

Study of Charge transfer complexes of chlorothiazide

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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 ($n \rightarrow \pi^*$) and to sigma-acceptor ($n-\sigma$). 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, ϵ_{CT} , the formation constant, K_{CT} , 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 pKa 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 oxatomide as donor with 2, 3-dichloro-5, 6-dicyanobenzoquinone as acceptor was determined spectrophotometric at different temperatures and solvents (Pandeewaran and Elango, 2006). Studies of complexes formed of colchicine with acceptors were determined in dichloromethane at 21°C (Arslan and Duymus, 2007).

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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 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

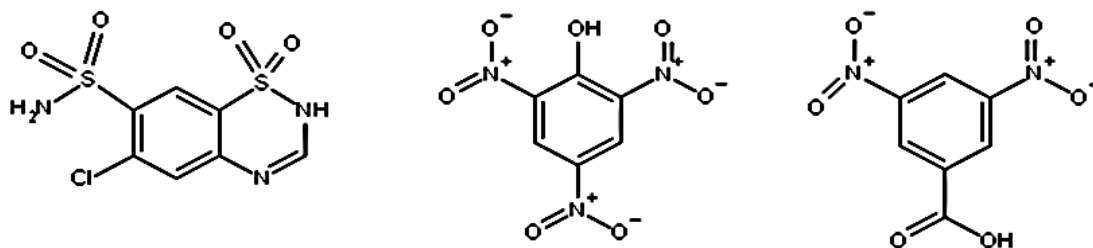
Where adding solution of chlorothiazide (2957 mg, 1mmol) to solution of iodine (1269 mg, 1mmol), picric acid (229 mg, 1mmol) and 3,5-dinitrobenzoic acid (212 mg, 1mmol). The reaction mixtures were stirred for about 3 h, kept overnight where the yield precipitated. The yields were filtered, washed and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

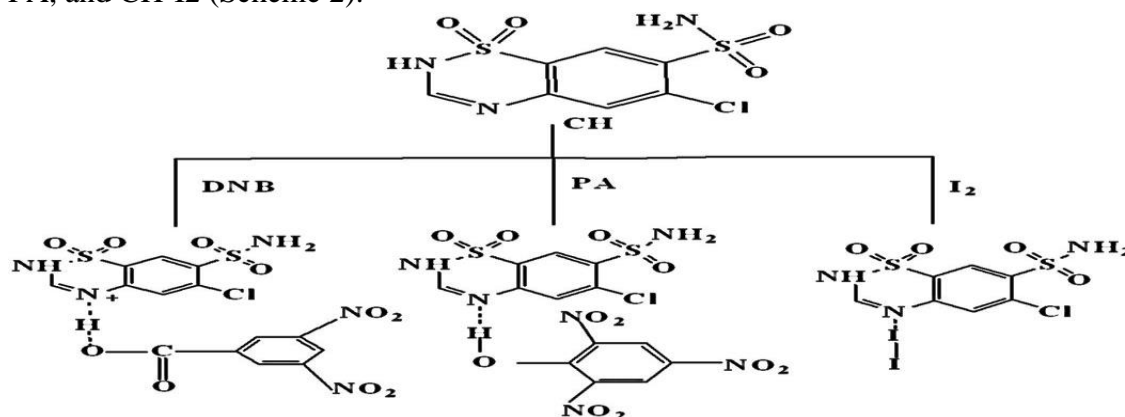


Scheme 1. The structure donor and acceptors (chlorothiazide (CH), picric acid (PA), 3,5-dinitrobenzoic acid (DNB)).

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).



Scheme 2. Proposed molecular structure of CT complexes

Table 1: Elemental analysis, color, melting point (MP, °C) and yield values of complexes

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

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-I ₂]	Assignments
3400 s	3462 mw	3416 s 3103 s	3334 m 2540 w	3332 m	3332 m	v (O-H); v (N-H)
3063 mw 3002 mw	3092 mw 2957 vw 2884 vw 2821 vw	2980 ms 2872 m	3092 mw	3101 m	3063 w	v(C-H);C=Cand combination Aromatic vs (C-H)
-	-	-	2962 w	2985w	2932 w	H-bonded
1676 mw 1608 mw	1858 m 1627ms 1609 w 1514 vs	1861 m 1632 m 1608 mw 1529 mw	1704 m	1610 mw 1555 mw	1617 mw 1596 mw	v(C=O) of DNB; vs(NO ₂) of PA + v(C=C) δ _{def} (N-H); +NH
1455 vs	1414 vs 1348 vs 1285 vs	1432 vs	1472 vs	1462 vs	1502vs	C-H deformation
1305 vs 1163 vs 1157 vs	1328 1302 1254	1343 vs 1312vs 1263 vs 1150 vs 1086 vs	1348 mw 1289 mw 1182 mw	1343 mw 1309 mw 1162 mw 1091 mw	1386 mw 1346 w 1306 mw	v(C-C)+ v(C-N) + v(C-O)
950 ms 930 vs 877 vs	952 ms 921 vs 806 s	917 w 829 w	985 w 951 w 809 w	985 mw 942 mw	984 mw 950 mw 882 mw	(C-H) bend δ _{rock} ; +NH
765 mw 710 mw 605 mw	776 ms 723 vs 699 vs	781 ms 732 vs 703 vs 652 vs	786 w 723 w 697 w	784 w 673 w	787 w 714 vw 612 vw	C-NH+v(C-N); CH; CH ₂ RockSkeletal vibrations
559 w	640 vs 620 ms 530 vs 452 ms	522 vs	698 w	528 w	-	δ(ONO); PA CNC+NH ₂ deformation

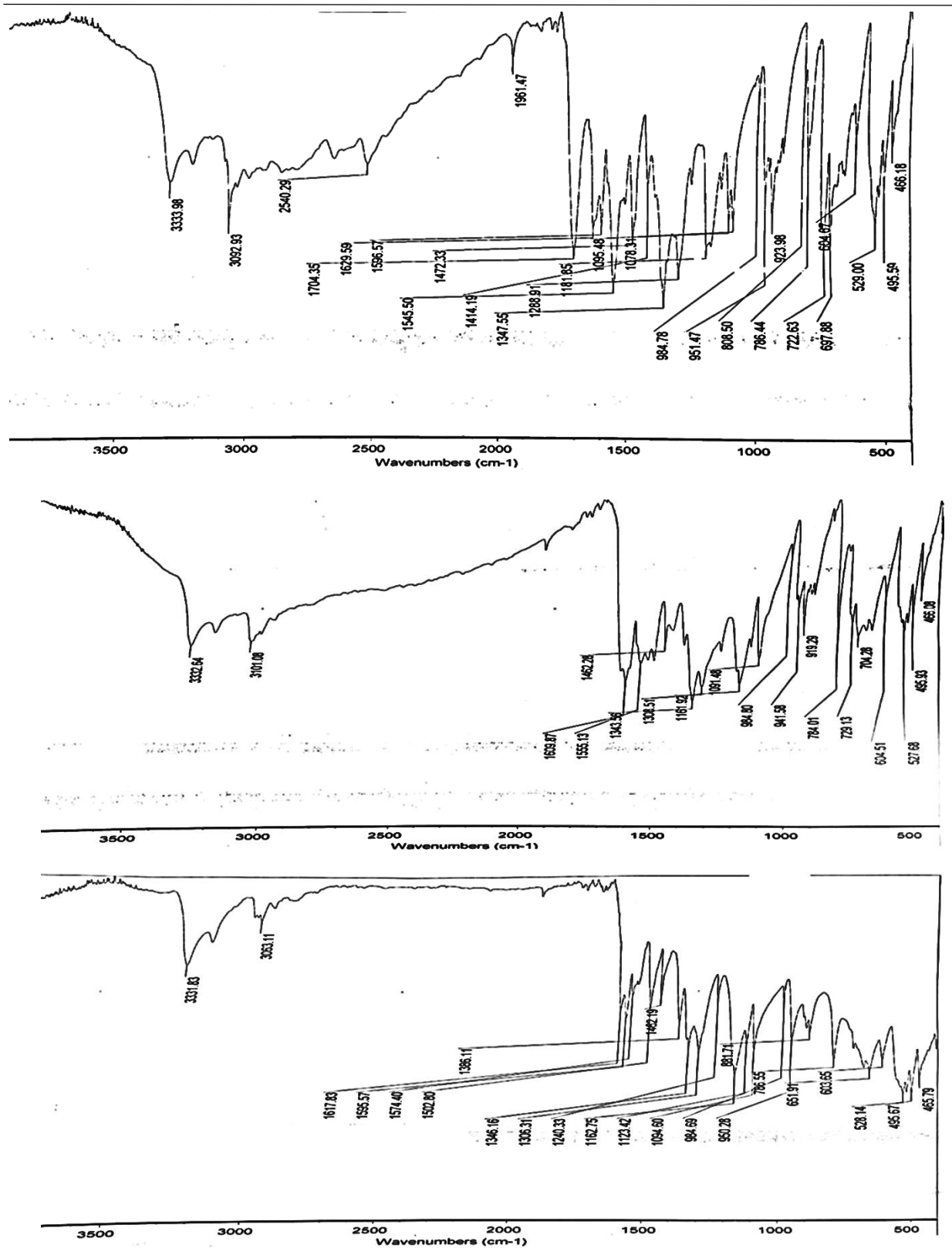


Figure 1. Infrared spectra of charge transfer complexes (CH-DNB, CH-PA and CH-I).

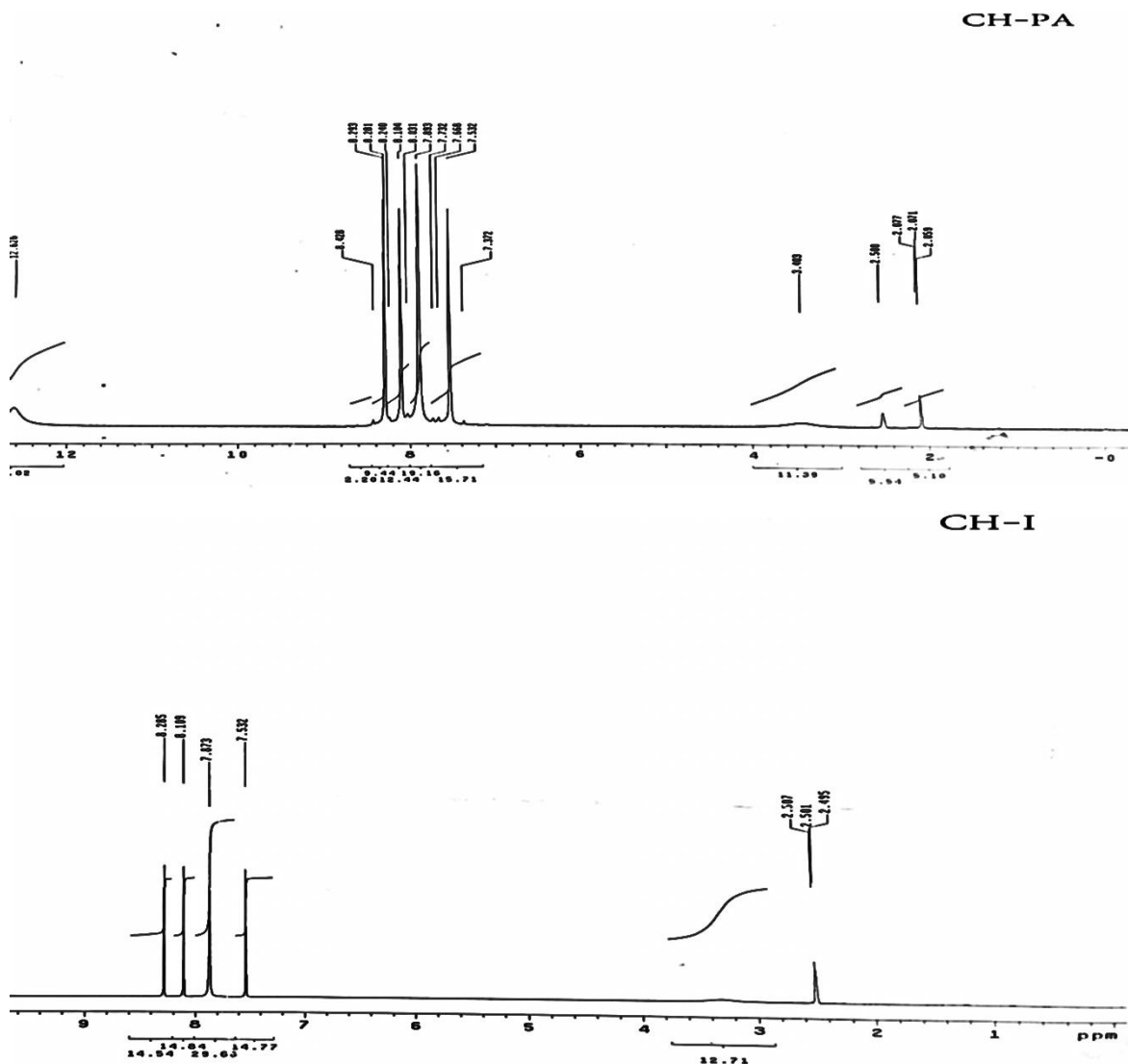


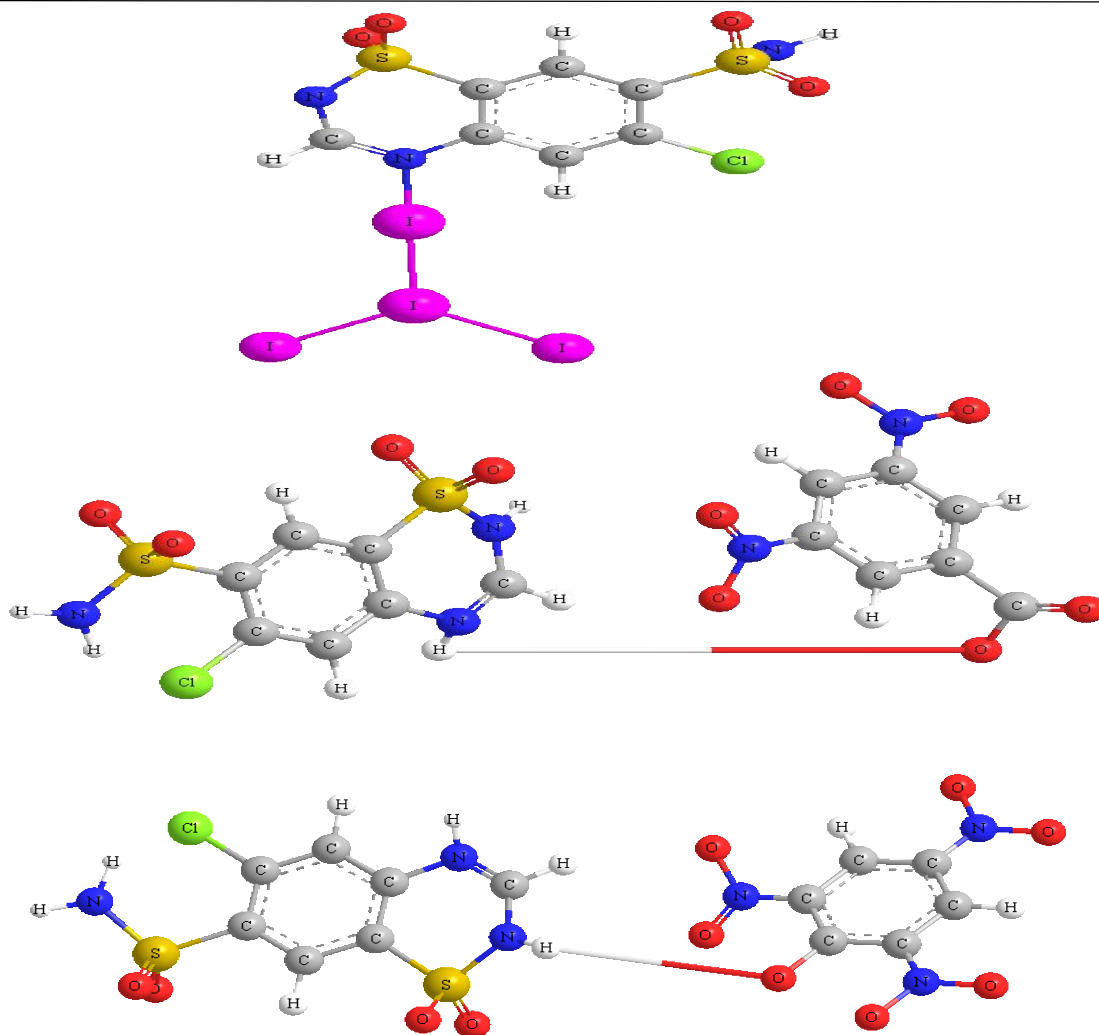
Figure2. The ^1H NMR spectra of charge transfer complexes (CH-DNB, CH-PA and CH-I).

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, 3,5-dinitrobenzoic acid and iodine at 375, 279 and 364 nm were given in Table (4), In Fig. 4, the solutions of complexes were color, appear above 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

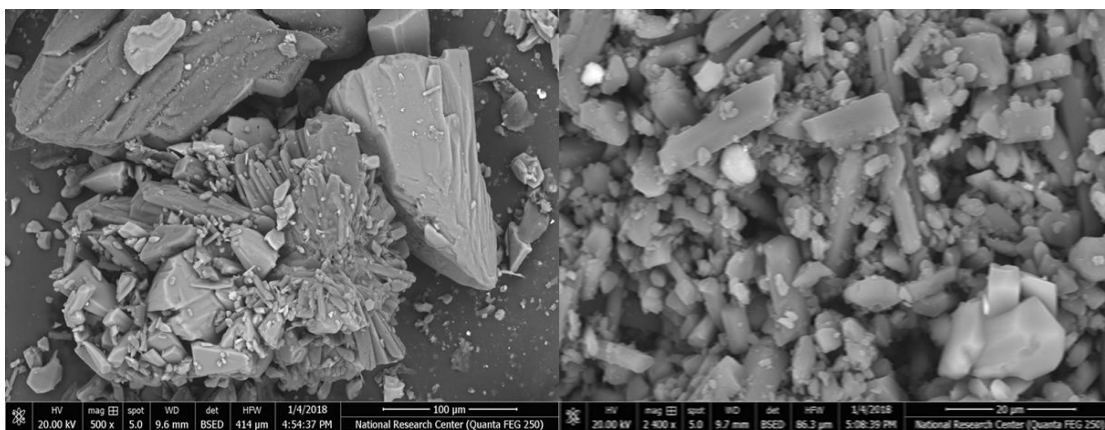


Figure 3. SEM images of CH-DNB complex

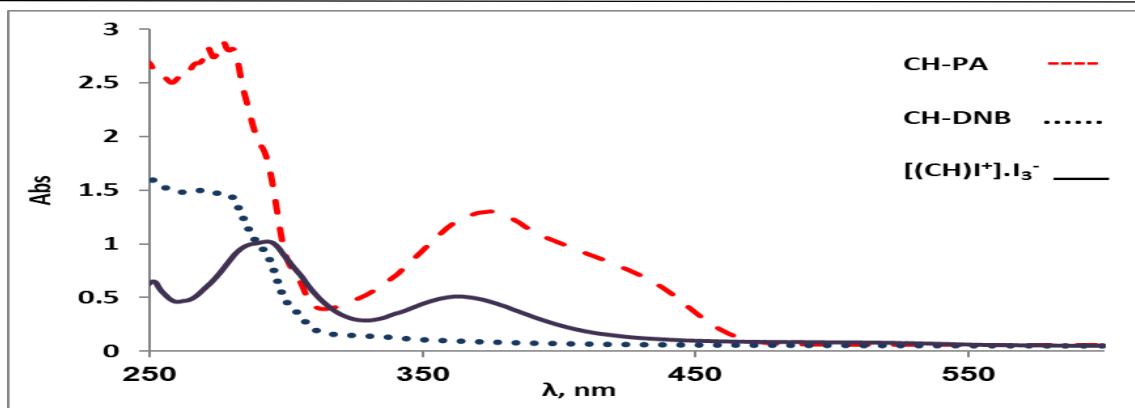


Figure 4. Electronic absorption spectra of $[(CH)I_2]$ in chloroform (-), CH-PA (----) and CH-DNB in acetonitrile (....).

Table 4: Spectroscopic data of charge transfer complexes

Property	$[(CH)I_2]^-$	CH-PA	CH-DNB
λ_{max} (nm)	364	375	279
equilibrium constant, $K_{CT} \times 10^3$ Lmol ⁻¹ at 20 °C	68.487	32.148	23.511
Extinction coefficient, $\epsilon_{CT} \times 10^3$ Lmol ⁻¹ cm ⁻¹ 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_{CT} (eV)	3.417	3.316	4.522
Ionization potential; I_p (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_{CT} (Lmol⁻¹cm⁻¹) and the formation constant, K_{CT} (Lmol⁻¹) for the CT-complexes at 20°C were calculate using the modified equation of Benesi-Hildebrand (Benesi and Hildebrand, 1949) as follows:

$$C_a C_d / A = C_a + C_d / \epsilon_{CT} + 1 / K_{CT} \epsilon_{CT}$$

Where C_a is the initial concentrations of picric acid, 3,5-dinitrobenzoic acid in acetonitrile or iodine in chloroform, and C_d is concentration of CH, A is the maximum absorption value of charge transfer band. Drawing the $C_a C_d / A$ values against $C_a + C_d$, gives straight lines. The slope of straight lines equal $1/\epsilon_{CT}$ and intercept equal $1/K_{CT}\epsilon_{CT}$, as shown in Figure (6).

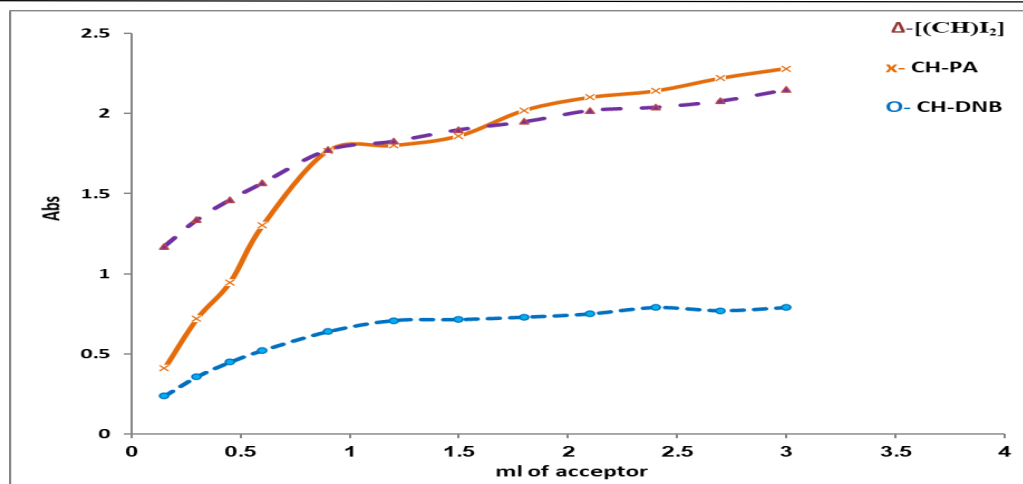


Figure 5. Photometric titration curves for CT complex CH-DNB (○-) and CH-PA (x-) in acetonitrile, [(CH)I₂] in chloroform (Δ-).

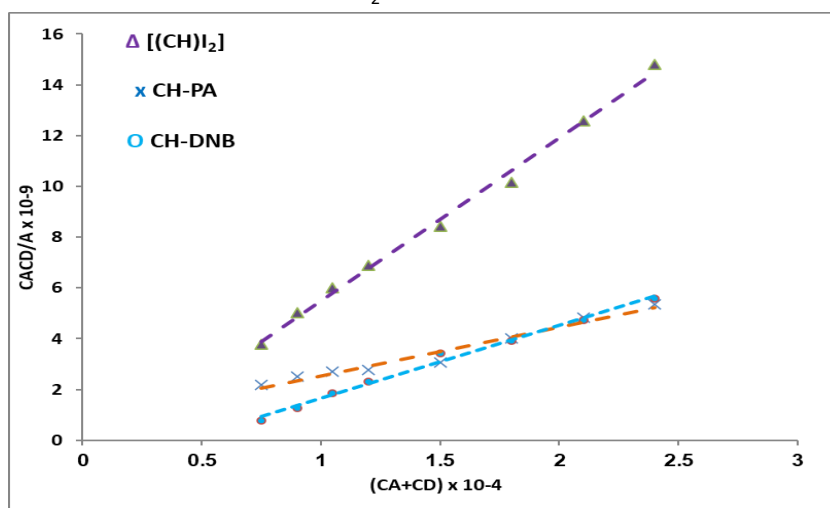


Figure 6. Relationship between $(C_a C_d / A)$ versus $(C_a + C_d)$

3.6. Physicochemical parameters

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

$$f = 4.319 \times 10^{-9} \epsilon_{CT} \nu^{1/2}$$

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

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

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

$$E_{CT} = h\nu_{CT} \text{ (eV)} = 1243.667 / \lambda_{CT} \text{ (nm)}$$

Where $\nu_{1/2}$ 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 I2 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):

$$\ln K_{CT} = -\Delta H^*/RT + \Delta S^*/R$$

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 20oC 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).

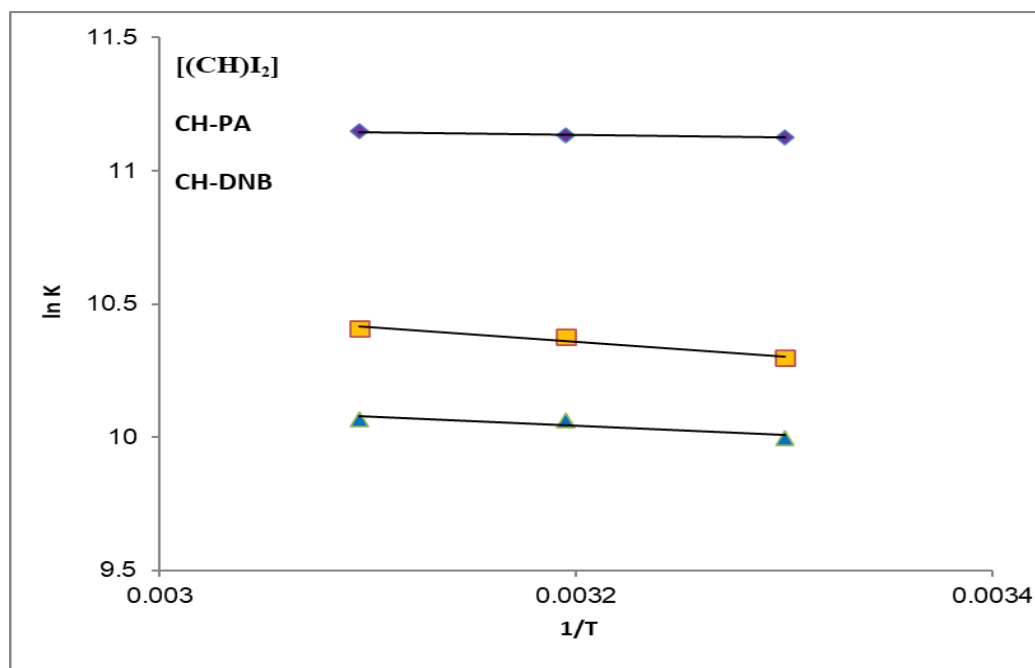


Figure 7. The relationship between $\ln K$ versus $1/T$.

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 ϵ_{CT} and thermodynamic parameters values of CT complexes.

Complex	T, K	$K_{CT} \times 10^3$ L mol ⁻¹	$\epsilon_{CT} \times 10^3$ L mol ⁻¹ cm ⁻¹	ΔG^* KJ mol ⁻¹	$\Delta H^* \times 10^3$ KJ mol ⁻¹	ΔS^* J mol ⁻¹ K ⁻¹
[(CH)I ₂]	283	67.890	15.238	27.102		
	293	68.487	15.561	27.123	0.908	95.486
	303	69.427	15.343	27.156		
CH-PA	283	29.632	51.631	25.082		
	293	32.148	51.800	25.281	4.568	100.749
	303	33.136	51.305	25.354		
CH-DNB	283	21.988	34.922	24.355		
	293	23.511	34.863	24.518	2.875	92.693
	303	23.565	34.777	24.525		

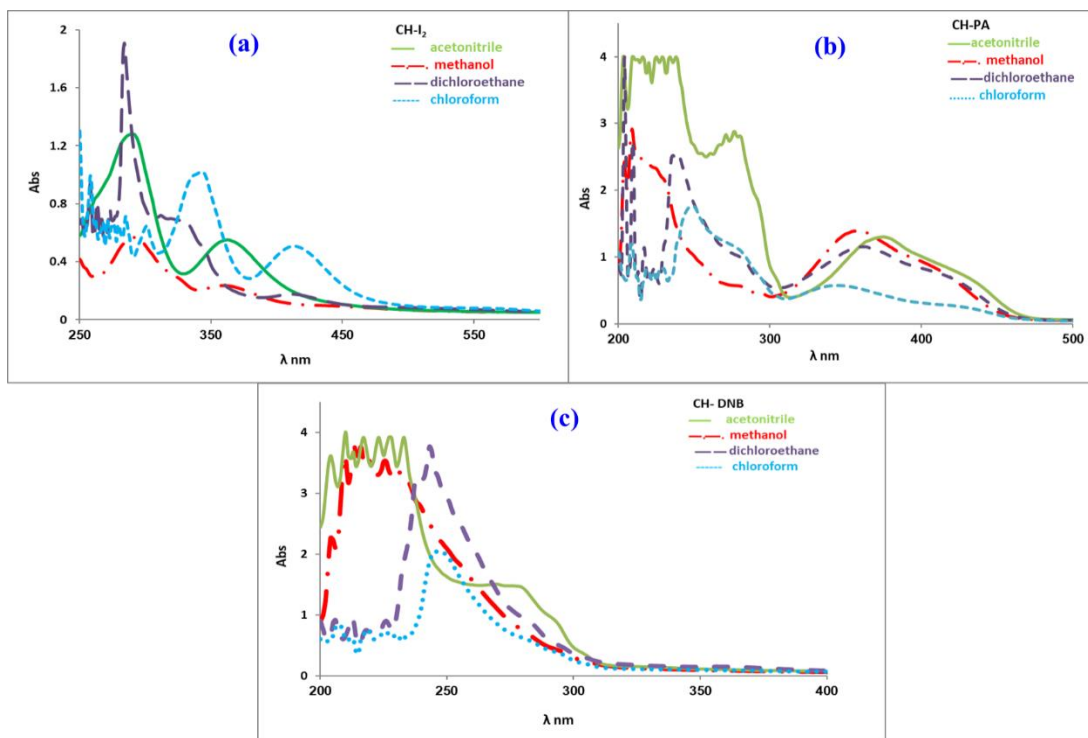


Figure 8. Electronic absorption spectra of CH with I₂(a), PA (b) and DNB (c) in different solvents :—acetonitrile, -.- methanol, ...1,2-dichloroethane andchloroform.

3.8.1. Determination molar transition energy and transition energy

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

$$Z - Val. = \frac{2.8259}{\lambda_{(nm)}} (K Ca l mol^{-1})$$

The calculation the transition energy (E_{CT}) of the π - π^* interaction between CH and acceptors from this relation (EL-Mossalamy et al., 2016):

$$E_T (K Ca L mol^{-1}) = 2.829 \times 10^{-3} \bar{\nu} (cm^{-1})$$

The dielectric constant of the solvents and refractive index given in the equation (Suppan, 1968):

$$F(D) = 2(D-1)/(2D+1)$$

$$F(n) = (n^2-1)/(2n^2+1)$$

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	λ	Z value	E_T	D	ν	$F(D)$	(n)	$F(n)$
		Nm	K Cal mol ⁻¹	K Cal mol ⁻¹		cm-1			
[(CH)I 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	7.88	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	28985.51	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 ⁴ /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-I₂ 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 alternata* as the latter three compounds inhibited its growth to almost the half.

Table 7: The bacteria activity of CT complexes

Means of zones of bacterial growth inhibition				
Compound	Dose	Staphylococcus aureus	Escherichia coli	
		(Gram +ve)	(Gram -ve)	
		Result	Result	
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)

	<i>Penicillium corylophilum</i>	<i>Alternaria alternata</i>	<i>Fusarium verticillioides</i>
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.

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