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Charge-transfer Complexes Formed between the Sweeteners Saccharin Drug and Acido Acceptors: Structural, Thermal and Morphological Features

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ABSTRACT
Saccharin (sacH) is a sugar substitute sweetening agent used extensively in dietary products. It is about 300 times sweeter than sucrose. This study highlighted the structural chemistry of Charge Transfer (CT) complexes formed from the interactions of two acido acceptors (CLA and PA) with sacH. The IR and ^{1}H NMR revealed evidence of significant intermolecular interactions between N-H group in the sacH and O-H group in the acido acceptors based on their characteristic shifts. The TG and DTA experiments were carried out to investigate the thermal properties of the obtained complexes. Their morphological features were also investigated using Optical Light Microscope (OLM). The OLM micrograph patterns indicate the formation of high quality colored crystals. This study provided the essential basics for understanding the complexation chemistry of saccharin.

Key words: Dietary sugar, saccharin, CT interaction, TG, DTA, OLM

INTRODUCTION

Saccharin (sacH; also named 1,2-benzisothiazoline-3-(2H)-one-1,1-dioxide or o-sulphobenzimide, $C_6H_4COSO_2NH$) is a well-know and widely used non caloric artificial sweetener. It was discovered accidentally by Fahlberg and Remsen (1879), while they were studying the oxidation of o-toluene-sulfonamides. Saccharin is about 300 times sweeter than sucrose and was employed as a sweetener in foods and beverages from more than a century. It is also used to sweeten personal care products such as toothpaste, mouthwash and pharmaceuticals (Assumpcao *et al*., 2008). Saccharin represents condensed organic molecule having the benzene and heterocyclic rings in its structure. In its acidic form, sacH is not particularly water-soluble, so, it is commercially available as the sodium salt [Na(sac). $2H_2O$]. Saccharin in solutions easily loses the imine hydrogen forming the corresponding saccharinate (sac) anion. This monoanion coordinates to various metal ions readily by means of its imino nitrogen, carbonyl oxygen, or sulfonyl oxygen atoms (Icsel and Yilmaz, 2014). The coordination chemistry of sacH has been comprehensively reviewed by several works and its biochemical and toxicological studies were extensive reported. But its Charge Transfer (CT) interactions have not been reported in the literature. As a continuation of our works on the synthesis, characterization and application of CT complexes (Adam, 2012, 2013, 2014a, b; Adam *et al*., 2012, 2013a, b, c; Eldaroti *et al*., 2013a, b, c, 2014; Refat *et al*., 2013, 2014a, b, c, d, e, 2015a; Refat and Adam, 2014; Salman *et al*., 2013), in this paper, two new CT complexes formed between sacH as the donor with chloranilic acid (CLA) and Picric Acid (PA) as π-acceptors have been structurally, thermally and morphologically studied (Fig. 1). These complexes are readily prepared from the reaction of sacH with

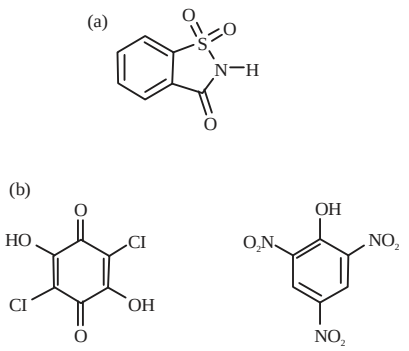

Fig. 1(a-b): Molecular structure of (a) Saccharin (sacH) and (b) Acido acceptors (CLA, PA)

CLA and PA in organic media. The synthesized sacH complexes were characterized to interpret the behavior of interactions using IR and ^{1}H NMR spectroscopy and CHN elemental analyses, as well as TG and DTA techniques. Furthermore, the microstructure properties of the obtained complexes have also been investigated using Optical Light Microscope (OLM).

MATERIALS AND METHODS

Materials: All of the reagents used were of high analytical grade chemicals and were used as purchased. Saccharin (purity of 99.3%) (saccharin; $C_6H_4COSO_2NH$; 183.18) was purchased from Sigma-Aldrich Chemical Company (USA). The electron acceptors chloranilic acid (CLA; $C_6H_2Cl_2O_4$; 208.98) and picric acid (PA; $C_6H_3N_3O_7$; 229.10) obtained from Sigma-Aldrich Chemical Company (USA) and were used without modification. Methanol of HPLC grade was from E. Merck (Darmstadt, Germany).

Synthesis: The solid sacH CT complexes were prepared as follows. Saccharin (2 mmol, 20 mL) was added to 20 mL of methanolic solutions containing CLA or PA (2 mmol) and stirred at room temperature for 1 h. A change in color developed and the volume of the solution was reduced to one-half by evaporation on a water bath. These changes in colors represent strong evidence of the CT interactions between the donor and each of the acceptors. The resulting solutions were allowed to stand at room temperature. The formed crystals were isolated, filtered off and washed twice thoroughly with the minimum given solvent to obtain the pure products. The crystals were then collected and dried *in vacuo* for 48 h. The obtained crystals were characterized by spectroscopy (IR and ^{1}H NMR), elemental and thermal analyses. The sacH-CLA and sacH-PA crystals have a violet and shiny yellow color, respectively (Khan and Ahmad, 2010).

Measurements and experimental conditions

Elemental analyses: Elemental analyses for the C, H and N contents of the solid compounds were performed by the microanalysis facility at Cairo University, Egypt, using a Perkin-Elmer CHN 2400 (USA).

Infrared spectra: The infrared (IR) absorption spectra of the solid CT complexes (as KBr discs) were acquired at room temperature using a Shimadzu FT-IR spectrophotometer instrument (Japan) in the range of 4000-400 cm^{-1} for 30 scans at a 2 cm^{-1} resolution.

^{1}H NMR spectra: The ^{1}H NMR spectra were collected by the Analytical Center at King Abdul Aziz University, Saudi Arabia, on a Bruker DRX-250 spectrometer operating at 600 MHz with a dual 5 mm probe head. The measurements were performed at ambient temperature using DMSO-d_6 (dimethylsulfoxide, d_6) as a solvent and TMS (tetramethylsilane) as an internal reference. The ^{1}H NMR data is expressed in parts per million (ppm) and are internally referenced to the residual proton impurity in the DMSO solvent.

Thermal analyses: Thermogravimetric (TG) and Differential Thermal Analyses (DTA) were performed under nitrogen atmosphere between room temperature and 800°C at a heating rate of 10°C min^{-1} using a Shimadzu TGA-50H thermal analyzer at the Central Lab at Ain Shams University, Egypt.

Optical Light Microscope (OLM): Microstructures of the obtained crystals were examined by optical light microscope model Meiji 7800 Techno Microscopy.

RESULTS AND DISCUSSION

Stoichiometry determination of complexes: The stoichiometry relationship between sacH and acido acceptors in CT complexes was determined using CHN elemental analysis technique. The result of the elemental analyses in terms of carbon, hydrogen and nitrogen content, of the formed CT complexes is given as; for the (sacH-CLA) $C_{13}H_7Cl_2NO_7S$ complex (Mol. wt.=392.16); Calc.: C, 39.78%, H, 1.79%, N, 3.57%. Found: C, 39.81%, H, 1.74%, N, 3.62%. For the (sacH-PA) $C_{13}H_8N_4O_{10}S$ complex (Mol. wt. =412.28), Calc.: C, 37.84%, H, 1.94%, N, 13.58%. Found: C, 37.80%, H, 1.88%, N, 13.63%. The elemental analyses data was in satisfactory agreement with the calculated values. The stoichiometry of the CT complexes sacH-CLA and sacH-PA was found to be 1:1. The formation of 1:1 complexes was strongly supported by thermal analyses. So, these complexes can be formulated as [(sacH)(CLA)] and [(sacH)(PA)].

Infrared spectroscopy: Infrared spectral study shed light on the donation location in the donor species and the differences occur in the spectra of the obtained CT complexes. Herein, IR measurements were carried out to gain insight into possible molecular level interaction between sacH and acido acceptors.

The IR absorption spectra of the sacH solid CT complexes were registered in the frequency range 4000-400 cm^{-1} using KBr disc. The IR spectra of the products were recorded and are shown in Fig. 2(a, b) and their peak assignments for the important characteristic bands are reported in Table 1. The spectrum of free sacH donor displays a series of significant bands as: 3092, 2920, 1724, 1258, 1150, 950 cm^{-1}, which were corresponded to ν(N-H), ν(C-H), ν(C=O) (in carboxylic acid group), $\nu_{as}(SO_2)$, $\nu_s(SO_2)$ and ν_{as}(CNS), respectively. The formation of CT complexes during the reaction of sacH with CLA or PA is strongly supported by observing of main infrared bands of the sacH donor and acceptors in the product spectra. However, the bands of the donor and acceptors in the complexes spectra reveal small in frequency and changes in their band intensities compared with those of the free donor and acceptors. This result could be attributed to the expected changes in symmetry and electronic structure changes upon the formation of the CT complexes.

Table 1: Assignment of the most characteristic infrared bands of saccharin and its change transfer complexes

sacH	sacH-CLA	sacH-PA	Assignments
-	-	3536	ν(OH); PA
-	3492	-	ν(OH); CLA
3092	3260	3350	ν(N-H)
2920	2875	3096	ν(C-H)
-	2617, 2580	2654, 2577	Hydrogen bond
1724	1691	1705	ν(C=O)
1258	1250	1260	$\nu_{as}(SO_2)$
1150	1166	1159	$\nu_s(SO_2)$
950	970	972	ν_{as}(CNS)

SacH: Saccharin, PA: Picric acid, CLA: Chloranilic acid

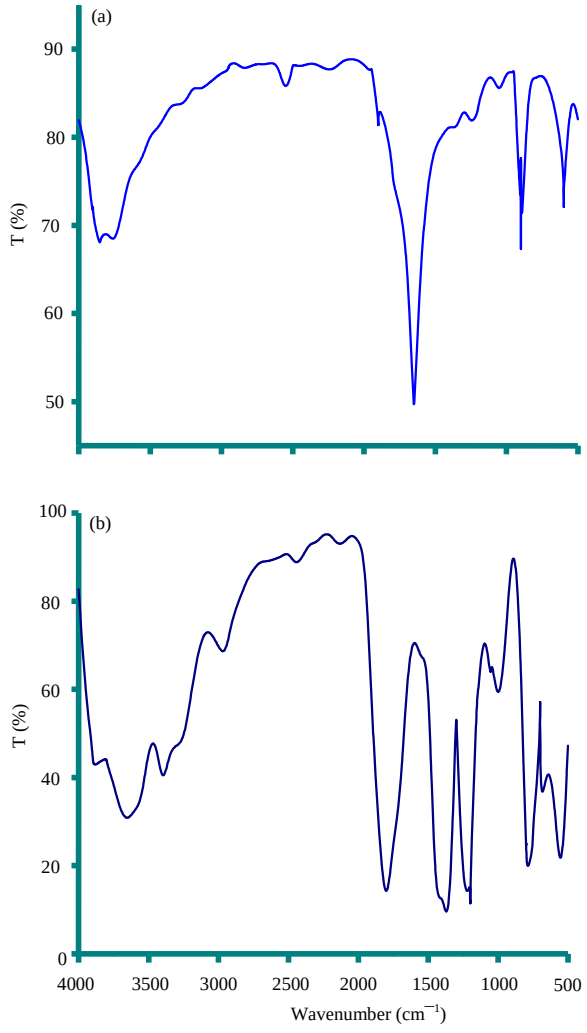

Fig. 2(a-b): Infrared spectrum of (a) sacH-CLA and (b) sacH-PA complex

When the acido acceptors were complexed with the sacH donor, the characteristic bands of the free donor and acceptor were shifted and decreased in the intensities. The outlined changes in the bands of ν(N-H) (for sacH donor) and ν(O-H) (for acceptor) upon complexation clearly supports the formation of the CT complexes between donor and acceptor. The characteristic band of ν(N-H) group observed at 3092 cm^{-1} in the free sacH, is shifted to (3260 cm^{-1} for CLA complex and 3350 cm^{-1} for PA complex). The stretching vibrational of ν(O-H) absorption band of free CLA and PA appeared at (3230 cm^{-1} for CLA and 3416 cm^{-1} for PA) was shifted to higher frequency (3492 cm^{-1} for CLA complex and 3536 cm^{-1} for PA complex) and become more broadening. The observed shift in the ν(O-H) band upon complexation clearly indicated the -OH moiety of the acceptor participated in the CT bonding with sacH. The [(sacH)(CLA)] and [(sacH)(PA)] complexes were also characterized by a medium bands appearing in the region between 2400 and 2800 cm^{-1}. These bands presence at 2617 and 2580 cm^{-1} for CLA complex; 2654 and 2577 cm^{-1} for PA complex was attributed to the stretching vibration of a proton attached to the donation site (N-H) of the donor. Furthermore, the SO_2 vibration bands; $\nu_{as}(SO_2)$ and $\nu_{as}(SO_2)$, slightly shifted with respect to those of the free sacH donor; this is most likely due to intermolecular CT interactions. All these observations clearly indicates that the complexation occurs through the formation of intermolecular H-bonding between the (N-H) group in the sacH donor and the (-OH) group in the acido acceptors (CLA or PA) (Singh *et al*., 2014a, b).

^{1}H NMR spectroscopy: The sacH CT interactions with CLA and PA acceptors were further confirmed by measuring the ^{1}H NMR spectrum of the formed complex. The nuclear magnetic resonance, 600 MHz ^{1}H NMR spectra of the CT complexes was measured in DMSO-d_6 solvent at room temperature using tetramethylsilane (TMS) as internal standard. The positions of chemical shift (d) of the different types of protons are expected to be shifted based on the changes in the electronic environment around the protons attached to the groups which contain the site of donation and involvement in the complexation. The reaction of sacH donor with CLA acceptor yielded a new CT complex, which produced signals at δ = 5.79 (s, 1H, chloranilic acid OH),

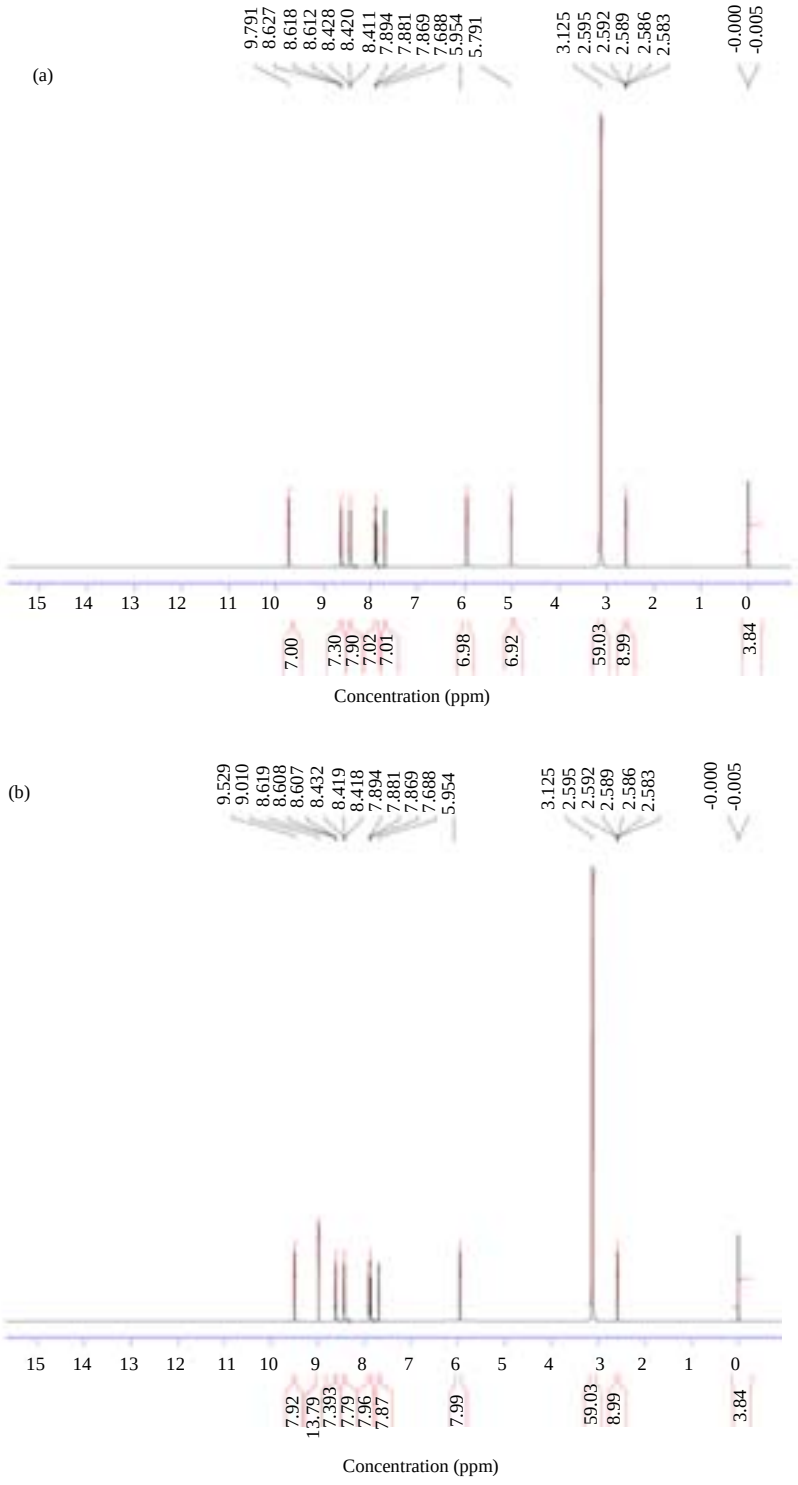

Fig. 3(a-b): ^{1}H NMR spectrum of (a) sacH-CLA and (b) sacH-PA complex

5.95 (s, 1H, hydrogen bonded OH of chloranilic acid), 7.68 (dd, 1H, saccharin $C_{(6)}H$), 7.86 (dd, 1H, saccharin $C_{(5)}H$), 8.41 (d, 1H, saccharin $C_{(4)}H$), 8.61 (d, 1H, saccharin $C_{(7)}H$), 9.79 (s, 1H, saccharin NH protons) (Fig. 3a). It has been found that, the phenolic proton (-OH) signal, which is observed at approximately δ = 9.15 ppm in the spectrum of the free CLA acceptor, decreased in intensity with a high up-field shift for the non-hydrogen-bonded one (δ = 5.79) in the spectrum of this complex. Instead, the peak appeared at 5.95 ppm, is attributed to the hydrogen bonded OH of CLA. This situation

confirmed the formation of the CT complex between one of the phenolic protons of CLA with the (-NH) group of sacH.

The reaction of sacH with PA yielded a new CT complex, which produced signals at δ = 5.95 (s, 1H, hydrogen bonded OH of picric acid), 7.68 (dd, 1H, saccharin $C_{(6)}H$), 7.86 (dd, 1H, saccharin $C_{(5)}H$), 8.41 (d, 1H, saccharin $C_{(4)}H$), 8.60 (d, 1H, saccharin $C_{(7)}H$), 9.01 (s, 2H, CH of picric acid), 9.52 (s, 1H, saccharin NH protons) (Fig. 3b). The peak at d =11.94 ppm, which is assigned to the (-OH) proton of free picric acid, is absence in the spectrum of this complex. Instead, the peak appeared at 5.95 ppm, is assigned to the hydrogen bonded OH of PA. It is clearly obvious that the formation of this new signal indicating the involvement of (-NH) group of donor and (-OH) group of acceptor in chelating through the deprotonation from the PA to the sacH. The intensities and chemical shifts of the aromatic signals were significantly affected by the existence of the intermolecular H-bond between the donor and the acceptor molecules.

Thermogravimetric and differential thermal analysis profiles: The thermal property of obtained CT complexes was characterized with thermogravimetric (TG) and Differential Thermal Analyses (DTA). The measurements were carried out under nitrogen atmosphere in the temperature range of 25-900°C. Their representative thermograms are illustrated in Fig. 4(a, b). The possible thermal degradation patterns for these compounds are collected in Table 2. Fairly close values of the calculated and experimental percentage of the moieties expelled from these complexes strongly support the experimentally determined stoichiometry of the complexes. The complex containing the CLA acceptor was thermally decomposed in nearly two decomposition steps within the 100-600°C temperature range (Fig. 4a). The first mass loss (obs.=21.35, cal. = 21.42%) with DTA_{max} of 134°C (endothermic) corresponds to the liberation of three CO molecules (Fig. 5a). The second decomposition step (250-600°C) is exothermically by fragments of C_2H_4+2CO+SO_2+NH_3+Cl_2 moieties with (obs.=59.90, cal.=60.18%) weight loss, leaving a few leaving residual carbon as final products. The TG and DTA thermograms of the PA complex indicated that this complex is thermally stable in the 25-175°C temperature range (Fig. 4b). The thermal decomposition of the complex proceeds via one degradation step, with four DTA maximum peaks, one single endothermic peak at 149°C and three exothermic peaks at 350, 600 and 800°C (Fig. 5b). The complex begins decomposed at ~175°C and was complete at ~600°C and the observed weight loss associated with this step is (obs.= 99.63, cal.= 100.0%), which can be attributed to the loss of the $C_{13}H_8N_4O_{10}S$ organic moiety.

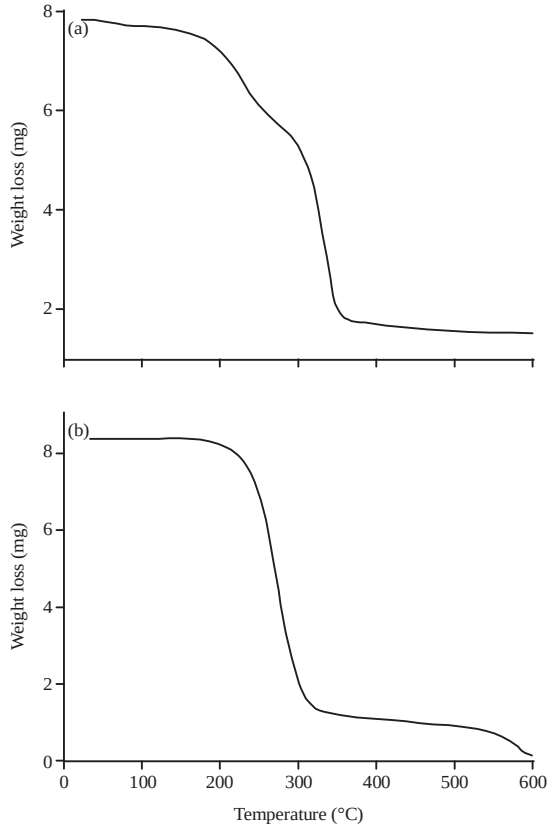

Fig. 4(a-b): Thermogravimetric analysis thermogram of the (a) sacH-CLA and (b) sacH-PA complex

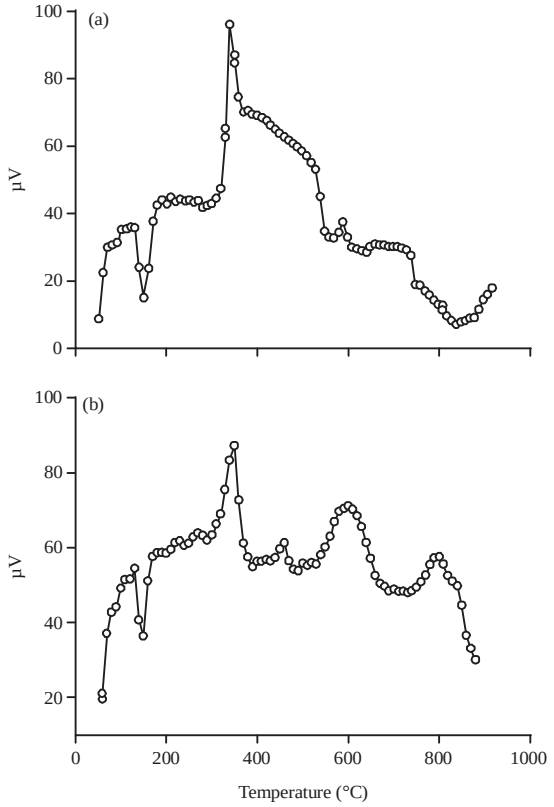

Fig. 5(a-b): Differential thermal analysis thermogram of the (a) sacH-CLA and (b) sacH-PA complex

Table 2: Summary of thermogravimetric and differential thermal analysis data of the obtained change transfer complexes

				TG mass loss (%)		
Complex	Stages	TG range (°C)	DTA max. (°C)	Found	Calculated	Lost species
[(sacH)(CLA)]	I	100-250	134	21.35	21.42	3CO
	II	250-600	353	59.90	60.18	C_2H_4+2CO+SO_2+NH_3+Cl_2
	Residue	-	-	18.40	18.36	6C
[(sacH)(PA)]	I	175-600	149, 350, 600, 800	99.63	100.00	$C_{13}H_8N_4O_{10}S$

TG: Thermogravimetric analysis, DTA: Differential thermal analysis, PA: Picric acid, CLA: Chloranilic acid, SacH: Saccharic

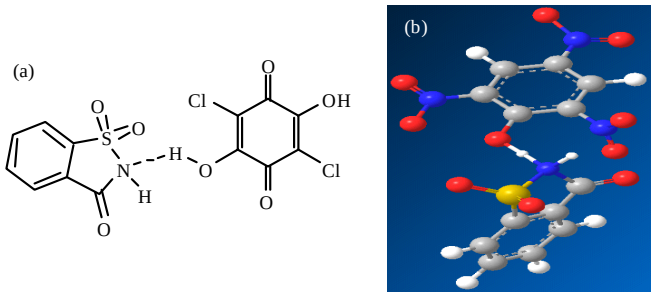

Fig. 6(a-b): Proposed molecular structure of sacH-CLA complex

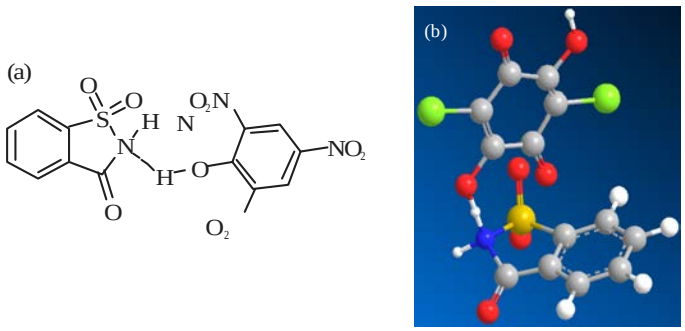

Fig. 7(a-b): Proposed molecular structure of sacH-PA complex

Complexation pathway: The structures of the synthesized complexes have been confirmed by IR and ^{1}H NMR spectral data. The data obtained by these techniques are consistent with each other and support the predicted structures. The complexation of the sacH with either PA or CLA acceptor leads to the formation of a hydrogen bonding. The suggested molecular structures of the complexes between sacH donor with CLA and PA acceptors are illustrated in Fig. 6 and 7, respectively.

These findings were supported by several previous studies. For examples, Gupta *et al*. (2015) synthesized a newly phthalocyanine-based derivative of Zn[Pc(O-Bn-CH_3)$_3$]. They reported that this complex forms an intermolecular hydrogen bond with picric acid *via* nitrogen atoms. Rok *et al*. (2015) obtained a new H-bonded crystals between 4,4'-di-t-butyl-2,2' -bipyridyl and chloranilic acid. They noticed the existence of an infinite hydrogen-bonded chains between the two molecules. Saravanabhavan *et al*. (2014) confirmed that the formation of adduct compound between carbazole and picric acid via. the (-OH) group of the picric acid. Refat *et al*. (2015b) indicated that the complexation of CLA and PA acceptors with two kinds of crown ethers leads to the formation of a hydrogen bonding with a proton transfer. They indicated that each nitrogen atom of the crown ether molecule accepts one hydrogen bond from the hydroxyl group of the CLA or PA molecule. So, the donor and acceptor molecules in these complexes are linked by intermolecular hydrogen-bonding interactions. Also, Refat *et al*. (2015c) showed that the interaction between the drug metronidazole and PA acceptor occurs through the formation of intermolecular H-bonding between the basic center on the donor (C=N group) of the drug and the acidic center (OH group) of the acceptor. Al-Amoudi *et al*. (2015) studied the charge-transfer interaction between the Ponceau S fluorescent dye with some π-acceptors. They found that a hydrogen bonding is existed between the two protons (-OH) of $S(=O)_2$–OH group of the dye and the acidic central position (-OH) of the CLA and PA acceptors. The morphology and nanometry of nanostructured products formed from the interaction between drug theophylline and some organic acceptors were investigated by Adam and Refat (2015). They indicated that the complexation of theophylline with PA acceptor leads to the formation of a hydrogen bonding with a proton transfer. The basic center (C=N) on the theophylline

molecule accepts one hydrogen atom from the acidic center on the PA acceptor molecule (OH group). Gaballa and Amin (2015) suggested that, an acid-base interaction between 2-hydrogxypyridine with PA acceptor is associated with a proton migration followed by hydrogen bonding formation based on IR and ^{1}H NMR spectra. Al-Ahmary (2014) shed new light on the charge-transfer interaction between 2,3-diaminopyridine with CLA acceptor. She reported that, the formed CT-complex included proton transfer between CLA acceptor and 2,3-DAP. Finally, nanostructured complexes derived from the reaction of the reserpine and quinidine drugs with CLA acceptor were fully characterized using physicochemical techniques by Adam (2014b). He reported that the pairs molecules in drug-CLA complexes are linked by intermolecular hydrogen-bonding interactions.

Morphology profile: Optical Light Microscope (OLM) provides colorful micrographs. Color is an advantage for residue identification and characterization and can also help to recognize potential contamination. The OLM was employed to observe the morphology of the prepared complexes. The surface micrographs obtained with the OLM technique provide general information regarding the microstructure, surface morphology and porous structures of the surfaces. The series of micrographs observed through OLM revealed the following observations:

- The morphological phases of the complexes showed a uniform matrix in the OLM micrographs indicating the formation of a homogeneous material
- The obtained complexes are crystalline, as indicated by the formation of single-phases with well-defended shape
- Visible morphological change is observed between the sacH complexes. The PA complex shows a much smoother homogenous surface than that of CLA complex
- From the multi OLM micrographs with various degrees of enlargement, most of the crystals of CLA complex exhibit different angular shapes
- The complexation of sacH with PA leads to a very interesting morphology. A magnified OLM micrograph at a high magnification of this complex shows a rod-shaped morphology. This high quality and well-focused micrograph indicates this complex have a highly well-defined morphology.
- Comparing the morphology of sacH complexes; one can see they are quite different in microstructure

CONCLUSION

The CT complexes derived from the reaction of sacH, a sugar substitute sweetening agent used extensively in dietary products, with organic acceptors (CLA and PA) were prepared, isolated and characterized by a range of physicochemical methods. The results indicate that all complexes are formed based on a 1:1 stoichiometric ratio. The IR and ^{1}H NMR revealed evidence of significant intermolecular hydrogen bonding interactions between sacH and each acceptor based on their characteristic shifts. The OLM micrograph patterns indicate the formation of high quality colored crystals.

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