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INTERACTION OF DIMETHYLTIN(IV) DICHLORIDE WITH, BIDENTATE AMINE: SYNTHESIS AND EQUILIBRIUM STUDIES.

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Abstract

The interaction of dimethyltin(IV) with some selected aliphatic and aromatic diamines was described. A series of diamine complexes were synthesized and characterized by elemental analysis. The stoichiometry and stability constants for the complexes are estimated at 25°C and 0.lM ionic strength. The concentration distribution diagrams of the complexes were evaluated. The effect of pKa of the diamine on the stability constant of the complex was elucidated.

Introduction

Many coordination compounds exhibit interesting antitumoural activity against several human cancer cell lives.(1) Cis-platin, Carboplatin and Iproplatin have high activity against testicular and bladder tumors, ovarian carcinomas, head and neck cancer etc. The mechanism of the antitumour activity is believed to be due to mainly to the formation of an interstrand cross link with DNA(2-4). In an attempt to discover more metal based anticancer drugs with higher activity and lower toxicity, several hundreds of coordination and organometallic synthesized and tested.(5)

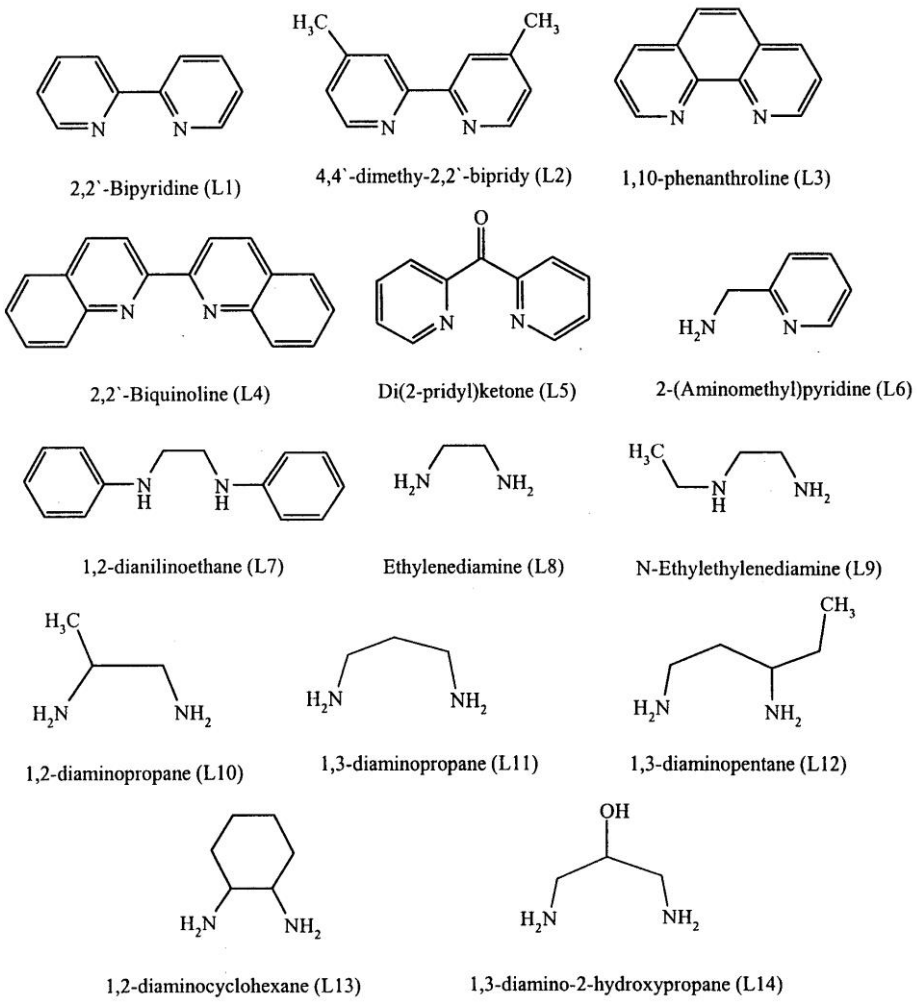
Recently, many organometallic complexes of Sn(IV) showed compounds were high antitumour activity in vitro in a wide variety of human tumors. In contrast to Cis-platin the antitumour action of Sn(IV) compounds is very understood at present. Thus the antitumour activity of the coordination compounds $R_2SnX_2L_2$ is controlled by the nature of R, leaving group (X) and ligand (L). The coordinated ligand favors in some way the transport of the drugs into cells and that, for the diorganotins, the antitumour activity arises from $R_2Sn(IV)$ moieties released by slow hydrolysis of the complexes. Such a mechanism also adds weight to the proposition that a relatively long Sn-N bonds was a requirement for activity, and that the predissociation of the ligand L2 may be an important feature of the mode of action of this particular class

of compounds. Therefore, there IS arelationship between the stability of the organotin compounds and their antitumour activity.[6] With this in mind and in conjunction with our previous studies[7-11] on organotin(IV) complexes, the present paper aims to study dimethyltin(IV) complexes with a series of diamines. The solid complexes are synthesized and characterized by elemental analysis and the complex formation equilibria is investigated with the hope that such types of coordinating ligands might possess favorable properties, possibly as carries in body fluids.

Experimental

Materials and reagents

Dimethyltin(IV) dichloride (DMT) was supplied by Merk Chem. Co. The amines investigated are: 2,2'-bipyridine, 4,4'-dimethyl 2,2'-dipyridine), 1,10-phenanthroline, 2,2'-biqiunoline, Di(2-pridyl)ketone), 2-(Aminomethyl) pyridine, ethylenediamine, N-ethylethylenediamine, 1,2-dianilinoethane, 1,2-diaminopropane, 1,3-diaminopropane, 1,3-diaminopentane, 1,2-diamino cyclohexane and 1,3-diamino-2-hydroxypropane. These materials were provided by Sigma Chem. Co. The structure formulae of these compounds are shown in scheme 1. Sodium hydroxide stock solutions were prepared by diluting the content of BDH concentrated volumetric solution vials. These solutions were systematically checked by titration against potassium hydrogen phthalate. The amine solutions were prepared in the diprotonated form by dissolution in two equivalents of nitric acid solution.



Scheme 1. Ligands used in this study

Synthesis

A mixture of amine (lmM) and $(CH_3)_2SnCl_2$(l mM) in 20ml dichloromethane was stirred for 2 hours. The resulting precipitate was filtered and washed thoroughly with ethanol and finally with diethyl ether. The analytical data of the formed complexes are given in Table 1.

Table 1. The analytical data of the complexes.

Complex	Empirical Formula	Calor	Melting Point	(%C Exp. (Calcd.)	% H Exp. (Calcd.)	%N Exp. (Calcd.)
1	$C_{12}H_{14}N_2SnCl_2$	white	227-232	38.24 (38.35)	3.84 (3.75)	7.32 (7.45)
2	$C_{14}H_{15}N_2SnCl_2$	white	248-252	41.75 (41.63)	4.56 (4.49)	6.81 (6.94)
3	$C_{14}H_{14}N_2SnCl_2$	pink	256-260	42.13 (42.05)	3.48 (3.53)	7.15 (7.01)
4	$C_{20}H_{15}N_2SnCl_2$	yellow	142-147	50.34 (50.47)	3.81 (3.81)	5.89 (5.89)
5	$C_{13}H_{14}N_2OSnCl_2$	buff	70- 75	38.52 (38.66)	3.58 (3.49)	7.05 (6.94)
6	$C_8H_{14}N_2SnCl_2$	buff	190-195	29.19 (29.31)	4.45 (4.30)	8.63 (8.54)
7	$C_{16}H_{22}N_2SnCl_2$	buff	80-85	44.61 (44.49)	(5.13) 5.01	(6.48) 6.60
8	$C_4H_{14}N_2SnCl_2$	white	238-242	17.11 (17.17)	5.19 (5.04)	9.88 (10.01)
9	$C_6H_{18}N_2SnCl_2$	white	235-240	23.41 (23.32)	5.89 (5.95)	9.10 (9.01)
10	$C_5H_{16}N_2SnCl_2$	white	225-229	20.39 (20.44)	5.52 (5.49)	9.42 (9.53)
11	$C_5H_{16}N_2SnCl_2$	white	245-250	20.36 (20.44)	5.54 (5.49)	9.45 (9.53)
12	$C_7H_{20}N_2SnCl_2$	white	248-255	26.12 (26.19)	6.26 (6.35)	8.70 (8.59)
13	$C_5H_{20}N_2SnCl_2$	pale brown	285-290	28.78 (28.69)	6.04 (6.17)	8.39 (8.24)
14	$C_5H_{16}N_2OSnCl_2$	white	178-183	19.51 (19.38)	5.16 (5.21)	9.13 (9.04)

Instruments

Potentiometric titrations were performed with a Metrohm 686 titroprocessor. The titroprocessor and electrode were calibrated with standard buffer solutions[12] potassium hydrogen phthalate (pH 4.008) and a mixture of KH_2PO_4 and Na_2HPO_4 (pH 6.865) at 25°C.

Procedure and Measurements

The protonation constants of the amines and the hydrolysis constant of the dimethyltin(IV) were determined by titrating 40ml of the protonated amines (1.25 mM) or the dimethyltin(IV) (1.25 mM) solutions in 25% dioxane-water system. The stability constants of the dimethyltin(IV) complexes were determined by titrating 40ml of dimethyltin(IV) (1.25 mM.) and the amines with concentrations of 1.25 mM and 2.50 mM. All solutions were adjusted to 0.1M ionic strength by addition of $NaNO_3$, and were titrated against standard 0.05 M NaOH.

The equilibriurn constants (β) were evaluated from titration data, defined by Eqs. (1) and (2)

$$1(M) + p(L) + q(H) \rightleftharpoons (M)_1(L)_p(H)_q \qquad (1)$$

$$\beta_{1pqr} = \frac{[(M)_1(L)_p(H)_q]}{[M]^1[L]^p[H]^q} \qquad (2)$$

Where, M, L, and H represent dimethyltin(IV), amine and proton, respectively. The calculations were performed using the computer program[13] MINIQUA-75. The stoichiometries and stability constants of the complexes formed were determined by trying various possible composition models. The model selected gave the best statistical fit and was chemically constituent with the titration data without giving any systematic drift in the magnitude of various residuals, as described elsewhere[13]. The fitted model was tested by comparing the experimental titration data points and the theoretical curve calculated from the values of acid dissociation constants of the amine and formation constants of the corresponding complexes. Table 2 lists the formation constants together with their standard deviations and sum of square of residuals as obtained from the program MINIQUAD-75[13]. The concentration distribution diagrams were obtained using the program SPECIES[14].

Results and Discussion

The acid-dissociation constants of the amines in the protonated form were determined under the same experimental conditions of ionic strength (0.1M) and temperature (25°C) used for the study of dimethyltin(IV) complex equilibria.

Hydrolysis of dimethyltin(IV)

The hydrolysis of dimethyltin(IV) cation in aqueous solution was studied by

several research groups[15-18]. The potentiometric data were fitted considering the formation of the species 10-1, 10-2, 10-3, 10-4, 20-3 and 20-4, Table 2. The dimerization ability of the aquo-hydroxo-comp1exes is described by The general equilibrium (3).

$$2\ DMT(H_2O)_3OH^+ \rightleftharpoons [(DMT)_2(OH)_2(H_2O)_4]^{+2} + 2H_2O \quad (3)$$

The dimerization constant (Kd) can be determined by Eq. (4):

$$\text{Log } K_d = \log \beta_{20-2} - 2\log \beta_{10-1} \quad (4)$$
$$= -3.12 - 2\ (-3.03)$$
$$= -3.12 + 0.06 = 2.94$$

in the same way the dimerization constant of the species 10^{-2} is calculated by Eq (5).

$$\text{Log Kd} = \log \beta_{20-4} - 2 \log \beta_{10-2}$$
$$= -13.59 - 2\ (-8.21)$$
$$= -13.59 + 16.42 = 2.83 \quad (5)$$

The concentration distribution diagram for the hydrolysis of dimethyItin(IV) is shown in Fig 1. The hydrolyzed species 10–1 and 20–2 start to form at pH 2 and their concentration increases with increase of pH up to 4.0, reaching a maximum concentration of 42%. The species 10–2 and 20–4 reach a constant concentration of 54% and 49%, respectively, in the pH 6.2–9.8. The hydrolyzed species, 10–2, predominates with formation degree of 18% at pH 5. However, the species 10–3 and 10–4 start to form after pH 9.

Complex formation equiIibria

The potentiometric titration curves of protonated amine in the presence and absence of dimethyltin(IV) are compared. The titration curves of 1,3-diaminopropane in the presence and absence of dimethyItin(IV), taken as a representative, are given in Fig. 2. The complex titration curve is significantly lower than the amine curve. This corresponds to the formation of a complex species through release of hydrogen ion. The titration data were fitted with model composed of the 110, 11-1 and 11-2 species. The pKa of the two coordinated water molecules are calculated[19] by Eqs (5) and (6).

$$pKa_1 = \log \beta_{110} - \log \beta_{11-1} \quad (5)$$

$$pKa_2 = \log \beta_{11-1} - \log \beta_{11-2} \quad (6)$$

These values are higher than Those of water molecules coordinated to the free dimethyltin(IV) ion. This may be due to the elongation of Sn(IV) - H_2O bond caused by the coordination of the amine. Also, it is to be noted that the pKa of the coordinated water molecules incorporated in dimethyltin(IV) complexes of aromatic amine is lower than that in aliphatic amine. This may be due to n-acceptor property of the aromatic amine, which increases the electrophilcity of the Sn(IV) ion and consequently decreases the pKa value of the coordinated water molecules.

It is well known that for metal complexes with a series of structurally-related ligands, a linear relationship holds between the stability constants of the complex and the overall acid dissociation constant of the ligand ($\log\beta_{012}$).[20]. The importance of these plots is that they afford a mean of estimating the stabilities of complexes that have not been studied. Fig. 3 demonstrates such a relationship. Estimation of the concentration distribution of various species in solution provides a useful picture of dimethyltin(IV) binding. Concentration distribution of various species as a function of pH in the equimolar solution mixture of amine and dimethyltin(IV) is evaluated. The distribution diagram of 1,3-diaminopropane system, taken as a representative example, is given in Fig. 4. The 110 complex species reaches the maximum concentration of 90% at pH 4-5, while its hydrolyzed form 11-1 predominates with maximum formation percentage of 95% at pH 8.5. From the biological point of view, it is interesting to note that in the physiological pH range both 110 and 11-1 complex species predominate and the hydrolyzed form of dimethyltin(IV) has no contribution. Therefore the interaction of dimethyltin(IV) complex with DNA constituent the main target in the antitumour activity is quite feasible.

Conclusion

The present investigation describes the synthesis and complex formation equilibria of dimethyltin(IV) with some selected aliphatic and aromatic diamines. The biological significance of the present data is due to the fact that the stability of the $R_2SnX_2L_2$ is a controlling factor for the antitumour activity. A moderate stability is required for the antitumour activity as the is an important feature of the predissociation of the ligand (L) mode of action of this particular class of compounds.

Table (2) Formation constants for complexes of Dimethyltin(IV) with some ligands in 25% dioxane-water system and at 25°C and 0.1M ionic strength.

System	1 p q[a]	Log β[b]	pKa[C]	S[d]
$Sn(CH_3)_2$–OH				
	1 0 -1	-3.03(0.01)	3.03	4.3×10^{-8}
	1 0 -2	-8.21(0.01)	5.18	
	1 0 -3	-18.73(0.03)	10.52	
	1 0 -4	-29.54(0.03)	11.81	
	2 0 -2	-3.12(0.01)		
	2 0 -3	-8.13(0.02)		
	2 0 -4	-13.59(0.02)		
2,2'-bipyridine				
	0 1 1	4.34(0.01)	4.34	5.58 x $l0^{-8}$
	0 1 2	5.64(0.03)	1.30	
	1 1 0	4.36(0.03)	4.25	2.12 x $l0^{-7}$
	1 1 -1	-0.11(0.05)	5.98	
	1 1 -2	-5.87(0.06)		
4,4' -dimethy-2,2' –dipridine				
	0 1 1	5.65(0.02)	5.65	6.10×10^{-8}
	0 1 2	7.95(0.03)	2.30	
	1 1 0	5.92(0.04)		1.3110^{-7}
	1 1 -1	1.30 (0.05)	4.62	
	1 1 -2	-4.84(0.06)	6.14	
1,10-phenanthroline				
	0 1 1	3.04(0.03)	3.04	8.26 x $l0^{-7}$
	0 1 2	4.44(0.05)	1.40	
	1 1 0	3.96(0.03)		1.80 x $l0^{-7}$
	1 1 -1	-0.05(0.03)	4.01	
	1 1 -2	-5.78(0.04)	5.73	
2,2' -Biquinoline				
	0 1 1	3.42(0.02)	3.42	1,01x $l0^{-8}$
	0 1 2	4.61(0.04)	1. 19	
	1 1 0	4.29(0.04)		425 x $l0^{-7}$
	1 1 -1	0.18(0.05)	4.11	
	1 1 -2	-5.78(0.05)	5.96	
Di(2-pridyl)ketone				
	0 1 1	3.16(0.02)	3.16	1.53 x $l0^{-7}$
	0 1 2	5.21 (0.02)	2.05	
	1 1 0	3.91(0.03)		1.20 x $l0^{-7}$
	1 1 -1	0.27(0.04)	3.64	
	1 1 -2	-5.32(0.07)	5.59	

Table (2) Continued

2-(Aminomethyl)pyridine						
	0	1	1	8.49(0.01)	8.49	1.41×10^{-8}
	0	1	2	11.18(0.02)	2.69	
	1	1	0	8.90(0.03)		9.99×10^{-8}
	1	1	-1	3.86(0.04)	5.04	
	1	1	-2	-3.79(0.06)	7.65	
1,2-dianilinoethane						
	0	1	1	4.34(0.02)	4.34	9.70×10^{-8}
	0	1	2	5.90(0.03)	1.56	
	1	1	0	4.56(0.03)		2.19×10^{-7}
	1	1	-1	0.83(0.04)	3.73	
	1	1	-2	-5.53(0.06)	6.36	
Ethylenediamine						
	0	1	1	9.80(0.02)	9.80	2.36×10^{-7}
	0	1	2	16.55(0.03)	6.75	
	1	1	0	13.66(0.03)		2.03×10^{-7}
	1	1	-1	7.23(0.04)	6.38	
	1	1	-2	-2.20(0.05)	9.48	
N-Ethylethylenediamine						
	0	1	1	9.91(0.03)	9.91	1.04×10^{-7}
	0	1	2	16.81(0.05)	6.90	
	1	1	0	13.80(0.04)		1.33×10^{-7}
	1	1	-1	7.46(0.06)	6.34	
	1	1	-2	-2.34(0.07)	9.80	
1,2-diaminopropane						
	0	1	1	9.81(0.02)	9.81	5.6×10^{-8}
	0	1	2	16.66(0.03)	6.85	
	1	1	0	14.12(0.04)		1.09×10^{-7}
	1	1	-1	7.08(0.04)	7.04	
	1	1	-2	-3.57(0.05)	10.65	
1.3-diaminopropane						
	0	1	1	10.36(0.03)	10.36	2.81×10^{-7}
	0	1	2	17.95(0.03)	7.59	
	1	1	0	14.20(0.03)		1.31×10^{-7}
	1	1	-1	7.05(0.04)	7.15	
	1	1	-2	-3.66(0.05)	10.71	

Table (2) Continued

1,2-diaminocyclohexane						
	0	1	1	10.01(0.02)	10.21	4.26×10^{-7}
	0	1	2	17.53(0.02)	7.85	
	1	1	0	13.84(0.03)		1.36×10^{-7}
	1	1	-1	7.50(0.04)	7.26	
	1	1	-2	-2.41(0.05)	11.13	
1,3 -diamino-2-hydroxypropane						
	0	1	1	9.48(0.02)	9.48	1.76×10^{-8}
	0	1	2	16.49(0.03)	7.01	
	1	1	0	13.98(0.02)		1.22×10^{-7}
	1	1	-1	7.48(0.03)	6.50	
	1	1	-2	-3.21(0.04)	10.69	

[a]1, p and q are the stoichiometric coefficients corresponding to dimethyltin(IV), Ligands and H^+; respectively; [b]Standard deviations are given in parentheses; [C]pKa of ligands or pKa, = log β_{110} - log $\beta_{11\text{-}1}$ and $pKa_2 = \beta_{11\text{-}1} - \beta_{11\text{-}2}$ for coordinated water in the complex; [d]Sum of square of residuals.

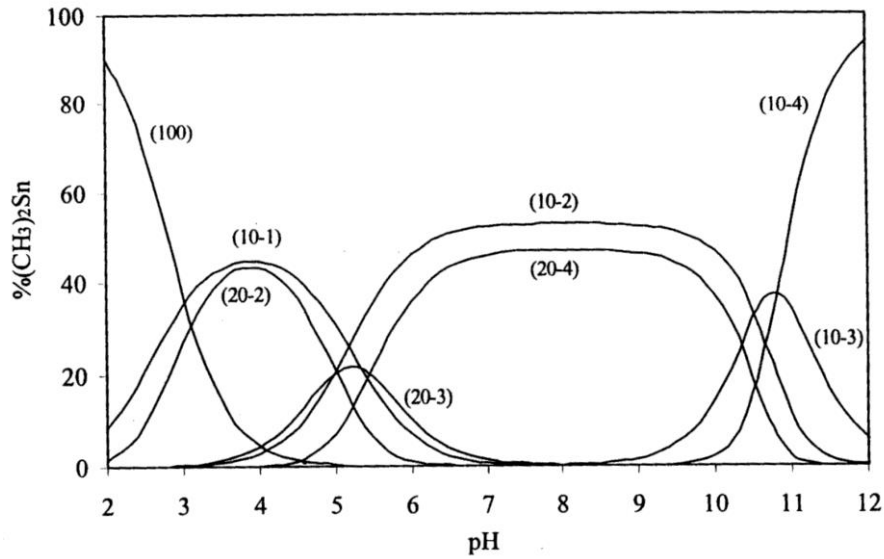


Fig. (1) Concentration distribution of various species as a function of pH in the $Sn(CH_3)_2$–OH system. (at concentrations of 1.25 mmol/liter for $Sn(CH_3)_2$).

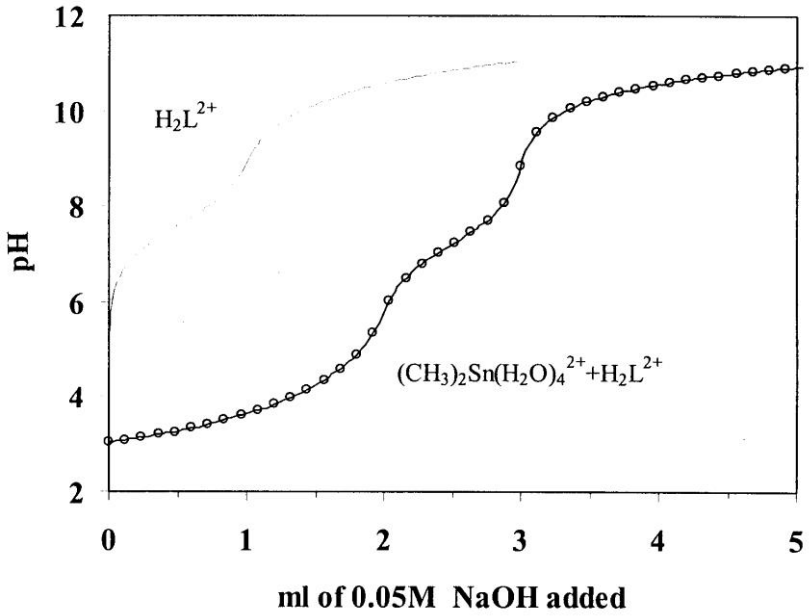


Fig. (2) Potentiometric titration curves of 0.05 mmoles of protonated 1,3-diaminoproane in presence and absence of $(CH_3)^2Sn(OH_2)_4^{2+}$(0.05 mmoles).

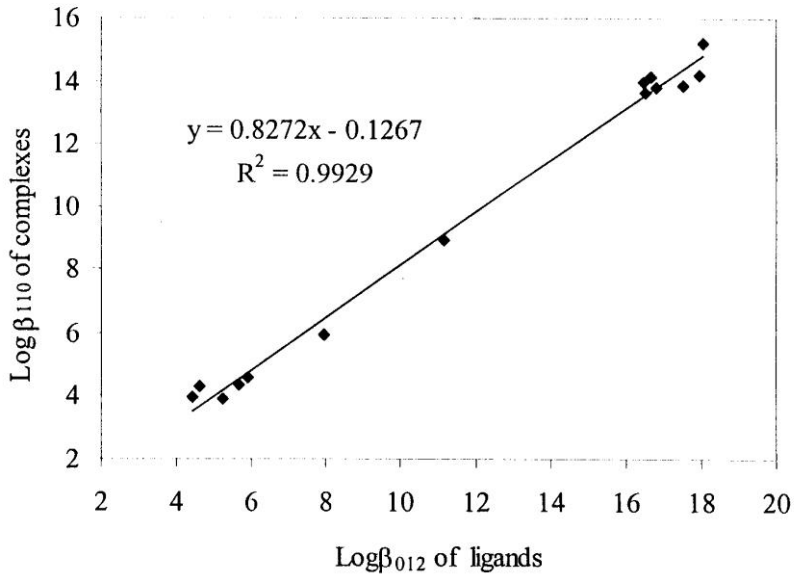


Fig. (3) Variation of $log\beta_{110}$ with overall dissociation constants of the ligands.

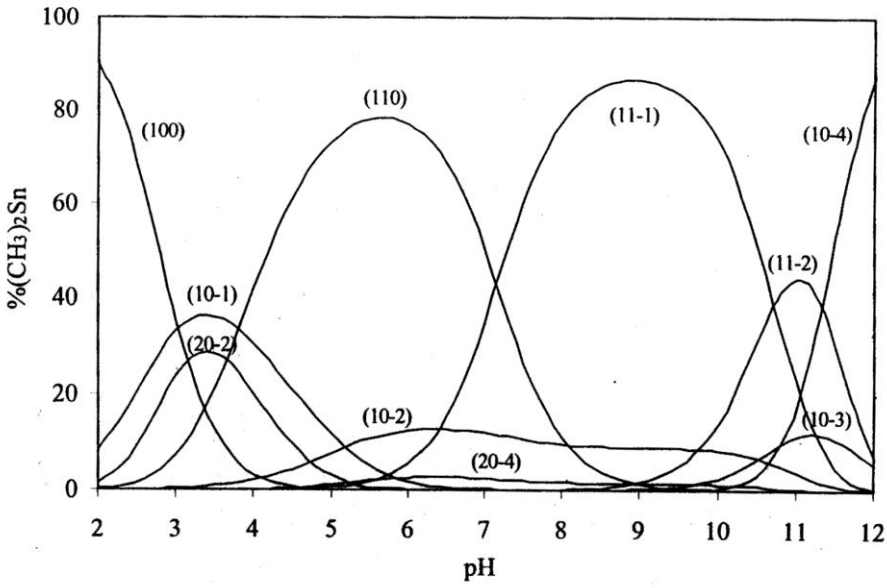


Fig. (4) Concentration distribution of various species as a function of pH in the $Sn(CH_3)_2$–1,3-diaminopropane system. (At concentrations of 1.25 mmol/liter for $Sn(CH_3)_2$) and 1,3-diaminopropane).

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