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# Crystal structure, thermal and dielectric studies of a new polymorph of thiamine iodide hydroiodide.

S. Prasanna<sup>1</sup>, K. Rajendra Babu<sup>1</sup>, M. Deepa<sup>2</sup> & C.M.K. Nair<sup>1</sup>\*

<sup>1</sup>Postgraduate Dept. of Physics and Research centre, M.G. College, Thiruvananthapuram-695004, India

<sup>2</sup>Dept. of Physics, All Saints College, Thiruvananthapuram – 695037, India

# \*Corres. author: prasannathekkekara@gmail.com, Tel. +914712442248

**Abstract:** The crystal structure of the polymorphic form of thiamine iodide hydro iodide has been determined using single crystal X ray diffraction method. The crystal data obtained are: space group : P21/n, a=13.7883(10)Å, b=7.4330(5)Å, c=17.8082(13)Å,  $\beta$ =101.621(2)° Z=4. The cations and anions are linked by O-H--I hydrogen bonds, C-H--I interactions and I-- thiazolium ring close contacts. The thiaminium cation adopts a F conformation. FT-IR and CHNS studies supports the crystal structure and the molecular formula. TG/DT analysis was carried out to study its thermal properties. UV-Vis –NIR spectroscopy and dielectric studies at ambient temperature were used to determine the energy gap (Eg) and polarisability of the grown crystals.

Key Words : Polymorph; SXRD; Dielectric property; Vitamin; Crystal packing.

# 1. Introduction

In recent years a large number of research work has been going on in the area of pharmaceutical materials and drug delivery systems. The absorption of a drug mainly depends on its physicochemical properties like solubility, partition coefficient, particle size and polymorphic forms. The existence of polymorphic forms of drugs can add significant effects on the bioavailability of the active drug substance, the shelf life of the drug and manufacturability of the drug substance [1,2,3]. Hence a knowledge of conformation of drug molecule is an important factor in drug design.

Thiamine, a factor for normal functioning of the intestine, cardiovascular and nervous systems, is a water soluble vitamin [4]. It is also required for proper circulation, blood formation, and metabolism of carbohydrates. It is a precursor to several

including neurotransmitters Gama-aminobutyric acid (GABA). GABA is a chemical that affects nervous system by preventing neurons from over firing, thus calming the brain. Due to its high water solubility, this vitamin is excreted through urine and its storage is limited and hence must be provided regularly. It consists of a pyrimidine and a thiazole ring system joined by a methylene bridge. Many drugs exist in polymorphic forms which have different rates of absorption because of the difference in solubilities [5]. Thiamine forms complexes with chloride, bromide and iodide anions. It is generally prepared as the chloride hydrochloride complex. Crystal and molecular structure of thiamine iodide hydroiodide has been reported earlier [6]. Haihu et al had synthesized a mono iodide complex of thiamine, thiamine iodide sesquihydrate, and determined its

crystal structure [7]. Here we report a new polymorphic form of thiamine iodide hydroiodide [THI2], a complex of thiamine and Iodine grown by slow evaporation method.

The grown crystals were subjected to single crystal XRD, FT-IR, elemental analysis, thermal and dielectric studies. The TGA/DTA studies are useful in the evaluation and comparison of thermal stabilities of pharmaceutical materials. A knowledge of kinetic and thermal parameters is essential for evaluating the quality of pharmaceutical products [8,9]. Dielectric analysis provides information about the motion of entities having an electric dipole moment, ie, about dipole reorientation, rotations of the main and segmental chains and conductivity mechanism which is an essential tool for the study of drug delivery systems [10].

## 2. Experimental procedure

Single crystals of THI2 were grown by mixing 10 ml of aqueous solutions of thiamine hydrochloride and 10 ml of potassium iodide in the molar ratio 1:2

and allowing to evaporate in a constant temperature bath at  $34^{\circ}$  C. Nucleation started after two days. Colourless single crystals of the title complex of size 3mm x 1mm x 0.5mm obtained after one week are shown in fig .1. Other molar ratios of the reactants yielded poor quality crystals.



## Fig. 1 Photo of THI2 crystal

The grown crystals were subjected to single crystal XRD (Brucker Kappa Apex 2 CCD diffractometer), FT-IR (Thermo Nicolet, Avatar 370 model, 0.9cm-1 resolution, DTGS detector), TGA/DTA (Perkin Elmer, Diamond, sample heated between ambient (32°C) and 1000°C) and CHNS analysis (Elementar Vario EL III model).

Tabl	e 1.	Cr	ystal	data	and	struct	ture	refin	ement	for	TH	2
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Empirical formula Formula weight Temperature Wavelength Crystal system Space group Unit cell dimensions	C12 H18 I2 N4 O S 520.17 293(2) K 0.71073 Å Monoclinic P21/n a = 13.7883(10) Å b = 7.4330(5) Å c = 17.8082(13) Å	$\alpha = 90^{\circ}.$ $\beta = 101.621(2)^{\circ}.$ $\gamma = 90^{\circ}.$
Volume	1787.7(2) Å <sup>3</sup>	
Z	4	
Density (calculated)	1.933 Mg/m <sup>3</sup>	
Absorption coefficient F(000)	3.636 mm <sup>-1</sup> 992	
Theta range for data collection Index ranges	2.98° to 28.23°. -18<=h<=18, -6<=k<=9, -23	3<=1<=23
Reflections collected	15516	
Independent reflections	4376 [R(int) = 0.0599]	
Absorption correction Max. and min. transmission	Semi-empirical from equival 0.403 and 0.291	lents
Refinement method Data / restraints / parameters	Full-matrix least-squares on 4376 / 0 / 202	F <sup>2</sup>
Goodness-of-fit on F <sup>2</sup> Final R indices [I>2sigma(I)] R indices (all data) Extinction coefficient	1.053 R1 = 0.0458, wR2 = 0.1306 R1 = 0.0540, wR2 = 0.1415 0.0090(6) 1.311 and -1.307 e $Å^{-3}$	
Largest and, pour una noio	1.511 and 1.507 0.11	

## 3. Results and Discussion

**3.1 Single crystal X- ray diffraction (SXRD) studies** The crystal structure has been solved by direct method and refined full matrix least square techniques based on F<sup>2</sup>. The non hydrogen atoms were refined with anisotropic displacement parameters. Computing data reduction, structure solution and refinement were done using the softwere packages SAINT/XPREP, SIR (5,6,7)92,SHELXL-97 respectively. The molecular graphics were obtained using MERCURY. Crystallo graphic data and processing parameters are given in table -1. The manner in which the pyrimidine and thiazolium rings are oriented around the bridging methylene group is defined in terms of torsional angles  $\varphi_t$  and  $\varphi_p$ . The values of these torsion angles give conformation of the thiamine cation. In the present structure, the value of  $\varphi_t$  (C3 -C6-N4-C7) is - 5.16° and  $\varphi_p$  (N4-C6-C3-C4) is 81.35° showing that the present structure has a F conformation [11]. The selected bond distances and angles which are found to be relevant are summarized in table -2.

C(1)-N(2)	1.310(6)
C(1)-N(1)	1.344(6)
C(1)-C(5)	1.500(7)
C(2)-C(3)	1.348(6)
C(2)-N(1)	1.349(6)
C(6)-N(4)	1.488(5)
C(7)-N(4)	1.308(6)
C(7)-S(1)	1.680(5)
C(8)-S(1)	1.721(5)
C(9)-N(4)	1.397(5)
C(9)-C(10)	1.482(7)
C(11)-C(12)	1.516(7)
C(12)-O(1)	1.418(7)
C(12)-O(1)-H(1C)	104.43(1)
N(2)-C(1)-N(1)	122.7(4)
C(11)-C(8)-S(1)	120.4(4)
C(8)-C(9)-N(4)	111.6(4)
C(8)-C(9)-C(10)	128.7(4)
N(4)-C(9)-C(10)	119.6(4)
C(8)-C(11)-C(12)	112.4(4)
O(1)-C(12)-C(11)	111.2(4)
C(1)-N(1)-C(2)	120.5(4)
C(1)-N(2)-C(4)	118.1(4)
C(9)-N(4)-C(6)	122.2(3)
C(7)-S(1)-C(8)	91.4(2)

Table 2. Important bond lengths [Å] and angles [°] for THI2.

The title compound is formed by the complexation of two iodine anions and one thiamine cation. The molecular structure and the crystal packing are given in (Figs. 2 & 3). Thiamine cation contains two positive charges, one with the protonated N(1) of the pyrimidine ring and the other with the sulphur in the aromatic thiazolium ring. Protonation of N(1) is confirmed by the bond angle C1-N1-C2 which is found to be equal to  $120.5^{\circ}$  in the present structure which agrees well with the literature [12, 13]. The protonated N(1) makes hydrogen bond with the neighbouring O(1) atom to make an infinite zigzag net work N(1)-H(1G)=0.873Å, H(1G)-O(1)=1.888Å and O(1)-N(1)=2.761Å. The iodine I(2) is involved in hydrogen bond with H(1C) in the hydroxyl group of pyrimidine ring with bond length of H(1C)-I(2) =2.726Å. The I(1) atom is found to be involved only in short contacts (< sum of van der Waal's radii ). However in the previously reported structure the charge transfer is suggested to occur between the  $N^+$ ion in the thiazolium ring and the I(2) anion [6]. The C(12) hydroxyethyl side chain is folded back towards thiazolium ring to make close contact between the electronegative oxygen atom and electro positive sulphur atom (O1-S1=2.947Å). This O1-S1 distance is less than that in the reported structure by 0.023Å. The values of the torsion angles  $\varphi_{5\alpha}$  (S1-C8-C11-C12) and  $\varphi_{5\beta}$  (C8-C11-C12-O1) determines the close proximity between O(1) and S(1) atoms to ensure electrostatic interaction. For this, they should satisfy the conditions  $\varphi_{5\alpha}$  less than 70° and  $\varphi_{5\beta}$  negative [14, 15]. These conditions are satisfied in the present structure with  $\varphi_{5\alpha}$ = 61.64° and  $\varphi_{5\beta}$  = -63.95°. The present structure shows a significant decrease in the bond angle C (12)-O(1)-H(1C) of the order of  $(6.57^{\circ})$  from the reported structure. This may presumably be due to the involvement of O (1) in forming three different bonds. The THI2 forms a supramolecular polymeric frame work through intermolecular hydrogen bonding and weak interactions [16,17].



Fig. 2 Molecular structure of THI2 with atom numbering. Hydrogen atoms omitted for clarity.



Fig. 3 View along the crystallographic c axis of the supramolecular polymer of THI2 crystal.

#### **3.2 Elemental analysis:**

The experimental data of elemental analysis of the title compound is in agreement with the calculated value for the formula  $C_{12}H_{18}N_4OS_1I_2$ 

Experimental S: 6.00%	C: 27.80%,	H: 3.40 %,	N: 10.70 %,
~	a		

Calculated C: 27.79%, H: 3.47 % N: 10.81% S: 6.18 %.

#### 3.3 FT-IR Spectroscopy

Hydrogen bonding lowers the stretching frequencies of both the groups involved in it and also changes the shape and intensity of the absorption bands [18]. The SXRD data of the title compound show a few hydrogen bonds and weak interactions. The OH group in the present structure is involved in two hydrogen bondings with iodine and nitrogen which reduces the O-H stretching frequency (3253cm <sup>-1</sup>) considerably. The band assigned to C-S stretching in the thiazole ring also shows a decrease in frequency due to the electrostatic interactions between electro positive sulphur and electro negative oxygen atom. The N-H stretching frequency usually found at 3494cm<sup>-1</sup> is absent in the present structure due to the aforesaid hydrogen bonding. A very strong peak found at 1655cm<sup>-1</sup> is due to the bending of N-H of the NH<sub>2</sub> group. The out of plane bending of S-C-N found at 464 cm<sup>-1</sup> also shows a decrease in frequency [19].

#### 3.4 Thermal analysis

The thermogravimetric analysis of the title compound was done in nitrogen atmosphere at a heating rate of  $10^{\circ}$  C /min. and for a temperature range from ambient to 1000 ° C in alumina cups. The thermographs are shown in fig.4. The sample is thermally stable up to 248 <sup>o</sup>C. The DSC curve shows a sharp endothermic peak at 248 °C. This may be the melting point of the complex after which the decomposition starts. The melting point of the previously reported structure is 230<sup>°</sup> C, implying that the present structure is thermally more stable. The decomposition process is continuous and more steep in the initial stage up to about 400°C, with no intermediate steps. A residual carbon 8.25% is left over at about 1000 °C. The kinetic parameters viz. order of reaction = 3, activation energy (E) = 299.49  $KJmol^{-1}$ , preexponential term log(A) = 27.40, were determined using Coats-Redfern method [20]. The thermodynamic parameters such as entropy of activation ( $\Delta S$ ) = 276.47 JK<sup>-1</sup> mol<sup>-1</sup>, enthalpy = 291.34 KJmol<sup>-1</sup> and Gibb's free energy =147.55KJmol<sup>-1</sup> were also calculated [21].





#### Table-3 Plasma energy and polarisability of THI2 crystal

Parameters	Values
Plasma energy (ev)	16.03
Penn gap (ev)	8.53
Fermi energy(ev)	11.92
Polarisability (cm <sup>3</sup> )	
(a) Penn analysis	5.27x10 <sup>-23</sup>
(b) Clausius - Mossotti	6.85x10 <sup>-23</sup>
(c) from band gap	6.09x10 <sup>-23</sup>

The positive value of entropy suggests that the process is a spontaneous one. The stability of a crystal increases with increase in activation energy needed for decomposition [22]. The high value of activation energy in the present structure is an evidence for good stability.

## 3.5 Dielectric studies

The variation of dielectric constant of the sample with frequency is studied at room temperature by H10K1 3532 LCR HITESTER in the frequency range 300Hz to 3MHz and is shown in fig.5. The high values of dielectric constant at high frequency may be due to the presence of all the four polarisations namely space charge, orientational, electronic and ionic. At high values of frequencies the significance of these polarisations decreases exponentially [23]. The value of dielectric constant at higher frequencies can be used to calculate Penn gap, Fermi energy and polarisability of the grown crystals [24]. The calculated values are depicted in table-3.



Fig. 5 Variation of dielectric constant of THI2 with frequency

### 3.6 UV- Visible Spectroscopy

UV- Visible- NIR absorbance spectrum of the grown crystals were recorded with a Varian Cary 5000 UV - Vis - NIR spectrometer in the range 200 to 1000 nm. A plot of absorption coefficient versus energy hu is shown in fig.6. It shows a sharp absorption edge at higher energies. At lower energies the absorption is represented by Urbach's tail [25]. Extrapolation of the linear portion of the graph to make absorption coefficient zero gives the energy gap which in this case is found to be 3.1 eV. The polarisability  $\alpha$  is sensitive to band gap and the value of  $\alpha$  calculated from the empirical formula  $\alpha$ =[1-(Eg)<sup>1/2</sup>/4.06]M/px0.396x10<sup>-24</sup> is found to be equal to 6.01x10<sup>-23</sup>cm<sup>-1</sup>[26].



Fig.6 Plot of ahv versus photon energy

## 4. Conclusion

Single crystals of THI2 were grown successfully by slow evaporation method at ambient temperature. The single crystal X ray diffraction studies confirmed the F conformation of the thiamine molecule. The bite site of iodine in the present structure is hydrogen of the hydroxyl group where as in the reported structure it is the  $N^+$  ion in the thiazolium ring. The folding of hydroxyl ethyl side chain in this structure is greater than that in the reported structure and this makes the electrostatic interaction between electropositive sulphur and electronegative oxygen more intact. The complex attains a supramolecular polymeric framework through hydrogen bonding and inter molecular weak inter actions. The CHNS analysis confirmed the molecular confirmed the formula and FT-IR spectroscopy molecular bindings. The thermal stability of the crystal was found to be more than that of the reported structure. The kinetic and thermodynamic parameters were also calculated. The energy gap (Eg ) was determined from UV -vis -NIR spectroscopy. The value of polarisability determined from UV-Vis-NIR and dielectric studies agrees well with that calculated using Clausius - Mossotti relation.

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#### Supplementary data

CCDC No. 810234 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam. ac.uk/data request/cif.

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