Synthesis, Characterization and Equilibrium Studies of Diorganotin (IV)$^{2+}$ Complexes with 4-Amino-6-Hydroxy-2-Mercapto Pyrimidine (AHMP)

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SUMMARY

Diorganotin(IV) dichlorides react with 4-amino-6-hydroxy-2-mercapto pyrimidine (AHMP) forming the complexes $R_2SnCl(L)$ and $R_2Sn(L)_2$ (L = AHMP; R = CH_3; n-Bu). The bonding sites of the dimethyltin (IV) complexes with (AHMP) are investigated by means of elemental analyses, FTIR and ^1H NMR. Complex formation equilibria of dimethyltin (IV) with 4-amino-6-hydroxy-2-mercapto pyrimidine (AHMP) have been investigated. Stoichiometry and stability constants for the complexes formed are determined at different temperatures and ionic strength 0.1 M $NaNO_3$. The results show the formation of 1:1 and 1:2 complexes (dimethyltin : AHMP). The concentration distribution of the complexes in solution is evaluated. The thermodynamic parameters ΔH^0 and ΔS^0 calculated from the temperature dependence of the equilibrium constants are investigated.

INTRODUCTION

The chemistry of the organotin (IV) derivatives is a subject of growing interest /1/, not only because of the environmental consequences of the widespread use of these compounds /2/, but also due to the increasing importance of their medical assays for bactericide, fungicide and antitumour purposes /3-7/. In recent years many organotin compounds have been tested for a large variety of tumor lines and have been found to be as effective, or better, than traditional heavy metal anticancer drugs such as *cis*-platin /8/. Also increasing investigation on organotin (IV) complexes has been focused on acquiring established structures to learn the nature of their versatile bonding modes /1/, especially those of some organotin (IV) derivatives from heterocyclic thionates /9/. Heterocyclic thionates contain at least one deprotonated heterocyclic thioamide group (N-C-S)- and can act as monodentate, chelating and bridging ligands. Mercapto group is often coordinated to the metal ions in many biological molecules /10,11/, and information about the relative reactivity of the coordinated mercapto group might give insight into the specific reactivity of the active sites

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in some metalloproteins. Ligands containing a thioamide group have been selected for anticancer screening by the National Cancer Institute, Bethesda, Maryland, U.S.A. 2-mercaptopyrimidine nucleotides have been detected in *Escherichia coli* **sRNA** and yeast t**RNA**, and were found to inhibit the synthesis of t**RNA**, and thus they act as an antitumour and antithyroid agent /12/. A similar inhibitory effect has been found for pyrimidine-2-thione (Hpymt) and the compound also shows pronounced *in vitro* bacteriostatic activity /13/. Thus they may act as valuable substances for synthesizing antitumour active organotin compounds. In view of the above facts, it seems therefore to be of considerable interest to conduct several investigations covering the coordination of dimethyltin (IV) moiety by thiol sulfur and heterocyclic nitrogen. From the above consideration, and also as a part of our studies on the coordination chemistry of organotin (IV) compounds /14-18/, we chose another ligand: 4-amino-6-hydroxy-2-mercapto pyrimidine (AHMP), similar to the 2-mercaptopyrimidine (MP) /19/. It belongs to the same class as the nucleic acid bases. Studies on organotin complexes with 2-mercaptopyridine essentially concern diorganotin derivatives of the type $R_2Sn(MP)_2$ or $R_2SnCl(MP)$ /20-22/. The present work deals with the preparation and characterization of four new organotin (IV) complexes with AHMP ligand.

EXPERIMENTAL

Materials and reagents

4-amino-6-hydroxy-2-mercapto pyrimidine. H_2O (AHMP) was obtained from Aldrich Chem. Co. Dimethyltin(IV) dichloride (DMT) and dibutyltin(IV) dichloride (DBT) were supplied by Merck Chem. Co. Dioxane was provided by Aldrich Chem. Co. Carbonate- free NaOH (titrant) was prepared by diluting the content of BDH concentrated volumetric solution vials and standardized against potassium hydrogen phthalate solution. All solutions were prepared in deionized H_2O.

Synthesis

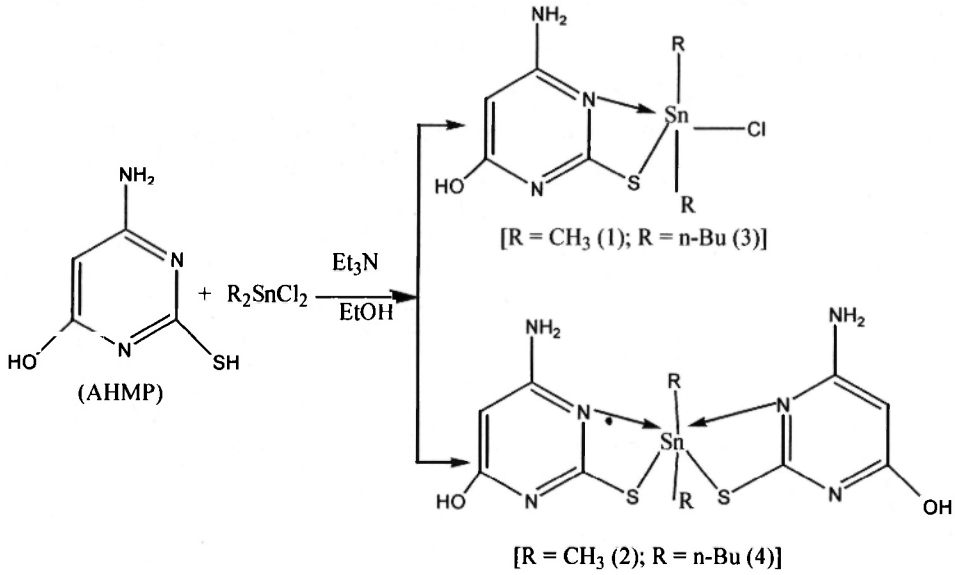
The organotin (IV) derivatives were obtained by reacting stoichiometric amounts of AHMP , triethylamine (Et_3N) and corresponding organotin chlorides in the presence of absolute ethyl alcohol (EtOH). The resulting solution mixture was stirred for two days under inert atmosphere of dry nitrogen. The obtained solid was recrystallized from a 1:1 (v/v) mixture of dichloromethane-n-hexane and filtered off, washed with EtOH, and dried *in vacuo*. The synthesis procedure is given in Scheme 1.

$Me_2SnCl(AHMP)$ (1) is a white powder with yield, 80 %. Anal. Calc. for $C_6H_{10}N_3OSClSn$: C, 22.07; H, 3.06; N, 12.87; S, 9.80; Cl, 10.88. Found: C, 22.15; H, 3.11; N, 13.11; S, 9.91; Cl, 10.67. IR (KBr, cm^{-1}): 3425 (OH), 3321 (NH_2), 520 $(Sn\text{-}C)_{as}$, 500 $(Sn\text{-}C)_S$, 315 (Sn-S), 485 (Sn←N), 285 (Sn-Cl). ^{1}HNMR (DMSO): 6.68 (s, 1H, C-H), 1.13 (s, 6H, $Sn\text{-}CH_3$).

$Me_2Sn(AHMP)_2$ (2) is a white powder with yield, 84 %. Anal. Calc. for $C_{10}H_{14}N_6O_2S_2Sn$: C, 27.70; H, 3.2; N, 19.4; S, 14.8. Found: C, 27.19; H, 3.1; N, 18.92; S, 14.4. IR (KBr, cm^{-1}): 3429 (OH), 3325 (NH_2), 515 $(Sn\text{-}C)_{as}$, 437 $(Sn\text{-}C)_S$, 308 (Sn-S), 482 (Sn←N). ^{1}HNMR (DMSO): 6.75 (s, 2H, C-H), 1.06 (s, 6H, $Sn\text{-}CH_3$).

$Bu_2SnCl(AHMP)$ (3) is a white powder with yield, 76 %. Anal. Calc. for $C_{12}H_{22}N_3OSClSn$: C, 35.1; H, 5.36; N, 10.2; S, 7.80; Cl, 8.60. Found: C, 34.78; H, 5.4; N, 9.89; S, 7.58; Cl, 8.36. IR (KBr, cm^{-1}): 3429 (OH), 3321 (NH_2), 525 $(Sn\text{-}C)_{as}$, 430 $(Sn\text{-}C)_S$, 311 (Sn-S), 487 (Sn←N), 278 (Sn-Cl). ^{1}HNMR (DMSO): 6.60 (s; 2H; C-H), 1.61 (t; 4H; Sn-CH_2-), 1.41(m; 4H;C-CH_2-C), 1.24 (m; 4H;CH_2-CH_3), 0.79 (t, 6H; Bu-CH_3).

$Bu_2Sn(AHMP)_2$ (4)is a white powder with yield, 81 %. Anal. Calc. for $C_{16}H_{26}N_6O_2S_2Sn$: C, 37.15; H, 5.06; N, 16.25; S, 12.38. Found: C, 37.25; H, 5.10; N, 16.15; S, 11.98. IR (KBr, cm^{-1}): 3425 (OH), 3321 (NH_2), 530 $(Sn\text{-}C)_{as}$, 502 $(Sn\text{-}C)_S$, 313 (Sn-S), 485 (Sn←N). ^{1}HNMR (DMSO): 6.65 (s; 2H; C-H), 1.60 (t; 4H; Sn-CH_2-), 1.42(m; 4H;C-CH_2-C), 1.27 (m; 4H;CH_2-CH_3), 0.81 (t, 6H; Bu-CH_3).



Scheme 1

Instruments

Potentiometric measurments were made using a Metrohm 686 titroprocessor equipped with a 665 Dosimat (Switzerland-Herisau). A thermostated glass-cell was used, equipped with a magnetic stirring system, a Metrohm glass electrode, a thermometric probe, a microburet delivery tube and a salt bridge connected with the reference cell filled with 0.1 M KCl solution in which saturated calomel electrode was dipped. The titroprocessor and electrode were calibrated daily with standard buffer solutions prepared according to NBS specifications at $25.0 \pm 0.1^0C^{(23)}$ and I = 0.1 mol-dm^{-3}, potassium hydrogen phthalate (pH 4.008) and a mixture of KH_2PO_4 and Na_2HPO_4 (pH 6.865). Elemental microanalyses and IR of the separated solid complexes were performed in the Microanalytical Center, Cairo University. The analyses were performed twice to check the accuracy of the analyses data. IR spectra were measured on a 8001-PC FTIR Shimadzu spectrophotometer using KBr pellets. ^{1}HNMR spectra were recorded on varian Gemini 200 spectrometer at 200 MHz using TMS as internal standard and DMSO-d_6 as solvent.

PROCEDURE AND MEASUREMENTS

The proton association constants of the ligands were determined potentiometrically by titrating the ligand (50 cm^3) solution ($8x10^{-4}$M) of constant ionic strength 0.1M, (adjusted with $NaNO_3$). The stability constants of the dimethyltin (IV) complexes with (AHMP) were determined by titrating 50 cm^3 of a solution mixture of dimethyltin (IV) ($8x10^{-4}$M) and the ligand ($1.6x10^{-3}$M). All solutions were adjusted to 0.1 M ionic strength by addition of $NaNO_3$ (0.1M) and were performed in a purified N_2 atmosphere, using aqueous 0.05 M NaOH as titrant. Temperature was maintained constant inside the cell at (25.0 ± 0.1) °C, by circulating thermostated water through the double-wall titration vessel and under a slow and constant stream of N_2 over the test solutions.The pH meter readings were converted into hydrogen ion concentration by titrating a standard acid solution (0.05 mol-dm^{-3}), the ionic strength of which was adjusted to 0.1 mol-dm^{-3}, with standard base solution (0.05 mol-dm^{-3}) at 25 °C. The pH is plotted against p[H]. The relationship pH - p[H] = 0.05 was observed. [OH^-] value was calculated using a pK_w value of 13.997[24]. The ionic strength was adjusted to 0.1 mol-dm^{-3} by using $NaNO_3$.

The equilibrium constants were evaluated from titration data, defined by Eqs. (1) and (2). A general three-component equilibrium can be written as follows (charges are omitted for simplicity)

$$pM + q(L) + r(H) \rightleftharpoons (M)_p (L)_q (H)_r \quad (1)$$

$$\beta_{pqr} = \frac{[(M)_p (L)_q (H)_r]}{[M]^p [L]^q [H]^r} \quad (2)$$

Calculations were performed using the computer program /25/ MINIQUAD-75. The model selected was that which gave the best statistical fit and which was chemically consistent with the titration data without any systematic bias in residuals /25/. The results obtained are shown in Tables 1 and 2. The concentration distribution diagrams were obtained using the program SPECIES /26/ under the experimental conditions described.

RESULTS AND DISCUSSION

Formation equilibria of dimethyltin (IV) complex with AHMP

The potentiometric titration curves of AHMP in the presence and absence of dimethyltin (IV) are compared. The complex titration curve is significantly lower than the AHMP titration curve. This corresponds to the formation of a complex species through release of a hydrogen ion. The pH titration data were fitted with the model composed of the 110 and 120 species.

Table 1

Formation Constants of Dimethyltin(IV) Complexes in Water at Different Temperatures.

System	Temp. (°C)	p	q	r[a]	log β[b]	S[c]
DMT	15	1	0	-1	-3.56(0.01)	5.4E-8
		1	0	-2	-9.05(0.01)	
		1	0	-3	-19.79(0.04)	
		1	0	-4	-30.41(0.04)	
		2	0	-2	-4.23(0.01)	
		2	0	-3	-9.52(0.01)	
		2	0	-4	-15.23(0.01)	
AHMP		0	1	1	7.08(0.02)	4.2E-8
DMT- AHMP		1	1	0	6.17(0.03)	4.5E-8
		1	2	0	9.97(0.05)	
DMT	20	1	0	-1	-3.31(0.01)	6.1E-8
		1	0	-2	-8.64(0.01)	
		1	0	-3	-19.27(0.05)	
		1	0	-4	-30.71(0.02)	
		2	0	-2	-3.77(0.01)	
		2	0	-3	-8.91(0.02)	
		2	0	-4	-14.44(0.01)	
AHMP		0	1	1	7.02(0.01)	1.4E-8
DMT- AHMP		1	1	0	6.27(0.02)	5.3E-9
		1	2	0	10.25(0.05)	
DMT	25	1	0	-1	-3.03(0.01)	4.3E-8
		1	0	-2	-8.21(0.01)	
		1	0	-3	-18.73(0.03)	
		1	0	-4	-29.54(0.02)	
		2	0	-2	-3.12(0.01)	
		2	0	-3	-8.13(0.02)	
		2	0	-4	-13.59(0.02)	
AHMP		0	1	1	6.95(0.01)	6.9E-8
DMT- AHMP		1	1	0	6.41(0.01)	4.9E-10
		1	2	0	10.51(0.01)	

Table 1 (continued)

DMT	30	1	0	-1	-2.81(0.01)	6.6E-8
		1	0	-2	-7.91(0.02)	
		1	0	-3	-18.38(0.05)	
		1	0	-4	-28.71(0.02)	
		2	0	-2	-2.87(0.02)	
		2	0	-3	-7.84(0.04)	
		2	0	-4	-13.06(0.04)	
AHMP		0	1	1	6.57(0.009)	4.9E-8
DMT- AHMP		1	1	0	6.73(0.07)	5.4E-8
		1	2	0	10.84(0.04)	
DMT	35	1	0	-1	-2.49(0.02)	6.9E-8
		1	0	-2	-7.54(0.02)	
		1	0	-3	-17.95(0.06)	
		1	0	-4	-28.20(0.03)	
		2	0	-2	-2.27(0.03)	
		2	0	-3	-7.11(0.04)	
		2	0	-4	-12.34(0.04)	
AHMP		0	1	1	6.82(0.006)	1.7E-8
DMT- AHMP		1	1	0	6.67(0.04)	1.3E-9
		1	2	0	11.07(0.03)	

[a] p, q and r are the stoichiometric coefficient corresponding to dimethyltin(IV) (DMT), AHMP and H^+, respectively; [b] Standard deviations are given in parentheses; [c] Sum of square of residuals.

Table 2

Thermodynamic parameters for the equilibria of AHMP and DMT-AHMP complexes[a].

Equilibrium[b]	$\Delta H°$kJmol^{-1}	$\Delta S°$JK^{-1} mol^{-1}	$\Delta G°$ [c]kJmol^{-1}
AHMP			
1) $L^- + H^+ \rightleftharpoons LH$	-22.41	57.81	-39.64
DMT-AHMP			
2) $[DMT(H_2O)_3]^{2+} + L^- \rightleftharpoons [M(H_2O)_2L]^+ + H_2O$	44.18	270.9	-36.60
3) $[DMT(H_2O)_2L]^+ + L^- \rightleftharpoons [M(H_2O)\,L_2] + H_2O$	50.63	248.7	-23.48

[a]DMT: denotes dimethyltin(IV), L: denotes AHMP, standard deviations are given in parentheses.

[b] Stepwise formation constants

[c] Obtained from $\Delta G^0 = \Delta H^0 - T\,\Delta S^0$, at 25^{0}C

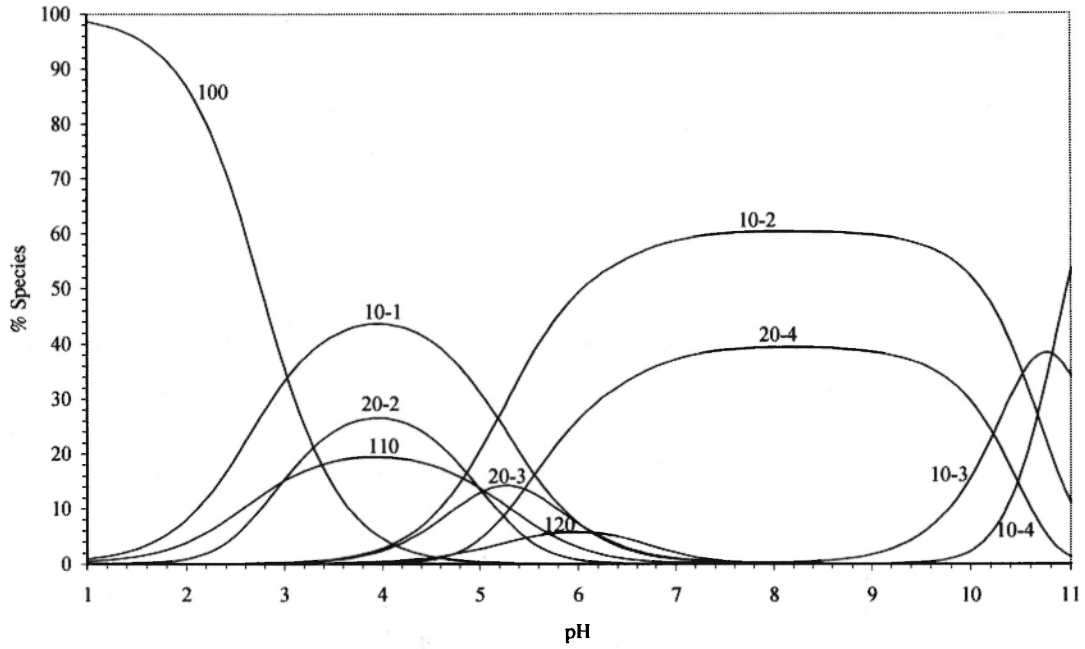


Fig. 1: Concentration distributions of various species as a function of pH in the DMT-AHMP system at concentrations of DMT = $8x10^{-4}$, AHMP = $1.6x10^{-3}$ mol dm^{-3}, I = 0.1 mol dm^{-3} ($NaNO_3$) and T = 25 ± 0.1 °C).

Species distribution curves

Estimation of equilibrium concentrations of DMT complexes with AHMP as a function of pH provides a useful picture of DMT binding in the biological system. The concentrations of DMT complexes increase with increasing pH. The species distribution pattern for DMT-AHMP complex is given in Fig. 1. The 1:1 complex starts to form at pH ~ 2 and reaches its maximum concentration of 20 % at pH ~ 4, while 1:2 complex species reaches a maximum concentration 6 % at pH ~ 6.

Effect of Temperature

The values obtained for the thermodynamic parameters ΔH^0, ΔS^0 and ΔG^0, associated with protonation of AHMP and its complex formation with dimethyltin(IV) ion, were calculated from the temperature dependence of the data in Table 1. ΔH^0 and ΔS^0 were obtained by linear least square fit (Figs. 2, 3) of log K *vs.* 1/T [log K = $(-\Delta H^0/2.303R)(1/T) + \Delta S^0/2.303R$], leading to an intercept $\Delta S^0/2.303R$ and slope $-\Delta H^0/2.303R$, where the gas constant R = 8.314 J K^{-1} mol^{-1}, K is the protonation constant for the ligand or the stability constant of the complex, and T is the absolute temperature. The calculated thermodynamic functions are recorded in Table 2 and can be interpreted as follows:

1. the protonation reaction (1) (Table 2) of AHMP is exothermic and the thermodynamic processes accompanying the protonation reactions are:

accompanying the protonation reactions are:

i) The neutralization reaction, which is an exothermic process;

ii) Desolvation of ions, which is an endothermic process;

iii) The change in the configuration and the arrangements of the hydrogen bonds around the free and protonated ligands.

2. A negative value of ΔH^0 for the protonation process of AHMP ligand shows that its protonation process is accompanied by a release of heat and the process is exothermic.
3. A negative value of ΔG^0 indicates that that the protonation process is spontaneous.
4. The protonation reaction (1) has a positive entropy, this may be due to increased disorder as a result of desolvation processes and the breaking of hydrogen bonds. Similar results were found by Kramer *et al* /27/.

The stepwise stability constants of the complexes formed at different temperatures were calculated. The thermodynamic parameters of the results may be discussed as follows :

1. The stepwise stability constants (log K_1 and log K_2) for AHMP complexes with DMT increase with increasing temperature, and the difference between log K_1 and log K_2 values is usually positive, since the coordination sites of the metal ions are more freely available for binding of the first molecule than the second one. For all systems studied here, this difference lies within 2.27 to 2.37 log units, revealing the importance of the electrostatic and steric effects resulting from the addition of the second ligand molecule, since the statistical effect contributes only 0.68 log units /28/.
2. The ΔS^0 values for all investigated complexes are positive, indicating that the increase in entropy by the release of bound solvent molecules on chelation is greater than the decrease resulting from the chelation process itself. This may happen because the solvent molecules were arranged in an orderly fashion around the ligand and the metal ion has acquired a more random configuration on chelation. This is referred as a gain in configurational entropy.
3. Complexation reactions (2) and (3) between dimethyltin (IV) and AHMP (Table 2) are surprisingly endothermic, with ΔH^0 values of 44.13 and 50.62 kJ mol^{-1}, respectively. This is similar to that found by Kramer /27/ and can be interpreted by assuming that the enthalpy change is a net summation of two opposing effects, namely the exothermic complexation and the endothermic liberation of ordered water molecules of hydration. This is confirmed by large ΔS^0 of 270.9 and 248.7 JK^{-1}mol^{-1} for reactions (2) and (3) respectively (Table 2). This contributes to a negative ΔG^0 -36.6 and -23.48 kJmol^{-1} for reactions (2) and (3) respectively.
4. It is generally noted that ΔG^0 and ΔH^0 for the 1:1 complexes are more negative than those corresponding to the 1:2 complexes (Table 2). This may be attributed to the steric hinderance produced by the entry of a second molecule and the charge neutralization concept. The electrostatic attraction in the 1:1 complex is more than that in the 1:2 complex. This is because the 1:1 complex is formed by the interaction of the dipositively charged metal ion and mononegatively charged ligand anion; while the 1:2 complex is formed by the interaction of the monopositively charged 1:1 complex and mononegatively charged ligand anion.

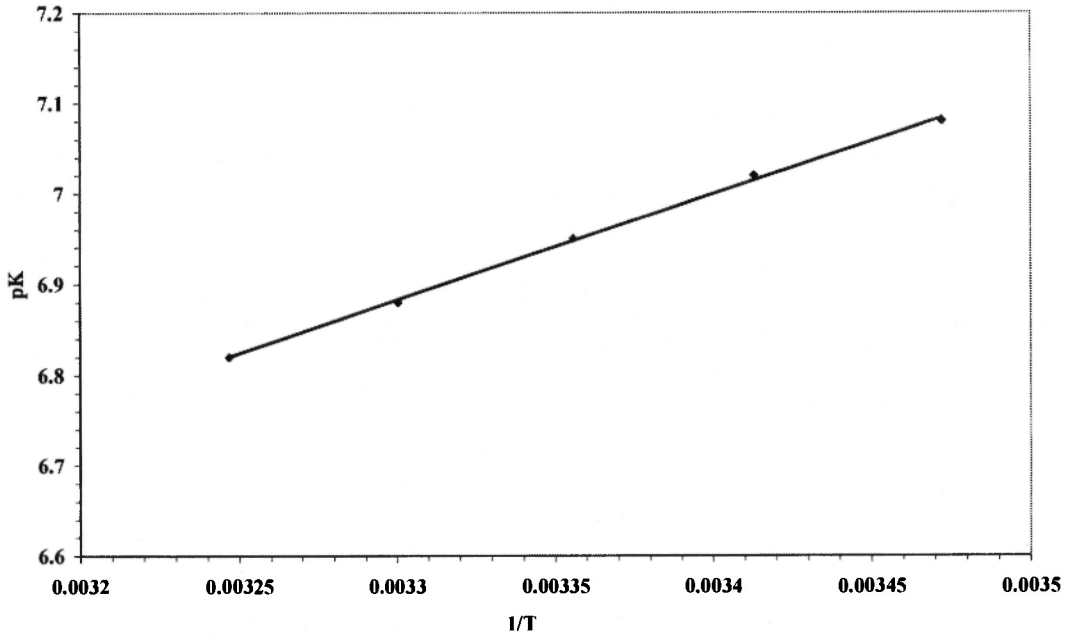


Fig. 2: Van'T Hoff plot of log $K_{protonation}$ of AHMP against 1/T.

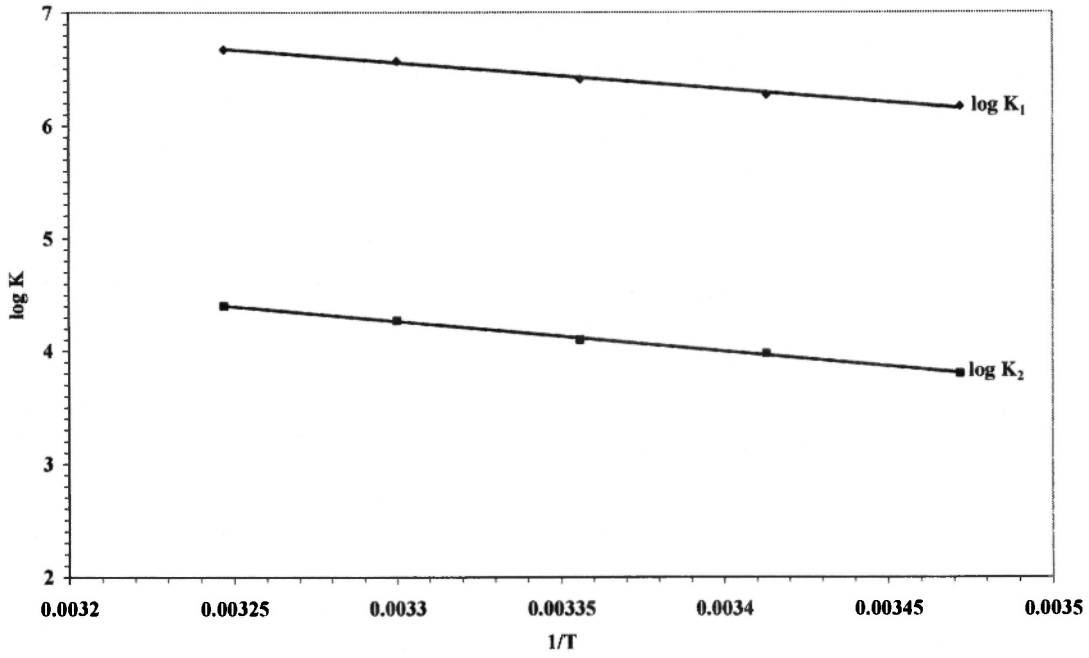


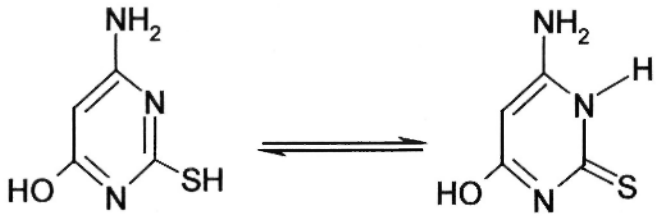
Fig. 3: Van'T Hoff plot of log K_1 and log K_2 of DMTcomplexes with AHMP against 1/T.

Characterization of the isolated solid complexes

Infrared spectra

The infrared spectra of the different isolated complexes are recorded and important infrared spectral bands that provide conclusive structural evidence for the structure of the isolated complexes are discussed. Careful examination of the recorded spectra of the different synthesized complexes reveals the following features:

1) In the IR spectrum of the uncoordinated ligand, two bands have been observed at 2569 and 1245 cm^{-1} which can be assigned to the $\nu_{(S-H)}$ and $\nu_{(C=S)}$ vibrational modes respectively. This reveals the coexistence of both thione and thiol forms in the solid state as shown in Scheme 2 as reported in the literature for 2-mercapto pyrimidine derivatives /29/.



(a) (b)

Scheme 2: Thiol and thione tautomers of (AHMP).

2) Comparing the IR spectrum of the free ligand with those of complexes 1-4, the band at 2569 cm^{-1} is absent in the complex spectra. This indicates the deprotonation of thiol form and tin-ligand bond formation occurs through this site. Similar results have been reported for organotin (IV) derivatives of 5-amino-3H-1,3,4-thiadiazole-2-thione /29/.

3) In the far IR spectra, the absorption in the range (305 – 320) cm^{-1} region for all complexes 1-4, which is absent in the spectrum of the ligand, is assigned to the Sn-S stretching mode of the vibration and all the values are located within the range for Sn-S vibration observed in common organotin (IV)-sulphur compounds /30-32/.

4) The medium-strength intensity bands observed at 1630 cm^{-1} in the spectra of all complexes 1-4 have been assignable to ν(C=N) /33-35/.

5) Furthermore, the medium-intensity absorptions in the region of 487-482 cm^{-1} in all complexes 1-4 have been assigned to Sn←N vibration /36,37/. The ν(Sn-Cl) absorptions at the region of 275 cm^{-1} in complexes 1,2 are close to those found in literature /38,39/, which suggests the incomplete substitution of chloride atoms of R_2SnCl_2.

6) In organotin compounds, The IR spectra can provide useful information concerning the geometry of the SnC_n moiety /40/. Two bands were assigned to SnC_2 asymmetric (515-530 cm^{-1}) and symmetric (430-502 cm^{-1}) vibrations of diorganotin (IV) derivatives, thus suggesting non-linear SnC_2 units for diorganotins.

7)The ν(NH_2) and ν(OH) frequency bands of the ligand remain practically unchanged upon complex formation, this result excludes both NH_2 and OH coordination of the ligand to organotin(IV) ion.

^{1}H NMR spectra

^{1}HNMR data showed that the signal of the –SH proton in the spectrum of the ligand is absent in the isolated complexes, indicating the release of the –SH proton and the formation of Sn-S bonds. The formation accords well with what the IR data have revealed. The Me_2Sn signal position depends on either the halide or the complex geometry, being observed at 1.06 ppm in $Me_2Sn(AHMP)_2$, upfield with respect to $Me_2SnCl(AHMP)$ at 1.13 ppm. ^{1}HNMR data showed a lowering of frequency in the chemical shift of the methyl and methylene groups connected directly with tin in the complexes (1-4), as compared to those of the corresponding precursors. This gives a further evidence of the coordination of the ligand to tin atom. This is in accordance with those reported in the literature /41/.

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