Cal.    | Cal.     |        |
| CH                | 330    | (28.43)            | (2.05)  | (14.21)  | white  | 85     |
|                   |        | 29.75              | 2.15    | 15.81    |        |        |
| (CH)(PA)          | 345    | (16.56)            | (1.62)  | (8.61)   | yellow | 85     |
|                   |        | 16.02              | 1.152   | 8.01     |        |        |
| (CH)(DNB)         | 340    | (33.65)            | (2.05)  | (13.22)  | light yellow | 80 |         |
|                   |        | 33.11              | 1.99    | 13.79    |        |        |
| (CH)(iodine)      | 335    | (16.14)            | (1.15)  | (8.41)   | white  | 75     |
|                   |        | 15.30              | 1.10    | 7.64     |        |        |

3.2. Infrared spectra of studied CT- complexes

The IR spectra of the complexes differed from free acceptors and donor. The infrared spectrum of chlorothiazide (CH) and complexes represented in Figure (1) and Table (2). The band of nitrogen (N) in (CH) is shifted to lower value in the CT complex and this may be attributed to N-H bond (Swaminathan et al., 2009). This has proven that –N atom of...
chlorothiazide (CH) protonation through H⁺ of hydroxyl group in picric acid. The bands of the picric acid were shifted to smaller wave numbers which reflects a chlorothiazide to picric acid charge transfer of n→π*, DHOMO →DLUMO transition (Bharathikannan et al., 2008). The IR bands of the CH and DNB compared with the IR bands of the charge transfer complex indicates that the CH bands show decreasing in intensity result the forming of the charge transfer complex as exhibited in Table (2) and Figure (1). The complex between CH and DNB comes through the hydrogen centered between -COOH with one of –N atom of CH (n→π*) to form hydrogen bond (Nash and Allison, 1963). The stretching frequency of the CH-I₂ complex has showed smaller changes in intensities and frequency than the data of CH as shown in Figure (1) and Table (2). This has proven that the charge transfer transition occurs from the nitrogen atom to iodine (n–σ*). Scheme 3, showed the charge transfer complex of CH with PA, DNB, and iodine.

**Table 2 The IR spectra of CH, PA, DNB and its CT complexes**

| CH   | DNB  | PA   | CH-DNB | CH-PA  | [CH-I₂]   | Assignments |
|------|------|------|--------|--------|-----------|-------------|
| 3400 s | 3462 mw | 3416 s | 3334 m | 3332 m | 3332 m | ν (O-H); ν (N-H) |
| 3063 mw | 3092 mw | 2980 ms | 3092 mw | 3101 m | 3063 w | ν(C-H); C=C and combination |
| 3002 mw | 2957 vw | 2872 m | 2884 vw | 2821 vw |           |             |
| 2962 w | 2985 w | 2932 w | 2980 m | 2872 m | 2932 w | H-bonded           |
| 1676 mw | 1858 m | 1861 m | 1704 m | 1610 mw | 1617 mw | ν(C=O) of DNB; ν(NO₂) of PA |
| 1608 mw | 1627 ms | 1632 m | 1555 mw | 1596 mw |           |             |
| 1514 vs | 1529 mw | 1285 vs |        |        |           |             |
| 1455 vs | 1414 vs | 1432 vs | 1472 vs | 1462 vs | 1502 vs | C-H deformation         |
| 1305 vs | 1348 vs | 1285 vs |        |        |           |             |
| 1163 vs | 1302 vs | 1289 mw | 1309 mw | 1346 w |           |             |
| 1157 vs | 1254 vs | 1182 mw | 1162 mw | 1306 mw |           |             |
| 950 ms  | 952 ms  | 917 w  | 985 w  | 984 mw |           | (C-H) bend          |
| 930 vs  | 921 vs  | 829 w  | 951 w  | 942 mw |           | ν(C-O)             |
| 877 vs  | 806 s   | 809 w  | 882 w  | 950 w  |           | ν(C-O)             |
| 765 mw  | 776 ms  | 781 ms | 784 w  | 787 w  |           | C-NH+ν(C-N); CH₂; CH₁₂ |
| 710 mw  | 732 vs  | 732 w  | 673 w  | 714 vw |           | RockSkeletal vibrations |
| 605 mw  | 699 vs  | 703 vs | 697 w  | 612 vw |           |             |
| 559 w   | 640 vs  | 522 vs | 698 w  | 528 w  |           | δ(ONO); PA         |
| 620 ms  | 530 vs  | 652 vs |        |        |           | CNC+NH₂ deformation |
| 452 ms  |        |        |        |        |           |             |
Figure 1. Infrared spectra of charge transfer complexes (CH-DNB, CH-PA and CH-I).
3.3. Proton nuclear magnetic resonance spectrum (\(^1\)HNMR)

\(^1\)HNMR for the chlorothiazide were collected in Table (3) (Jakobsen and Treppendahl, 1979). The data obtained from IR spectrum and elemental analyses meet at the same point with \(^1\)HNMR spectra which interpret complex formation between the CH and acceptors as follows: (i) Signal for a proton of the OH of picric acid at \(\delta = 8.9\) ppm disappeared due to a protonation from picric acid to the CH. The corresponding signals of \(\delta\)H of NH in (CH) appeared at \(\delta = 11-13\) ppm, in case of picric acid complex, it appeared at 12.62 ppm. The signal appeared in the CH-PA complex at 8.29 ppm is indicated to the form of hydrogen bond, whereas peak in free picric acid occurs at \(\delta =11.94\) ppm (Adam, 2012). (ii) Another changes occur in the chemical shifts of CT-complex differing from that of free (CH), for example, (\(\delta =11-13\) ppm of NH) and DNB (\(\delta = 8.77\) and 9.01 ppm of Ar-H) to 9-12 ppm. (iii) The signals of COOH of DNB (\(\delta =2.42\) ppm) disappeared. The proton of COOH of DNB is attached to –N atom of chlorothiazide form hydrogen bond as seen in Figure (2) and Scheme (3).

| Compound | ppm        | Assignments          |
|----------|------------|----------------------|
| CH       | 11-13      | H, NH(CH)            |
|          | 8.26, 7.51 | H ; aromatic         |
|          | 8.10       | H at Cl              |
|          | 2.42       | (s, 1H, Ar-COOH)     |
| DNB      | 8.77       | (s, 2H, Ar-H)        |
|          | 9.01       | (s, 1H, Ar-H)        |
|          | 11.94      | OH                   |
| PA       | 8.72       | 2H aromatic          |
|          | 11.8       | 2H, NH               |
| CH-DNB   | 8.52       | H aromatic           |
|          | 12.62, 8.24| 2H, NH               |
| CH-PA    | 8.29, 7.89, 8.43 | H aromatic          |

Table 3: The \(^1\)HNMR data of CH, PA, DNB and its CT complexes

CH–DNB
Figure 2. The $^1$HNMR spectra of charge transfer complexes (CH-DNB, CH-PA and CH-I).

3.4. Scanning electron microscopy (SEM)

Scanning electron microscopy of complexes using SEM-Quanta FEG 250 instrument showed images of chlorothiazide with 3,5-dinitrobenzoic acid at different magnifications as displayed in Figure (3). The image indicates that the produced complex is crystalline with a rod-like shape as the major crystals shapes. Also, the particle size is not uniform and it is clear from the SEM images that the particle sizes of the complex range from 10 to 100 μm. This non-uniform particle size may indicate different stages during the crystal formation process.

3.5. Absorption spectra

The electronic spectra of 1:1 CT-systems of chlorothiazide (white color) with picric acid, 3,5dinitrobenzoic acid and iodine at 375, 279 and 364 nm were given in Table (4). In Fig. 4, the solutions of complexes were color, upper abve 250 nm. The spectrum of chlorothiazide exist at 200 nm.
Scheme 3. The MESP map of chlorothiazide with iodine, 3,5-dinitrobenzoic acid and picric acid

Figure 3. SEM images of CH-DNB complex
Ibrahim et al., 2021

Figure 4. Electronic absorption spectra of [(CH)I₂] in chloroform (−), CH-PA (----) and CH-DNB in acetonitrile (…..).

Table 4: Spectroscopic data of charge transfer complexes

| Property                      | [(CH)I₂] | CH-PA | CH-DNB |
|-------------------------------|----------|-------|--------|
| λ<sub>max</sub> (nm)          | 364      | 375   | 279    |
| equilibrium constant, K<sub>CT</sub> x10<sup>3</sup> Lmol<sup>-1</sup> at 20 °C | 68.487   | 32.148 | 23.511 |
| Extinction coefficient, ε<sub>CT</sub>x10<sup>3</sup> Lmol<sup>-1</sup>cm<sup>-1</sup> at 20 °C | 15.561   | 51.80  | 34.863 |
| Oscillator strength; f        | 11.201   | 21.307| 37.643 |
| Dipole moment; μ              | 29.434   | 41.205| 45.901 |
| resonance energy; RN          | 0.976    | 0.947 | 1.292  |
| Energy value; E<sub>CT</sub> (eV) | 3.417    | 3.316 | 4.522  |
| Ionization potential; Ip (eV) | 9.881    | 10.107| 11.324 |

3.5.1. Photometric method

The photometric method was obtained according to Skoog methods (Skoog, 1985) by plotting the maximum absorption values against the X mL of acceptors solutions. The CT-complexes formed is 1:1 ratio is shown in Figure (5).

3.5.2. The extinction coefficient and formation constant of CT complexes

The value of the extinction coefficient, ε<sub>CT</sub> (Lmol<sup>-1</sup>cm<sup>-1</sup>) and the formation constant, K<sub>CT</sub> (Lmol<sup>-1</sup>) for the CT-complexes at 20°C were calculated using the modified equation of Benesi-Hildebrand (Benesi and Hildebrand, 1949) as follows:

\[
C_aC_d / A = C_a + C_d / ε_{CT} + 1 / K_{CT}ε_{CT}
\]

Where C<sub>a</sub> is the initial concentrations of picric acid, 3,5-dinitrobenzoic acid in acetonitrile or iodine in chloroform, and C<sub>d</sub> is concentration of CH, A is the maximum absorption value of charge transfer band. Drawing the C<sub>a</sub>C<sub>d</sub>/ A values against C<sub>a</sub>+C<sub>d</sub>, gives straight lines. The slope of straight lines equal 1/ε<sub>CT</sub> and intercept equal 1/K<sub>CT</sub>ε<sub>CT</sub>, as shown in Figure (6).
Figure 5. Photometric titration curves for CT complex CH-DNB (Ο-) and CH-PA (x-) in acetonitrile, [(CH)I₂] in chloroform (Δ-).

Figure 6. Relationship between ([CₐCₐd/ A] versus (Cₐ+Cₐd)

3.6. Physicochemical parameters

The oscillator strength (f) (Soltani et al., 2019), transition dipole moment (μ) (Voigt and Reid, 1964), resonance energy (Rₙ) (Briegleb, 1961), ionization potential (Aloisi and Pignataro, 1973) and transition energy (Eₜₜ) (Briegleb and Czekalla, 1960) values of the complex were determined from these equations:

\[ f = 4.319 \times 10^{-9} \varepsilon_C T \nu^{1/2} \]

\[ \mu \text{ (Debye)} = 0.0958 [\varepsilon_C T \nu^2/\nu_{CT}]^{1/2} \]

\[ \varepsilon_{CT} = 7.7 \times 10^{-4}/ [h\nu_{CT}/[R_N]-3.5] \]

\[ I_P = 5.76 + 1.52 \times 10^{-4} \nu_{CT} \]

\[ E_{CT} = h\nu_{CT} \text{ (eV)} = 1243.667/\lambda_{CT} \text{ (nm)} \]
Where ν_{1/2} is the bandwidth at the half of the absorption maximum, and ν_{CT} is wave number at the maximum absorption, h is Planck’s constant and λ_{CT} is wavelength of the CT complex band. The f, µ, R_N, I_P and E_{CT} values for the charge transfer complexes were listed in Table (4).

3.7. Thermodynamic parameters

Thermodynamic parameters (ΔG*, ΔS* and ΔH*) of the complex formation of CH with PA, DNB and I_2 were determined at 283, 293, 303 K and collected in Table (5). The values of these parameters determined by using the equation (Vant Hoff, 1884):

\[ \ln K_{CT} = -\frac{\Delta H^*}{RT} + \frac{\Delta S^*}{R} \]

Where ΔH* is the enthalpy and ΔS* is the entropy values, a draw of ln K_{CT} vs. 1/T Produces a straight line as illustrated in the figure (7). The ΔH* and ΔS* equal slope and intercept, respectively.

The Gibbs free energy ΔG* at 20°C were calculated from (Martin et al., 1983):

\[ \Delta G^* = -RT \ln K_{CT} \]

The free energy value were negative and entropy changes ΔS* were positive values. This indicates that the complexes formation were spontaneous process. Whereas the negative values of the enthalpy ΔH* suggesting that the reaction is exothermic as summarized in Table (5).

![Figure 7. The relationship between lnK versus 1/T.](image)

3.8. Effect of solvents

Figure (8) displays the effect of various solvents on the reactions of CH with iodine, PA and DNB which carried out in polar solvents (acetonitrile, methanol) and nonpolar solvents (dichloroethane and chloroform). The absorption intensities and the absorption maximum bands of the complexes were influenced by solvents. We have noticed that chloroform is an ideal solvent in case of iodine. However, acetonitrile found to be a perfect solvent for CH-PA and CH-DNB complexes.
Table 5: The formation constant, $K_{CT}$, the extinction coefficient $\varepsilon_{CT}$ and thermodynamic parameters values of CT complexes.

| Complex   | T, K | $K_{CT} \times 10^3$ L mol$^{-1}$ | $\varepsilon_{CT} \times 10^3$ L mol$^{-1}$ cm$^{-1}$ | $\Delta G^*$ KJ mol$^{-1}$ | $\Delta H^* \times 10^3$ KJ mol$^{-1}$ | $\Delta S^*$ J mol$^{-1}$ K$^{-1}$ |
|-----------|------|---------------------------------|---------------------------------|-----------------|-------------------|-----------------|
| [(CH)I$_2$] | 283  | 67.890                          | 15.238                          | 27.102          | 0.908             | 95.486          |
|           | 293  | 68.487                          | 15.561                          | 27.123          | 0.934             | 95.671          |
|           | 303  | 69.427                          | 15.343                          | 27.156          | 0.965             | 95.858          |
|           | 283  | 29.632                          | 51.631                          | 25.082          | 1.000             | 96.043          |
| CH-PA     | 293  | 32.148                          | 51.800                          | 25.281          | 4.568             | 100.749         |
|           | 303  | 33.136                          | 51.305                          | 25.354          | 4.609             | 101.009         |
|           | 283  | 21.988                          | 34.922                          | 24.355          | 2.875             | 92.693          |
| CH-DNB    | 293  | 23.511                          | 34.863                          | 24.518          | 2.875             | 92.693          |
|           | 303  | 23.565                          | 34.777                          | 24.525          | 2.875             | 92.693          |

Figure 8. Electronic absorption spectra of CH with I$_2$ (a), PA (b) and DNB (c) in different solvents: — acetonitrile, — methanol, — 1,2-dichloroethane and .... chloroform.

3.8.1. Determination molar transition energy and transition energy

The molar transition energy ($Z$) is obtained from the equation (Kosower, 1964):

$$ Z - Val. = \frac{2.8259}{\lambda_{(\text{nm})}} (K \text{ Calmol}^{-1}) $$

The calculation the transition energy ($E_T$) of the $\pi-\pi^*$ interaction between CH and acceptors from this relation (EL-Mossalamy et al., 2016):

$$ E_T (K \text{ Calmol}^{-1}) = 2.829 \times 10^{-3} \nu (cm^{-1}) $$
The dielectric constant of the solvents and refractive index given in the equation (Suppan, 1968):

\[ F(D) = \frac{2(D-1)}{(2D+1)} \]
\[ F(n) = \frac{(n^2-1)}{(2n^2+1)} \]

The Z, E_T, F(D) and F(n) data collected in Table 6.

Table 6: Effect of solvents on the position and intensity of CT complexes absorption.

| Complex   | Solvent       | A    | Z value | E_T  | D   | \( F(D) \) | \( F(n) \) |
|-----------|---------------|------|---------|------|-----|------------|------------|
|           |               | Nm   | K Cal mol\(^{-1}\) | K Cal mol\(^{-1}\) | cm\(^{-1}\) |           |           |
| [CH\(_2\)] | Acetonitrile  | 362  | 0.00781 | 78.15 | 37.5 | 27624.31 | 0.961 | 1.42 | 0.17 |
|           | Methanol      | 360  | 0.0785 | 7.858 | 32.7 | 27777.78 | 0.955 | 1.46 | 0.13 |
|           | dichloroethane| 412  | 0.006859 | 6.867 | 10.36 | 24271.84 | 0.862 | 1.44 | 0.12 |
|           | Chloroform    | 414  | 0.006826 | 6.833 | 4.81 | 24154.59 | 0.718 | 1.45 | 0.19 |
| CH-PA     | Acetonitrile  | 375  | 0.007536 | 7.544 | 37.5 | 26666.67 | 0.961 | 1.42 | 0.17 |
|           | Methanol      | 359  | 0.007872 | 7.768 | 32.7 | 27855.15 | 0.955 | 1.46 | 0.13 |
|           | dichloroethane| 363  | 0.007785 | 7.793 | 10.36 | 27548.21 | 0.862 | 1.44 | 0.12 |
|           | Chloroform    | 345  | 0.008191 | 8.2 | 4.81 | 28885.51 | 0.718 | 1.45 | 0.19 |
| CH-DNB    | Acetonitrile  | 279  | 0.0101   | 10.13 | 37.5 | 35842.29 | 0.961 | 1.42 | 0.17 |
|           | Methanol      | 230  | 0.012287 | 12.3 | 32.7 | 43478.26 | 0.955 | 1.46 | 0.13 |
|           | dichloroethane| 243  | 0.011629 | 11.642 | 10.36 | 41152.26 | 0.862 | 1.44 | 0.12 |
|           | Chloroform    | 245  | 0.011534 | 11.547 | 4.81 | 10\(^{-7}\)/245 | 0.718 | 1.45 | 0.19 |

3.9. Biological effect

3.9.1. The antibacterial activity

Two out of three compounds showed antimicrobial activity against target organisms, CH-PA, CH-I showed inhibition zone for *Staphylococcus aureus* at both dose concentrations used, while CH-DNB showed negative effect on both strains. In other hand, none of the three compounds showed inhibition zones for *Escherichia coli* (Table 7 and Figure 9).

Figure 9. Antibacterial activity of charge transfer complexes: 1- CH-PA, 2-CH-I and 3- CH-DNB.

3.9.2. Antifungal test using fungal growth rate technique

Some of the studied compounds had an effect on some of the tested fungi, Compound CH-DNB inhibited the growth of *Penicillium corylophilum* and *Alternaria alternata* but they have no effect on *Fusarium verticillioides*. *Fusarium verticillioides* was sensitive to the compound CH-I while the remaining fungi showed resistant to this compound. The compound CH-PA had no activity against all studied fungi (Table 8). The compound CH-DNB was showed similar results.
to 4a, 10 and 3a compounds which reported in (Abdel-Motaal and Raslan 2014) against Alternaria alternate as the latter three compounds inhibited its growth to almost the half.

**Table 7**: The bacteria activity of CT complexes

| Compound | Dose | Staphylococcus aurous (Gram +ve) | Escherichia coli (Gram -ve) |
|----------|------|---------------------------------|---------------------------|
| CH-DNB   | 1 M  | -ve                             | -ve                       |
|          | 0.5 M| -ve                             | -ve                       |
| CH-PA    | 1 M  | +ve                             | -ve                       |
|          | 0.5 M| +ve                             | -ve                       |
| CH-I     | 1 M  | +ve                             | -ve                       |
|          | 0.5 M| +ve                             | -ve                       |

**Table 8** The antifungal activity of CH-DNB, CH-PA and CH-I (10 mg/disc)

|          | Penicillium corylophilum | Alternaria alternata | Fusarium verticillioides |
|----------|--------------------------|----------------------|--------------------------|
| CH-DNB   | +                        | +                    | -                        |
| CH-PA    | -                        | -                    | -                        |
| CH-I     | -                        | -                    | +                        |

**4-CONCLUSIONS**

The complexes which obtained via reaction of chlorothiazide drug with acceptors defined by the IR and 1HNMR spectra. The CT- complexes formation was established in different solvents and temperatures. The formation constants, physicochemical and thermodynamic parameters valued for the CT-complexes were calculated.

**5-REFERENCES**

Abdine, H., Elsayed, M. A. H., and Elsayed, Y. M. (1978). Spectrophotometric determination of hydrochlorothiazide and reserpine in combination. Analyst, 103, 354-358.

Abdel-Moety, E. M., Abounassif, M. A., Gad-Kariem, E. R. A., and Khattab, N. A. (1993). Simultaneous determination of amoxycillin and dicloxacillin in capsules by potentiometric titrimetry and high-performance liquid chromatography. Talanta, 40(6), 811-817.

Abdel-Motaal, F. F. and Raslan M. A. (2014). Synthesis and antimicrobial evaluation of some 1,2,4 triazolo[1,5-a]pyridine, pyrimidine sulfonamides and sulfinyl derivatives." European Journal of Chemistry., 5 (3) 481-487.

Adam, A. M. A. (2012). Synthesis, spectroscopic, thermal and antimicrobial investigations of charge-transfer complexes formed from the drug procaine hydrochloride with quinol, picric acid and TCNQ. Journal of Molecular Structure, 1030, 26-39.

Alghanmi, R. M., and Alhazmi, L. Y. (2019). Spectrophotometric determination of mebendazole through charge transfer interaction. J. pharm. sci. res., 10(5), 2504-2515.

Aloisi, G. G., and Pignataro, S. (1973). Molecular complexes of substituted thiophens with σ and π acceptors. Charge transfer spectra and ionization potentials of the donors. Journal of the
Chemical Society, Faraday Transactions 1: Physical Chemistry in Condensed Phases, 69, 534-539.

Arslan, M., and Duymus, H. (2007). Spectroscopic studies of charge transfer complexes between colchicine and some π acceptors. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 67(3-4), 573-577.

Benesi, H. A., and Hildebrand, J. H. J. (1949). A spectrophotometric investigation of the interaction of iodine with aromatic hydrocarbons. Journal of the American Chemical Society, 71(8), 2703-2707.

Bharathikannan, R., Chandramohan, A., Kandhaswamy, M. A., Chandrasekaran, J., Renganathan, R., and Kandavelu, V. (2008). Synthesis, crystal growth and properties of the charge transfer complex adduct of 2-nitro aniline with picric acid–An organic nonlinear optical material. Crystal Research and Technology: Journal of Experimental and Industrial Crystallography, 43(6), 683-688.

Briegleb, G., and Czekalla, J. (1960). Electron transfer through light absorption and emission in electron donor acceptor complexes. Angewandte Chemie International Edition, 72 (12), 401-413.

Briegleb, G. 1961. Konfiguration der Elektronen-Donator-Acceptor-Komplexe. In Elektronen-Donator-Acceptor-Komplexe (pp. 167-181). Springer, Berlin, Heidelberg.

Cohen, A. I., Keeler, B. T., Coy, N. H., and Yale, H. L. (1962). Polarographic Reduction of 1, 2, 4-Benzothiadiazine-1, 1-Dioxides and Related Compounds. Analytical Chemistry, 34(2), 216-219.

El-Mossalamy, E. H., Aal, S. A., El-Batouti, M., and Al-Harbi, N. F. (2016). Theoretical Calculations of Molecular Charge Transfer Complexes of Aryl 2-Azomethine dibenzothiophene with Nitrobenzene Derivatives as [π]-Acceptors. Asian Journal of Chemistry, 28(5), 947.

Habeeb, M. M., Al-Attas, A. S., and Al-Raimi, D. S. (2015). Spectroscopic studies and molecular orbital calculations of charge transfer complexation between 3, 5-dimethylpyrazole with DDQ in acetonitrile. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 142, 196-203.

Hasani, M., and Akbari, S. (2007). A spectrophotometric and thermodynamic study of the charge-transfer complexes of iodine with 2-aminomethyl-15-crown-5 in chloroform and 1, 2-dichloroethane solutions. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 67(1), 139-144.

Ibrahim, A. A., El-Mossalamy, E. H., and Abdel-Aal, S. (2017). Molecular Charge-Transfer Complex between Thymol Drug and Bromocresol purple. Journal of Chemical, Biological and Physical Sciences (JCBPS), 7(2), 320.

Jakobsen, P., and Treppendahl, S. (1979). The structure of 1, 2, 4-benzothiadiazine-1, 1-dioxides. Tetrahedron, 35(18), 2151-2153.

Kosower, E. M. (1964). Spectroscopie ultraviolette et mesure empirique de la polarité du solvant (constante Z). Journal de Chimie Physique, 61, 230-235.

Martin, A., Swarbrick, J., and Cammarata, A. (1983). Physical pharmacy, 3rd. Lee and Febiger, Philadelphia, 344.
Mohamed, H. A., EL-Medani, S. M., and Ramadan, R. M. (2005). Spectroscopic and X-ray crystal structure studies of 2-aminothiazole-3, 5-dinitrobenzoic acid and 3, 5-dinitrosalicylic acid derivatives. Journal of the Indian Chemical Society, 82(9), 799-806.

Naglah, A. M., Al-Omar, M. A., Adam, A. M. A., and Refat, M. S. (2015). Charge-transfer complexes formed between the sweeteners saccharin drug and acido acceptors: structural, thermal and morphological features. International Journal of Pharmacology, 11(8), 929-937.

Nash, T., and Allison, A. C. (1963). Charge transfer, hydrogen bonding and drug action. Biochemical pharmacology, 12, 601-602.

Pandeeswaran, M., and Elango, K. P. (2006). Solvent effect on the charge transfer complex of oxatomide with 2, 3-dichloro-5, 6-dicyanobenzoquinone. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 65(5), 1148-1153.

Salama, N. N., Abdel-Razeq, S. A., Abdel-Atty, S., and El-Kosy, N. (2011). Spectrophotometric determination and thermodynamic studies of the charge transfer complexes of azelastine-HCl. Bulletin of faculty of pharmacy, Cairo University, 49(1), 13-18.

Skoog, D. A. (1985). Solutions Manual for Principles of Instrumental Analysis: Supplement. Saunders college publishing, cop.

Soltani, S., Magri, P., Rogalski, M., and Kadri, M. 2019. Charge-transfer complexes of hypoglycemic sulfonamide with π-acceptors: Experimental and DFT-TDDFT studies. Journal of Molecular Structure, 1175, 105-116.

Sunshine, I. (1963). Use of thin layer chromatography in the diagnosis of poisoning. American journal of clinical pathology, 40(6), 576-582.

Supuran, C. T. (1996). Complexes with biologically active ligands. Part 4. Coordination compounds of chlorothiazide with transition metal ions behave as strong carbonic anhydrase inhibitors. Metal-Based Drugs, 3(2), 79-83.

Suppan, P. (1968). Solvent effects on the energy of electronic transitions: experimental observations and applications to structural problems of excited molecules. Journal of the Chemical Society A: Inorganic, Physical, Theoretical, 3125-3133.

Swaminathan, J., Ramalingam, M., Sethuraman, V., Sundaraganesan, N., and Sebastian, S. (2009). Corrigendum to “Vibrational spectroscopic studies and DFT calculations of 4-aminoantipyrine” [Spectrochim. Acta Part A 73 (2009) 593–600]. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 1(74), 305.

Van’t Hoff, J. H. (1884). Studies in Chemical Dynamics. Nature Publishing Group.

Voigt, E. M., and Reid, C. (1964). Ionization potentials of substituted benzenes and their charge-transfer spectra with tetracyanoethylene. Journal of the American Chemical Society, 86(19), 3930-3934.

Whitehead, C. W., Traverso, J. J., Marshall, F. J., and Morrison, D. E. (1961). Diuretics. IV. 6-Chloro-3-substituted 7-Sulfamoyl-1, 2, 4-benzothiazaine 1, 1-Dioxides. The Journal of Organic Chemistry, 26(8), 2809-2813.