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Electrochemical Study on complexation of the antitumor 1,3-dihydroxy thioxanthone with aluminum(III) ion in a mixed solution

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ABSTRACT

This work presents the results of investigating the complexation of 1,3-dihydroxy-9H-thioxanthen-9-one (DTX) with Al(III) by electrochemical techniques, cyclic voltammetry (CV), square wave voltammetry (SWV), and differential pulse voltammetry (DPV). To determine the nature and stoichiometry of the complexes, tetrabutylammonium chloride $(n\text{-}Bu)_4NCl.H_2O$ (TBAC) 0.01 M was found to be a suitable supporting electrolyte in a 1:1 ratio mixed acetonitrile:water solution as solvent. The results showed that reaction of the formed 1:1 and 1:2 (metal:ligand) complexes of Al(III) are electrochemically irreversible. The modified DeFord-Hume's method was used to evaluate the stability constants and the composition of the formed complexes. The overall stability constants β_1 and β_2 values for the above-mentioned complexes were of 4.17×10^1 and 1.86×10^4, respectively.

KEYWORDS

Aluminum(III);
Cyclic voltammetry;
Differential pulse voltammetry;
Thioxanthone;
Square-wave voltammetry.

INTRODUCTION

Thioxanthone (TX) and its derivatives are an important class of sulfunated heterocycles that they possess a number of interesting chemical activities including two useful properties such as medical and photoinitiation. They have attracted much attention in recent years owing to their broad spectrum of antitumor activities[1-6]. In addition, TXs are hydrogen-abstracting photoinitiators, which can exist in a multitude of conformations each having potential for its own electrochemical[7, 8] and spectroscopic properties[9, 10]. They have the most widely applications in photochemical processes[11-14].

Recently, the study of complexation of TXs with proper metal ions has been introduced in literature[15-18]. Many electrochemical and spectroscopic techniques have been used to study the behavior of these compounds towards other reactants[19-24].

Voltammetry has been applied to the trace and ultra-trace determination of both organic and inorganic electroactive species. Voltammetric techniques are fast and sensitive analytical tools to study formation of a complex. Application of voltammetric methods to the study of the metal-ligand interactions has also been widely explored[25-27].

Here, in order to obtain detailed information on the interaction of the ligand 1,3-dihydroxy-9H-thioxanthen-

9-one (DTX) toward Al(III) ion, we are reporting our electrochemical studies on the system carried out by using voltammetric techniques to determine the stability constants and the composition of the DTX/Al(III) complexes in acetonitrile-water mixed solution.

EXPERIMENTAL

Reagents

$Al(NO_3)_3.9H_2O$, acetonitrile (AN), supporting electrolyte tetrabutylammonium chloride $(n\text{-}Bu)_4NCl.H_2O$ (TBAC) (all from Merck) were used directly without any further purification. DTX (Figure 1) was prepared as described in the literature[28]. Double-distilled and deionized water was used throughout.

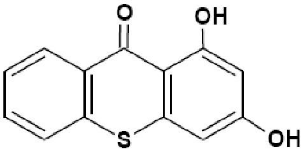

Figure 1 : 1,3-dihydroxy-9H-thioxanthen-9-one (DTX).

Instrumentation

Differential pulse voltammetry (DPV), Square-wave voltammetry (SWV) and Cyclic voltammetry (CV) measurements were performed on a three–electrode system provided by an EG&G Princeton applied research 263A polarographic analyzer potentiostat (Perkin Elmer, USA). A Glassy carbon (GC) and a platinum (Pt) wire were used as working electrodes (WEs) for DPV and SWV. A standard calomel electrode (SCE) was used as a reference electrode and a platinum wire fitted, as an auxiliary electrode (AE), with the working electrode.

General procedure

The SWV voltammograms were recorded at pulse amplitude of 600 mV, scan rate of 2 mV/s and frequency of 100 Hz. The DPV were also recorded at pulse height of 50 mV, pulse width of 0.02 s, scan increment of 4 mV, and scan rate of 20 mV/s. For CV, the instrument settings were as follows: equilibrium time of 5 s, scan rate (ν) of 50 mV/s and applied potential from –1.5 to 1.0 V. The temperatures of all experiments were kept constant at 20.0 ± 0.1 ºC by using a water-circulating thermostat system.

Synthesis of the ligand

The ligand DTX was synthesized and purified as follows: salicylic acid (0.138 g, 1 mmol) and 3-hydroxy-5-methyl phenol (0.124 g, 2 mmol) was added to a mixture of alumina (0.3 g, 3 mmol) and methane sulfonic acid (2 mL) in an oil-bath, at 150 ºC. After 5 min, the reaction mixture was transferred into a backer containing 150 mL water, extracted with ethyl acetate (2 × 100 mL), washed with 150 mL water and 100 mL sodium bicarbonate saturated solution. Then the mixture was dried over Na_2SO4 and evaporated to give DTX in 80.1% yield and mp= 138.4 ºC. The following spectral data confirmed the formation of the product: FT-IR (KBr): $\nu_{max}(cm^{-1})$ 1660 (s); 1613 (s); 1568 (w); 1493 (s); 1470 (m); 1380 (w); 1340 (w); 1235 (s); 1215 (s); 760 (s). MS (from GC-Mass): *m/z* 244 (M^+, 100, base peak); 227 (40.6); 77 (23.2); 51 (8.9). UV-Vis (λ_{max}, nm): 408.5 (s); 323.5 (s); 223.0 (s).

RESULTS AND DISCUSSION

Cyclic voltammetry

The CV of DTX (1.0 mM) in AN was performed at a Pt wire as WE. Trying to test some different compounds, TBAC (0.1 M) was found to be the best supporting electrolyte with no interfering voltammogram in the applied potential range. Under this condition, as shown in Figure 2, DTX revealed two oxidation peaks at –1.05, 0.45 and a weaker reduction peak at –0.3 V. There was a linear relationship between the peak current intensities and the increase in scan rate, so construction a plot for the oxidation peak currents (at E_p= –1.05 V) against the ($\nu^{1/2}$) resulted in a linear function indicative the system is governed by diffusion-controlled process (the inset in Figure 2). The optimized scan rate 50.0 mV/s was selected for subsequent studies.

As shown in Figure 3, addition of increasing amounts of Al(III) solution (0.01 M) to the DTX (1.0×10^{-3} M) solution resulted in increasing in i_p at E_p= –0.76 V (solid lines) that confirms the formation of new species in the solution. This new peak shifts from –1.05 V for DTX (dashed line) toward –0.76 V, about 0.24 V more positive than the un-complexed ligand. The dotted line indicates the CV for the case in which TBAC was the only component in the solvent.

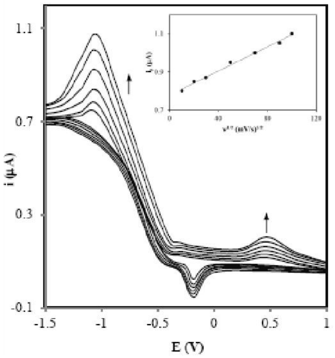

Figure 2 : The CV voltammograms of 1.0×10^{-3} M DTX in the presence of 0.1 M TBAC in AN. A plot for the oxidation peak currents (at $E_p = -1.05$ V) against $\nu^{1/2}$ is shown in the inset.

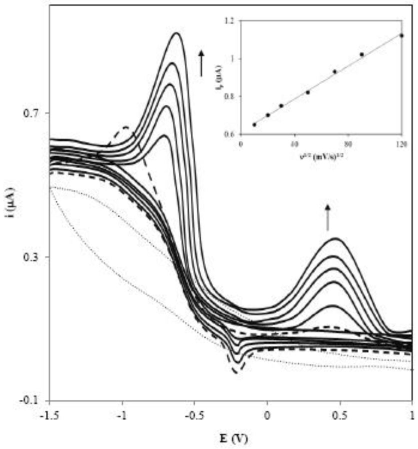

Figure 3 : The CV voltammograms for titration of the DTX (1.0×10^{-3} M) solution with Al(III) (1.0×10^{-2} M). The dotted line indicates the CV for the case in which TBAC was the only component in the solution. The graph demonstrated in the inset shows that the peak current (i_p) increases linearly as function of $\nu^{1/2}$ at $E_p = -0.76$ V.

A mixture solution of equal amounts of DTX and Al(III) (1.0×10^{-3} M) was examined at different increasing scan rates. The peak current (i_p) increased as the potential scan rate (ν) increased from 10.0 to 100.0 mV/s. The corresponding graph for i_p against $\nu^{1/2}$ is demonstrated as an inset in Figure 3. This straight-line also shows that the electrochemical reaction occurs under diffusion controlled phenomena at the surface of the electrode. When the scan rate increased, the peak potential (E_p) shifted in the negative direction, which confirms the irreversibility of the electrode process.

Square wave voltammetry

SWV has received growing attention as a voltammetric technique for routine quantitave analysis. In addition, the ability of SWV to fast scan of a wide potential range has been used to advantage by researchers. The shift of peak potentials dependent on the concentrations of ligand, the equilibrium constants and the compositions of complexes.

$$M^{n+} + qL \leftrightarrow ML_q \quad (1)$$

whose overall conditional stability constant is:

$$\beta_q = [ML_q]/([M^{n+}][L]^q) \quad (2)$$

$$\beta_q = 1 + \beta_1[L] + \beta_2[L]^2 + \beta_3[L]^3 + ... \quad (3)$$

The value of β_q can be obtained by the following equation[29]:

$$\Delta E_p = (E_p)_M - (E_p)_C = (2.303RT/nF) \times [\log(l + \sum \frac{q}{q} = 0\beta q\ [L]^q) + \log\{(i_p)_M/(i_p)_C\}] \quad (4)$$

where ΔE_p denotes the difference between the peak potentials measured in metal solutions without and with the ligand; $(E_p)_M$, $(i_p)_M$ and $(E_p)_C$, $(i_p)_C$ are the peak potentials and current for the metal in the presence and in the absence of the ligand, respectively; n, R, T and F have their usual meaning.

DeFord-Hume's method[30] has been used for determination of stability constants of metal complexes by voltammetric techniques. The DeFord-Hume's method was originally developed for reversible electrochemical systems. It has been shown that this method can be successfully applied to non-reversible systems in which the reversibility does not change during metal titration with the ligand[31-34].

Here, we are reporting the application of the modified DeFord-Hume method[35] to determine the stoichiometry and stability constants of irreversible DTX-Al(III) complexes. According to the following equation (5), this is the modified form of equation (4):

$$(0.434\ \alpha nF/RT)\,\Delta E_p + \log[(i_p)_M/(i_p)_C] = \log(\beta_q) + q\log(C_L) \quad (5)$$

where C_L is the concentration of the ligand in the solution.

From equation (5), it follows that a polynomial fits the experimental data (titrations of metal solutions with the ligand solution). Its degree gives the number of complexes and the coefficients correspond to the overall formation constants.

The SWV voltammograms of the complexation process are shown in Figure 4. The applied potential varied from –1.0 to 1.4 V (vs. SCE). In a typical run, the first voltammogram was recorded for a solution containing 1.96×10^{-4} M of Al(III) in 0.01 M electrolyte in

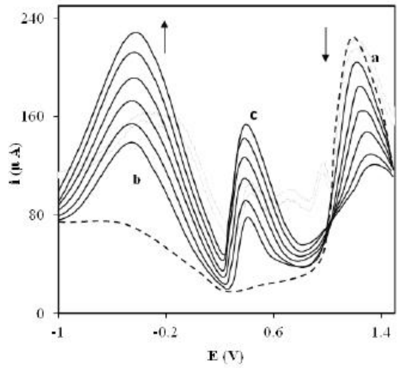

Figure 4 : The SWV voltammograms of the complexation process (vs. SCE) when a solution containing 1.96 × 10^{-4} M of Al(III) in the presence of TBAC (0.01 M) in 1:1 AN:H_2O solution titrated with DTX (1.0 × 10^{-3} M) solution. The peaks (a), (b) and (c) are for free Al(III) ion, Al(III)/DTX complex and DTX, respectively.

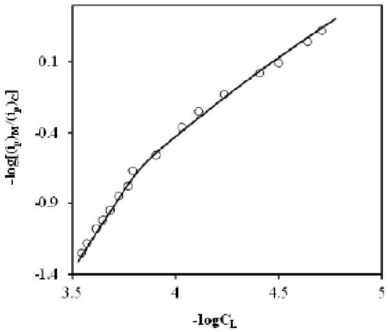

Figure 5 : The plot of $-\log[(i_p)_M/(i_p)_C]$ vs. $-\log C_L$ according to the Deford-Hume's method. This plot demonstrates two straight lines indicative formation of 1:1 and 1:2 (metal:ligand) complexes.

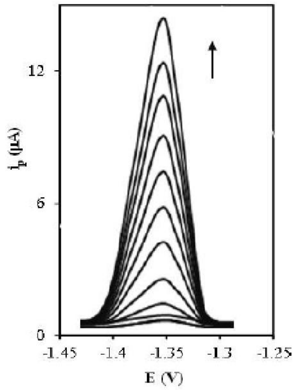

Figure 6 : The SWV voltammograms of the complexation process (vs. SCE) when a solution containing 1.96 × 10^{-4} M of Al(III) in the presence of TBAC (0.01 M) in 1:1 AN:H_2O solution titrated with DTX (1.0 × 10^{-3} M) solution on a different WE, GC. All conditions were the same as designed for the previous experiment on the platinum electrode.

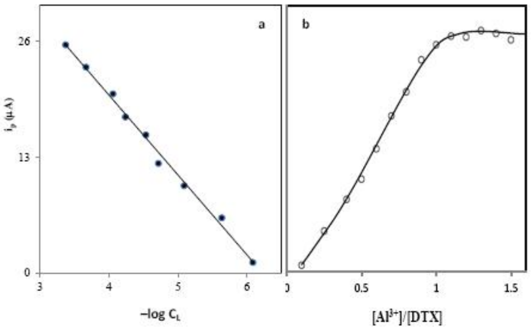

Figure 7 : (a) The DeFord-Hume's plot for the SWV voltammograms of titration 2.91 × 10^{-4} M Al(0) with 5.0 × 10^{-3} M of DTX in the presence of TBAC (0.01 M) as electrolyte in H_2O:AN (1:1) solution. The following conditions were used: pulse height 30 mV, frequency= 10 Hz, scan increment= 3 mV WE= glassy carbon, CE= Pt and RE= SCE. (b) i_p vs. metal/ligand molar ratio (circles) and KINFIT-study curve plot (solid line).

1:1 AN:H_2O solvent (dashed line), in which a new reduction peak has been appeared for Al^{3+} (a). Addition of excess DTX (1.0 × 10^{-3} M) resulted in peaks (b) and (c). Extra examinations were performed to determine the origin of peaks b and c, from which they could be attributed to the resulted complexes and DTX, respectively. Since no shift was observed in the peak potential (–0.4 V) of the complexes of DTX with Al^{3+} ions (where ΔE_p is constant), q values were calculated from the slopes of the plots of ?log$[(i_p)_M/(i_p)_C]$ versus –log(C_L). This plot is shown in Figure 5 that demonstrates two straight lines indicative formation of ML (1:1) and ML_2 (1:2) (metal:ligand) complexes. From the slopes of these lines, the corresponding q values are 1.05 (~1) and 2.07 (~2), respectively. The stability constants $\beta = 4.17 \times 10^1$ and $\beta_2 = 1.86 \times 10^4$ were calculated for the resulted complexes, respectively.

In order to investigate the influence of type of WE on DTX complexation of Al(III), another SWV measurement was carried out on a different WE, GC. All conditions were the same as designed for the previous experiment, on the platinum electrode. Figure 6 displays the corresponding oxidation peaks of the complexes. Using the modified DeFord-Hume's method (Figure 7, a) led nearly the same results for stability constants and stoichiometry of the complexes as were obtained on the Pt WE. Here, metal adsorption on GC electrode was considerable, while this process was not seen on the platinum electrode. This is the reason for the fact that the inflection points of plot of peak current, i_p, vs. metal/ligand molar ratio are not distinguishable, as shown in Figure 7 (b, circles). Based on the SWV studies on GC it was concluded that DTX complexes Al(III) ion in two forms 1:1 and 2:1 (DTX:Al(III)) in the solution, $\beta = 4.22 \times 10^{1}$ and $\beta_2 = 1.81 \times 10^{4}$. KINFIT (will be described in the next section) method (Figure 7 b, solid line) was also performed to find the complexation parameters, in which the above-mentioned stoichiometry was confirmed and 4.20×10^{1} and 1.88×10^{4} were obtained for β1 and β2, respectively.

Differential pulse voltammetry

The primary advantage of pulse voltammetric techniques, such as normal or differential pulse voltammetry, is their ability to discriminate against capacitance current. Therefore, these techniques are more sensitive to faradaic currents than conventional DC voltammetry.

We investigated the electrochemical behavior of interaction of DTX with Al(III) by DPV. A set of differential pulse voltammograms showed well-shaped DPV peaks for Al(III)-DTX system in which the intensities of each peak increase after increasing addition of A(III) concentrations ($1.95 \times {}^{-}10^{5}$ to $1.98 \times^{-} 10^{4}$ M) to a solution of DTX (1.96×10^{-4} M) solution containing 0.01 M TBAC. As shown in Figure 8, the growth of a new voltammogram at –1.35 V is indicative the formation of new species in the solution. As shown in Figure 9 (circles), the plot of i_p as a function of $[Al^{3+}]/[DTX]$ at E_p = –1.35 V showed a distinct inflection point at ligand/metal molar ratio 1 (ML). The minor curvature in the curve plot at about mole ratio 0.5 could be attributed to the formation the weak 1:2 (ML_2) complex. There is no separated current peak for this type of complex, so the current is sum of the currents of two possible complexes formed by the reaction between DTX and Al(III) in the solution.

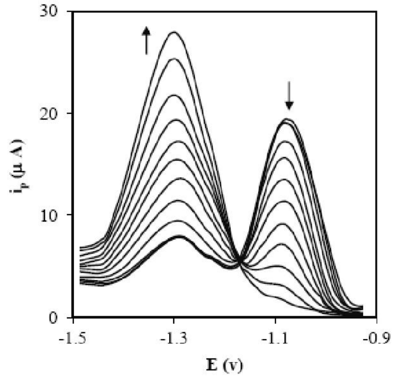

Figure 8 : A set of differential pulse voltammograms for Al(III)-DTX system in which the intensities of each peak increase after increasing addition of Al(III) concentrations ($1.95 \times^{-} 10^{5}$ to $1.98 \times^{-} 10^{4}$ M) to a solution of DTX (1.96×10^{-4} M) containing 0.01 M TBAC.

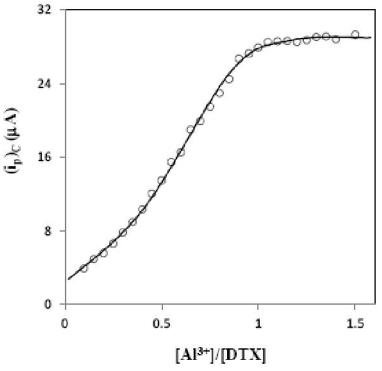

Figure 9 : The DPV plot of $(i_p)_C$ vs. metal/ligand to determine the stoichiometry of the interaction of DTX with Al(III) ion in the solution from the DPV data of the titration curves at E = –1.35 V. The circles show the experimental values while the line indicates the theoretical predicted data from the proposed complexation model ($ML+ML_2$).

$(i_p) = (i_p)_{ML} + (i_p)_{ML2}$ (6) When the ligand, DTX, reacts with Al(III), M, it may form a ML, ML_2 or both ML + ML_2 complexes or any other possible forms. According to the experimental results, we only encountered one type of complexation, ML + ML_2 (following model) in the solution.

$$\mathbf{(i_p) = (i_p)_{ML} + (i_p)_{ML2}} \qquad \mathbf{(6)}$$

When the ligand, DTX, reacts with Al(III), M, it may form a ML, ML_2 or both ML + ML_2 complexes or any other possible forms. According to the experimental results, we only encountered one type of complexation, ML + ML_2 (following model) in the solution.

$$\mathbf{M + L\ ?\ ML, K_1 = [ML]/[M][L]} \qquad \mathbf{(7)}$$

$$\mathbf{ML + L\ ?\ ML_2, K_2 = [ML_2]/[ML][L]} \qquad \mathbf{(8)}$$

The mass balances of this possible model in the solution can be solved to obtain the required equations for the concentration of free metal [M] or free ligand [L]:

$$\mathbf{C_M = [M] + [ML] + [ML_2], C_L = [L] + [ML] + 2[ML_2]}$$

$$\mathbf{\beta_2[L]^3 + K_1(1 + K_2(2C_M - C_L))[L]^2 + (1 + K_1(C_M - C_L))[L] - C_L = 0} \qquad \mathbf{(9)}$$

where C_M, C_L and $\beta_2(= K_1.K_2)$ denote the initial metal ion concentration, the initial ligand concentration and the overall stability constant, respectively. The following equation (10) can interpret the predictable current values for this case:

$$\mathbf{(i_p) = K£½[ML] + K£½£½[ML_2] = K£½\beta_1[M][L] + K£½£½\beta_2[M][L]^2} \qquad \mathbf{(10)}$$

where K£½ and K” values are DPV constants for the relationship between current intensities and the concentration of the measuring species in the solution.

To evaluate the stepwise stability constants from the calculated current values the non-linear least-squares curve-fitting program KINFIT [36] was used, in which the predicted current intensities of the solution are given by equation (10). The program is based on the iterative adjustment of calculated values of current intensities to the observed values by using the Wentworth matrix technique[37] or the Pawell procedure[38]. Adjustable parameters are the stepwise stability constants of the complexes present in solution and the corresponding current intensities depending on the model adopted. The free ligand concentrations, [L], were calculated by using the Newton–Raphson procedure. Once the values of [L] had been obtained by using the estimated values of the stability constants at the current iteration step of the program, the refinement of the parameters was continued until the sum-of-squares of the residuals between calculated and observed values of the current intensities for all experimental points were minimized. The output of the program KINFIT comprises the refined parameters, the sum-of-squares, and the standard deviations of the data.

All the resulting current/molar ratio data (circles, in Figure 9) were best fitted to the corresponding model (solid line) with sum-of-squares of the residuals less than 0.002, which further supports the formation of the species in the solution and confirm the proposed complexation model, $ML+ML_2$ (see Figure 9 for details). Thus, the stepwise formation constants of the complex species were evaluated as 4.30×10^{1} and 1.92×10^{4} for ML and ML_2 complexes, respectively. These values are near to the previously evaluated formation constants obtained in SWV study.

CONCLUSION

The complexation reaction between Al(III) ion and 1,3-dihydroxy-9H-thioxanthen-9-one can be followed by using CV, SWV and DPV, which allow the identification of the complexes formed as well as the determination of their stability constants .In addition, the results show that the DeFord-Hume's method is applicable even in the presence of electrochemically irreversible complexes. It has shown that the methodology based on the DeFord-Hume's principle can successfully be applied to treat data obtained from irreversible voltammograms, from which complexation parameters such as complex(es) molar ratio and stepwise stability constant(s) could be evaluated.

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