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Equilibrium studies of diethyltin(IV) dichloride and divinyltin(IV) dichloride with 1-(2-aminoethyl)-pyrrolidine

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ABSTRACT

The interaction of diethylltin(IV) (DET) and divinyltin(IV) (DVT) with 1-(2-aminoethyl)-pyrrolidine (AEPY) was investigated using potentiometric technique at ionic strength of 0.1 mol dm^{-3} $NaNO_3$. The hydrolysis constants of diethyltin(IV) and divinyltin(IV) cations and the stepwise formation constants of the complexes formed in solution were calculated at different temperatures and in solutions of dioxane-water solutions of different compositions. The stoichiometry and stability constants for the complexes formed were reported. The results showed the formation of 1:1 complex and the corresponding hydroxo complexes. The concentration distributions of the various complex species were evaluated as a function of pH. The thermodynamic parameters ΔH° and ΔS° calculated from the temperature dependence of the equilibrium constants were investigated for DET and DVT complexes with AEPY. The equilibrium constant for the displacement of 1-(2-aminoethyl)-pyrrolidine coordinated to diorganotin(IV) by thymine and thymidine as representative examples of DNA constituents was calculated from calculations based upon equilibrium properties. The results are expected to contribute to the chemistry of tin(IV) based anticancer agents.

1. Introduction

The biological aspects of pyrrolidine derivatives have got attention as they have selective inhibition activity [1] against matrix metalloproteinase-2 and characteristics of potent anti-tumour agents [2–4]. Copper(II) complex of pyrrolidine dithiocarbamate has been reported to have potent anti-cancer activity against cisplatin resistant neuroblastoma cells [5]. Recently pyrrolidine based inhibitors of the drug resistant mutant of HIV-1 protease have been reported [6]. Pt(II) derivatives of 1,2 alkyl substituted 3-aminopyrrolidines showed antiproliferative activity [7,8]. A variety of organotin complexes structurally related to *cis*-platin and its derivatives [9] have been investigated for their antitumour properties [10,11]. Among organotins, dialkyl derivatives exhibit greater antitumour activity than the corresponding mono-, tri-, and tetra-alkyl derivatives [12]. If one ranks specific alkyl organotins in terms of antitumour activity of the parent compounds, the diethyl derivatives have the highest activity in vivo provided that one takes no cognizance of their toxicity [13]. The antitumour activity of diorganotin(IV) compounds of the type R_2SnX_2L, where L is generally bidentate ligand has been reported [14]. The coordinated ligand plays an important role in this activity as it favors the transport of diorganotin(IV) into the cell. The mechanism of antitumour activity is based on the dissociation of the ligand with subsequent binding to DNA. In the case of nitrogen bearing ligands [15], increasing stability is thought to reduce activity by hindering the dissociation of the ligand that is necessary for binding between tin and DNA. Therefore, there is a relationship between the stability of the organotin compounds and their antitumour activity. During the last two decades, the interest of many scientists in the chemistry of methyl, ethyl, and butyl derivatives of tin(IV) has risen, but very rare studies are available on the solution chemistry of divinyltin(IV). Also, to the best of our knowledge the literature contains no studies regarding the stability constants of DVT and DET complexes with 1-(2-aminoethyl)-pyrrolidine (AEPY) (Scheme 1) in dioxane-water mixtures. As part of our project dealing with the study of metal complexes of expected biological activity [16–20] and as a continuation of our previous studies on organotin(IV) complexes [21–23], the present paper aims to study the diethyltin(IV) and divinyltin(IV) complex formation equilibria with 1-(2-aminoethyl)-pyrrolidine (AEPY). AEPY is selected due to the hydrophobic nature of pyrrolidine moiety, which may help its organotin(IV) complex to transport

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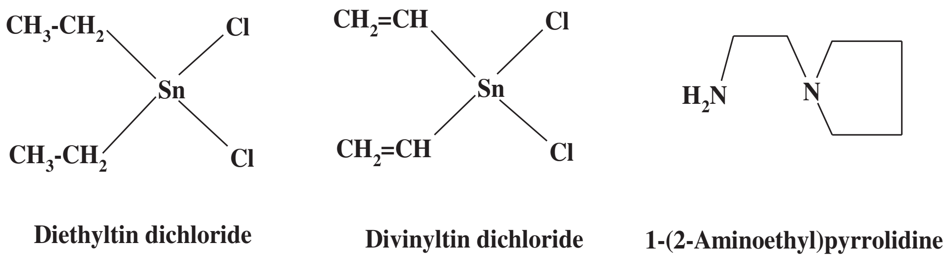

Scheme 1. Structural formulae of DET, DVT and AMPY.

across membranes. In the present study, the complex formation equilibria of the complexes formed in solution was investigated. The stoichiometry and stability constants of the complexes formed in solution were determined at different temperatures and in dioxane-water solutions of different compositions.

2. Experimental

2.1. Materials and reagents

Diethyltin(IV) dichloride and divinyltin(IV) were supplied by Merck Chem. Co. 1-(2-aminoethyl)-pyrrolidinewas provided by Sigma Chemicals Co. Carbonate-free NaOH solutions (titrant) was prepared by diluting the content of BDH concentrated volumetric solution vials. These solutions were systematically checked by titration against potassium hydrogen phthalate solution. All solutions were prepared in deionized H_2O.

2.2. Instruments

Potentiometric measurements were made using a Metrohm 686 titroprocessor equipped with a 665 Dosimat (Switzerland-Herisau). A thermostatted glass-cell was used equipped with a magnetic stirring system, a combined Metrohm glass electrode (6.0220.100), a thermometric probe, a microburet delivery tube and a salt bridge connected with the reference cell filled with 3 mol dm^{-3} KCl solution in which Ag/AgCl electrode was dipped. The titroprocessor and electrode were calibrated with standard buffer solutions, potassium hydrogen phthalate (pH 4.008) and a mixture of KH_2PO_4 and Na_2HPO_4 (pH 6.865) at 25.0 °C.

2.3. Procedure and measurements

The following mixtures were prepared and titrated potentiometrically with 0.05 M NaOH solution.

A- 40 ml of solution containing 1.25×10^{-3} mol dm^{-3} of ligand (H_2AEPY), of constant ionic strength 0.1 mol dm^{-3}, (adjusted with $NaNO_3$);
B- 40 ml of solution containing 1.25×10^{-3} mol dm^{-3} of DET/DVT cation and 0.1 mol dm^{-3} $NaNO_3$;
C- 40 ml of solution containing 1.25×10^{-3} mol dm^{-3} DET/DVT cation, $1.25 \times 10^{-3}/2.50 \times 10^{-3}$ mol dm^{-3} ligand (H_2AEPY) and 0.1 mol dm^{-3}, $NaNO_3$;

The proton dissociation constants of the protonated AEPY were determined potentiometrically by titrating mixture (A). The hydrolysis constants of DET and DVT were determined by titrating mixture (B). The formation constants of DET and DVT complexes with AEPY were determined by titrating mixture (C). All titrations were performed in a purified N_2 atmosphere, using aqueous 0.05 mol dm^{-3} NaOH as titrant. 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 13.921 at 25 °C [21]. The ionic strength was adjusted to 0.1 mol dm^{-3} by using of $NaNO_3$. For the variable temperature studies the following values of pK_w were employed at 20 °C ($pK_w = 14.126$), at 30 °C ($pK_w = 13.753$) and at 35 °C ($pK_w = 13.660$) [21]. As is known, pH-meters read $-\log a_{H+}$ (pH), whereas the potentiometric method we used for the calculation of stability constants requires $-\log[H^+]$ (p[H]). Hence, the first step in computations was to convert the pH-meter readings (B) recorded in dioxane-water solutions to hydrogen ion concentration $[H^+]$. This can be achieved by using the widely used relation given by the Van Uitert and Hass equation, Eq. (1) [24] as shown below,

$$-\log_{10}\left[H^+\right] = B + \log_{10} U_H \tag{1}$$

where $\log_{10} U_H$ is the correction factor for the solvent composition and ionic strength for which B is read. Values of pK_w in dioxane-water mixtures were taken from [25].

The equilibrium constants evaluated from the titration data (summarized in Table 1) are defined by Eqs. (2) and (3), where M, L and H stand for the DET/DVT(IV) ion, AEPY-ligand and proton, respectively.

$$pM + qL + rH \rightleftharpoons M_pL_qH_r \tag{2}$$

$$\beta_{pqr} = \frac{\left[M_pL_qH_r\right]}{[M]^p[L]^q[H]^r} \tag{3}$$

2.4. Data processing

Calculations were performed using the computer program MINIQUAD-75 [26]. The program was described in detailed with all FORTRAN commands in Ref. [27]. The stoichiometry and stability constants of the complexes formed were determined by trying various

Table 1
Formation constants of diethyltin(IV) complexes with AEPY.

p q r[a]	$\log_{10}\beta$[b]				
	15 °C	20 °C	25 °C	30 °C	35 °C
1 0-1	−4.04 (0.01)	−3.79 (0.01)	−3.69 (0.01)	−3.58 (0.01)	−3.52 (0.01)
1 0-2	−10.19 (0.01)	−9.65 (0.01)	−9.39 (0.01)	−9.18 (0.01)	−9.04 (0.01)
1 0-3	−21.57 (0.07)	−20.90 (0.06)	−21.12 (0.05)	−19.62 (0.07)	−19.10 (0.06)
0 1 1	9.75 (0.01)	9.50 (0.02)	9.42 (0.02)	9.39 (0.02)	9.21 (0.02)
0 1 2	19.69 (0.03)	16.28 (0.03)	16.08 (0.03)	15.97 (0.03)	15.65 (0.03)
1 1 0	10.19 (0.04)	10.32 (0.05)	10.44 (0.05)	10.58 (0.07)	10.66 (0.05)
1 1-1	3.02 (0.03)	3.32 (0.05)	3.58 (0.04)	3.87 (0.06)	4.01 (0.04)
1 1 1	15.61 (0.05)	15.63 (0.07)	15.67 (0.06)	15.72 (0.07)	15.71 (0.04)

[a] p, q and r are stoichiometric coefficients corresponding to DET, ligand and H^+, respectively, The formation constants are as follows: 10–1 ($DET^{2+} + H_2O \rightleftharpoons DET(OH)^+ + H^+$), 10–2 ($DET^{2+} + 2H_2O \rightleftharpoons DET(OH)_2 + 2H^+$), 10–3 ($DET^{2+} + 3H_2O \rightleftharpoons DET(OH)_3^- + 3H^+$), 011 ($L + H^+ \rightleftharpoons HL^+$), 012 ($L + 2H^+ \rightleftharpoons H_2L^{2+}$), 110 ($DET^{2+} + L \rightleftharpoons DET(L)^{2+}$), 10–1 ($DET^{2+} + L + H_2O \rightleftharpoons DET(L)(OH)^+ + H^+$) and 111 ($DET^{2+} + L + H^+ \rightleftharpoons DET(HL)^{3+}$).

[b] Standard deviations are given in parentheses. Sum of square of residuals are approximately $(1 - 5) \times 10^{-8}$.