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# Kinetics and mechanism of the oxidation of chromium (III) complex involving the antifibrinolytic drug Tranexamic acid by periodate

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## Abstract

Tranexamic acid (TXA) have antifibrinolytic properties and finds wide applications in pharmaceuticals, most used in cardiac, orthopaedic, urological, gynaecological, and obstetric surgery. Complexes of tranexamic acid with some metal ions show antimicrobial and anti-tumor activity. Oxidation-kinetic study is of much importance in understanding the mechanistic profile of Cr-TXA complex in biological systems. Kinetics of oxidation of $[Cr^{III}(TXA)(H_2O)_5]^{2+}$ by periodate has been spectrophotometrically studied under pseudo order conditions over 293-313 K, pH (3.20-4.20) range, and ionic strength of 0.30 M for a set of periodate concentrations. The initial oxidation product is the unstable Cr(V) which is then oxidized to the final product of Cr(VI). The reaction is first order dependent on complex concentration. The pseudo-first order rate constant, $k_{obs}$ increased with decreasing proton concentration, indicating that the deprotonated form of the chromium (III) complex is the reactive species. An inner sphere mechanism has been proposed for the oxidation process. The thermodynamic activation parameters are also reported.

*Keyword:* Tranexamic acid; Chromium (III) complexes; Oxidation; Kinetics; periodate; Reaction mechanism; Electron transfer.

## 1. Introduction:

Chromium is an essential nutritional metal that play a role in metabolic syndrome and cardiovascular disease, also support the transportation of amino acids through the cell membrane [1]. Chromium (III) complexes show capacity in enhancing insulin activity in patients with type 2 diabetes, especially glucose tolerance factor which is synthesized from absorbed dietary chromium, which enhancing the insulin action about three-fold [2]. The study of chromium (III) complexes with amino acids are biologically important since these complexes can be used as enzymatic labels by substitution of the activator or inhibitor [3]. The biological oxidation of chromium from Cr(III) to Cr(VI) state is an important environmental process because of the high mobility, toxicity and carcinogenic effect of chromium (VI) [4]. The formation of chromium(III) or other intermediate oxidation states such as chromium (V) and (IV) is supposed to play a role in

adverse biological effects of chromium (VI) compounds; which have toxic and carcinogenic effect [5, 6].

Tranexamic acid, trans- 4- amino methyl cyclohexane carboxylic acid, is a member of lysine amino acid synthetic derivatives, a plasmin inhibitor that acts by blocking lysine-binding sites on plasminogen, inhibiting the activation of plasmin, consequently, prevents bleeding, consequently it is used in many surgical situations [7, 8]. It reduces blood loss and the risk of exposure to allogenic blood transfusion in off-pump coronary artery bypass, joint arthroplasty, open heart, and prostate surgery [9-13]. It has the potential to decrease blood loss in patients with hip fractures [14]. TXA is good for a reduction in transfusion requirements in liver transplantation with no indication for an increase in thrombotic complications [15]. It appears to be an active treatment for antepartum and postpartum

hemorrhage, safe and effective in the prevention and management of bleeding during pregnancy [16]. Also, it shows anti-inflammatory [17] and skin whitening effects [18,19]. Complexes of tranexamic acid with some metal ions were screened for microbiological activity, the results show that the metal complexes have a significant efficiency in comparison with free TXA ligand. TXA complexes with metal ions as yttrium (III), gallium (III), tungsten (VI), silicon (IV), and organotin (IV) exhibit antimicrobial activity [20, 21]. Also, complexes of TXA derivatives with copper (II) exhibited excellent anti-tumor and anti-fungal activities [22].

Periodate oxidations show a significant role in biological studies [23,24]. Periodate oxidation of caffeic acid was found to simulate the mechanism of polyphenol oxidase, the antioxidant product exhibits slightly enhanced antiradical activity compared to caffeic acid [25]. Periodate oxidation of lignin produce a lignin polymer, which is used as coagulant for aluminum oxide suspension in water and wastewater [26]. Periodate oxidation and reductive amination in the presence of tyramine, alginates are used for a modification of a new polymer with an increase in binding to the cell. This can be important in tissue engineering, drug delivery and enzyme immobilization applications [27].

An inner-sphere mechanism for oxidation of chromium(III) complexes of some amino acids by periodate has been expected with the hydroxy group acting as bridging ligand, or through the substitution of coordinated $H_2O$ by $IO_4^-$ [28, 29].

In our previous work [30], formation of chromium (III) complex with the antifibrinolytic drug tranexamic acid was studied by means of spectroscopic and potentiometric techniques, the results confirm the complex formation of chromium (III) with tranexamic acid. The choice of this complex is due to the therapeutic importance of tranexamic acid and its uses as a possible ligand for metal complexes. Chromium(III) is widely present in a variety of foods, therefore there is a probability to form binary complex with TXA in our bodies. In this study, we examine the kinetics of oxidation of TXA-$Cr^{III}$ complex by periodate in aqueous solution and suggest a suitable mechanism in order to study the stability of the formed complex towards oxidation.

## 2. Experimental:
### 2.1 Materials and solutions:
$[Cr^{III}(TXA)(H_2O)_5]^{2+}$ complex (0.01M) was prepared by mixing chromium (III) nitrate with that of TXA with a concentration ratio 1:1, 20% excess ligand was added to ensure complete formation of the complex. The mixture was heated on a water bath until the solution take a violet color. A solution of $NaIO_4$ is prepared in dark bottles to avoid the photolysis of $NaIO_4$, used as oxidizing agent. Tranexamic acid used in this study was purchased from Amoun Pharmaceutical Company, Egypt. Chromium (III) nitrate, sodium nitrate, and sodium periodate were from Merck. Buffer solutions were made from $CH_3COOH$ and $CH_3COONa.3H_2O$. $NaNO_3$ was used to adjust the ionic strength of the solutions. Doubly distilled water was used in all runs.

### 2.2 Kinetic procedure:
The rate of reaction was measured by monitoring the absorbance of the oxidation products as a function of time. The UV–Visible absorption spectra of the products of $[Cr^{III}(TXA)(H_2O)_5]^{2+}$ oxidation by $NaIO_4$ were followed spectrophotometrically for a definite period using JASCO UV-530 spectrophotometer.

Kinetic experiments were conducted by mixing thermostatted solutions of complex at the required pH value with sodium periodate. A thermostated water bath was connected to spectrophotometer used to maintain the desired temperature. The calculated amount of the reactants i.e. $Cr^{III}$-TXA complex, sodium acetate, acetic acid, sodium nitrate and water, except $NaIO_4$ were taken in a reaction vessel which was kept in a thermostatic water bath for sufficient time to attain the temperature of the experiment, also the amount of $NaIO_4$ was thermostated at the same temperature, then mixed thoroughly and quickly transferred to an absorption cell. The oxidation rates were measured by monitoring the absorbance of Cr(VI) at 370 nm on a Jenway 6315 spectrophotometer, where the absorption of the oxidation products is maximal at the reaction pH. The pH of the reaction mixture was measured using a Jenway pH-meter fitted with a glass calomel electrode.

Pseudo first order conditions were always preserved using at least a ten-fold excess of sodium periodate to complex. The ionic strength of the solution was preserved constant by using the desired concentration of $NaNO_3$ solution as supporting electrolyte. The total volume of reaction mixture was 10 ml in each case.

pH-potentiometric titrations were executed using a Metrohm 702 titroprocessor a 728 magnetic stirrer, coupled with a dosino burette model 700. The titroprocessor was coupled to a computer, and the titration software Vesuv version 3.0 was used to control the titration and data acquisition. Potentiometric measurements were achieved using the nonlinear least-squares (Version 2008) [31].

### 2.3 Oxidation products:
The UV–Visible absorption spectra of the oxidation products of $[Cr^{III}(TXA)(H_2O)_5]^{2+}$ by $NaIO_4$ were recorded over time (Fig. 1). The data show

that the two peaks of the chromium(III) at 570 and 408 nm for $[Cr^{III}(TXA)(H_2O)_5]^{2+}$ have disappeared and been replaced by a peak at 370 nm, this confirming the oxidation of complex producing Cr(VI), also the molar absorptivity of the product was similar to chromate ion, confirming that the Cr(VI) is the main product.

### 3.Results and discussion:

Oxidation of $[Cr^{III}(TXA)(H_2O)_5]^{2+}$ complex by periodate was studied over the pH range (3.20 - 4.20), 0.30 M ionic strength, $[IO_4^-]$ range (0.50 - 5.0) $\times 10^{-2}$ M and temperature range 293-313 K.

Pseudo-first order conditions were employed for most of the experiments. Plots of ln $(A_\infty - A_t)$ versus time were linear up to 98% from the beginning of reaction ($A_\infty$ absorbance at the end of the reaction and $A_t$ absorbance at time t). Values of pseudo-first order rate constants, $k_{obs}$, obtained from the slopes of these plots at fixed pH, ionic strength and temperature are independent on the initial concentration of $[Cr^{III}(TXA)(H_2O)_5]^{2+}$ as shown in Table 1, indicating first-order dependence on complex concentration, and represented by Eq. (1), as

$$Rate = k_{obs} \left[ Cr^{III}(TXA)(H_2O)_5^{2+} \right]$$
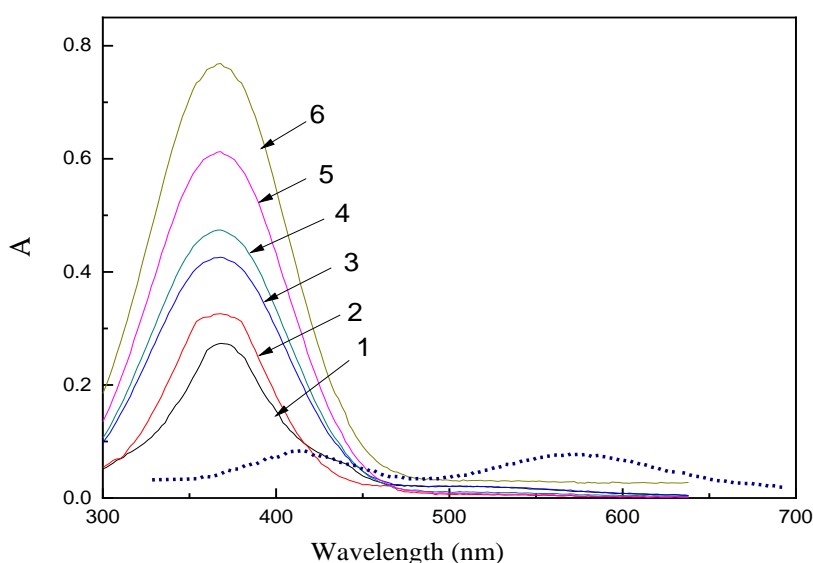


**Fig.1** Change in absorbance with time of the product of the oxidation of $[Cr(TXA)(H_2O)_5]^{2+}$ by NaIO₄. Curves (1-6) recorded at times 1, 2, 3, 5, 30 and 60 min respectively. [complex] = 5 x 10⁻⁴, $[IO_4^-]$ = 0.02 M, $I$ = 0.30 M, pH = 3.70 and T = 298 K. The dotted curve spectrum of the complex (5 x 10⁻⁴ M) at the same pH.

Variation of $k_{obs}$ with $[IO_4^-]$ at constant pH, ionic strength, and different temperatures is shown in Table 2. It is obvious from these results that $k_{obs}$ does not vary linearly with $[IO_4^-]$ and it increases with increasing temperature. l/$k_{obs}$ differs linearly with l/$[IO_4^-]$ at different temperatures (Fig. 2), The kinetics of the reaction are given by Eq. (2):

**Table 1.** Variation of $k_{obs}$ on the initial concentration of $[Cr^{III}(TXA)(H_2O)_5^{2+}]$ at $[IO_4^-]$ = 0.02 M, I =0.30 M, $[H^+]$ = 1.99 x10⁻⁴ M, T = 298 K.

| 10⁴$[Cr^{III}(TXA)(H_2O)_5^{2+}]$ M | 10²$k_{obs}$ s⁻¹ |
|---|---|
| 2.5 | 0.324 |
| 4 | 0.316 |
| 5 | 0.319 |
| 6 | 0.327 |
| 7.5 | 0.333 |
| 10 | 0.336 |

**Table 2**. Variation of $k_{obs}$ with $[IO_4^-]$ at different temperatures at $[H^+] = 1.99 \times 10^{-4}$ M, $[Cr^{III}(TXA)(H_2O)_5^{2+}] = 5 \times 10^{-4}$ M, and I = 0.30 M

| $10^2 [IO_4^-]$ | $10^2 k_{obs}$ (s$^{-1}$) | | | | |
|---|---|---|---|---|---|
| (M) | 293 K | 298 K | 303 K | 308 K | 313 K |
| 0.5 | 0.177 | 0.199 | 0.218 | 0.261 | 0.285 |
| 1.0 | 0.250 | 0.270 | 0.302 | 0.364 | 0.390 |
| 1.5 | 0.277 | 0.304 | 0.335 | 0.409 | 0.448 |
| 2.0 | 0.287 | 0.319 | 0.375 | 0.456 | 0.476 |
| 2.5 | 0.301 | 0.336 | 0.388 | 0.478 | 0.525 |
| 3.0 | 0.318 | 0.350 | 0.397 | 0.501 | 0.551 |
| 3.5 | 0.330 | 0.358 | 0.409 | 0.528 | 0.569 |
| 4.0 | 0.336 | 0.368 | 0.432 | 0.553 | 0.582 |
| 4.5 | 0.340 | 0.391 | 0.451 | 0.565 | 0.607 |
| 5.0 | 0.346 | 0.404 | 0.465 | 0.578 | 0.629 |
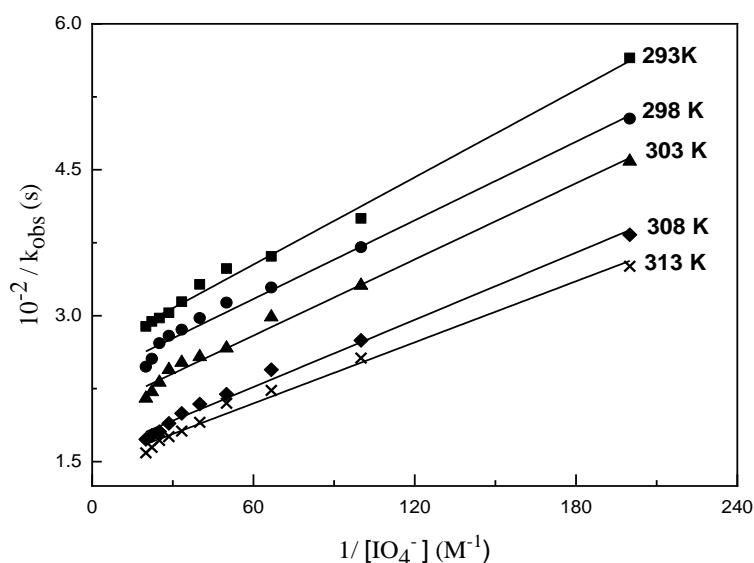


**Fig. 2** Plot of $1/k_{obs}$ vs. $1/[IO_4^-]$ at different temperatures. $[Cr(TXA)(H_2O)_5]^{2+} = 5 \times 10^{-4}$ M , I=0.30 M ,$[H^+]= 1.995 \times 10^{-4}$ M and $[IO_4^-]=(0.5-5) \times 10^{-2}$ M.

$$\frac{d[Cr^{VI}]}{dt} = \left\{ a[IO_4^-]_T / (1 + b[IO_4^-]_T) \right\} [Cr^{III}]_T \quad (2)$$

and

$$k_{obs} = a[IO_4^-]_T / (1 + b[IO_4^-]_T)$$

or

$$1/k_{obs} = 1/a[IO_4^-]_T + b/a \quad (4)$$

The reaction rate increases with increasing pH under constant reaction conditions (Table 3). Plots of $1/k_{obs}$ versus $1/[IO_4^-]$ at different pH values are linear having an intercept and a slope (Fig. 3). The slope is pH dependent (Fig.5). The result indicating that the deprotonated form of the complex is the most reactive species.

**Table 3.** Effect of pH on $k_{obs}$ at $[Cr(TXA)(H_2O)_5{}^{2+}]$ = 5x10$^{-4}$ M, I =0.30 M, T = 298 K.

| $10^2$ [IO$_4^-$] | $10^2$ $k_{obs}$ (s$^{-1}$) | | | |
|---|---|---|---|---|
| (M) | pH = 3.20 | pH = 3.70 | pH = 3.97 | pH = 4.20 |
| **0.5** | 0.130 | 0.199 | 0.224 | 0.245 |
| **1.0** | 0.182 | 0.270 | 0.291 | 0.326 |
| **1.5** | 0.205 | 0.304 | 0.329 | 0.377 |
| **2.0** | 0.219 | 0.319 | 0.359 | 0.399 |
| **2.5** | 0.225 | 0.336 | 0.374 | 0.417 |
| **3.0** | 0.239 | 0.350 | 0.394 | 0.429 |
| **3.5** | 0.243 | 0.358 | 0.401 | 0.446 |
| **4.0** | 0.253 | 0.368 | 0.411 | 0.458 |
| **4.5** | 0.257 | 0.391 | 0.417 | 0.479 |
| **5.0** | 0.264 | 0.404 | 0.443 | 0.503 |
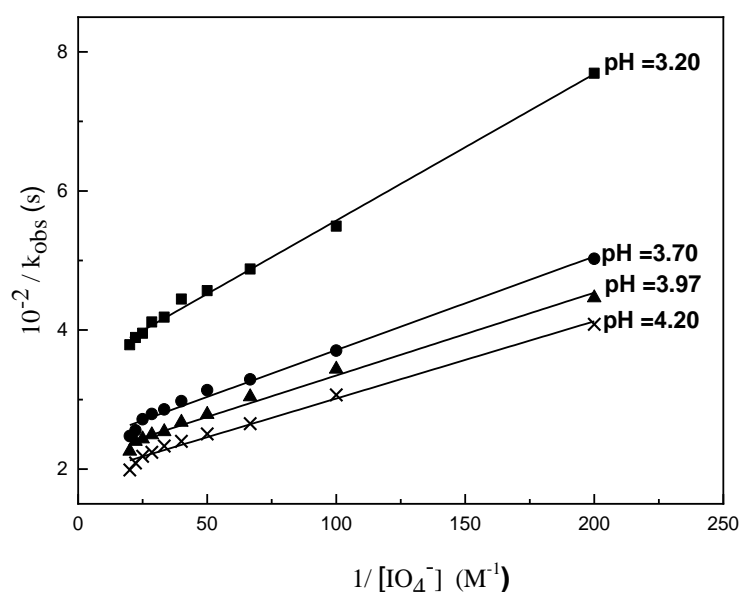


**Fig. 3** plot of $1/k_{obs}$ vs. $1/[$ IO$_4^-$] at different pHs. $[Cr(TXA)(H_2O)_5{}^{2+}]$ = 5 x10$^{-4}$ M, I=0.30 M, T= 298K and [IO$_4^-$]=(0.5-5) x10$^{-2}$ M.

The ionic strength of the medium was adjusted by NaNO$_3$ in the range of 0.10 –1.0 M (Table 4). Table 4 shows that $k_{obs}$ decrease by increasing the ionic strength of the medium. Applying the Bronsted Bjerrum equation [32].
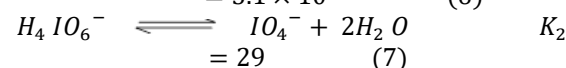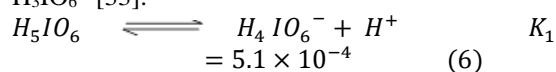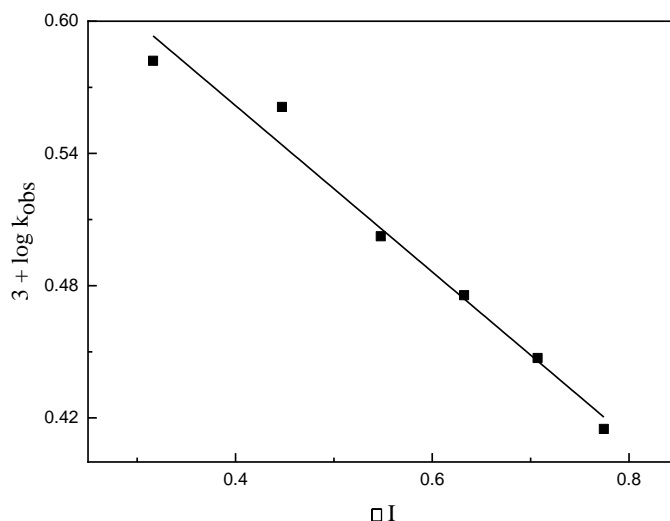
$$\log k = \log k_o + 2\beta\, Z_A Z_B \sqrt{I}$$

Where k is the rate constant, $k_0$ is the rate constant at zero ionic strength, $\beta$ constant for each solvent, $Z_A$ and $Z_B$ correspond to the charges on the reactants A and B, and I is the ionic strength. Plotting log $k_{obs}$ versus $\sqrt{I}$ (Fig. 4), gives a straight line with negative slope, demonstrating that the reaction is taken place between oppositely charged species.

**Table 4.** Effect of ionic strength on $k_{obs}$ at $[Cr(TXA)(H_2O)_5{}^{2+}]$ = 5x10$^{-4}$ M, [IO$_4^-$] = 0.02 M, T = 298 K.

| I (M) | $10^2$ $k_{obs}$ (s$^{-1}$) |
|---|---|
| **0.1** | 0.382 |
| **0.2** | 0.364 |
| **0.3** | 0.318 |
| **0.4** | 0.299 |
| **0.5** | 0.280 |
| **0.6** | 0.260 |

In aqueous solution, periodate ion is known to be involved in complex equilibria as shown in equations (6-8). Under the reaction conditions, the most likely periodate species are IO$_4^-$, H$_4$IO$_6^-$, and H$_3$IO$_6^{2-}$ [33].

$$H_5IO_6 \rightleftharpoons H_4IO_6^- + H^+ \qquad K_1 = 5.1 \times 10^{-4} \qquad (6)$$

$$H_4IO_6^- \rightleftharpoons IO_4^- + 2H_2O \qquad K_2 = 29 \qquad (7)$$

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**Fig. 4** plot of log k$_{obs}$ vs $\sqrt{I}$ , [IO$_4^-$] = 0.02 M, [Cr(TXA)(H$_2$O)$_5$ $^{2+}$] = 5x10$^{-4}$ M, T = 298 K.

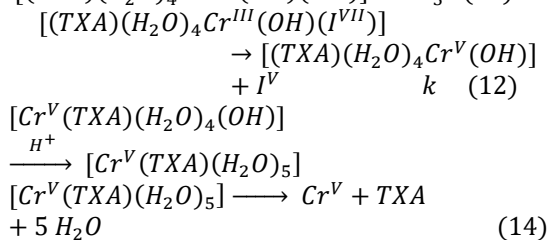$$H_4 IO_6^- \rightleftharpoons H_3 IO_6^{2-} + H^+ \qquad K_3 = 4.9 \times 10^{-9} \quad (8)$$
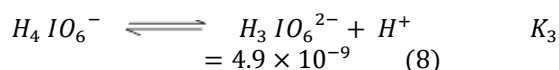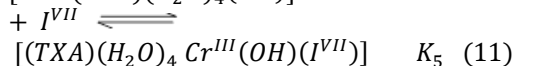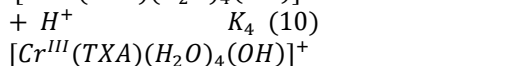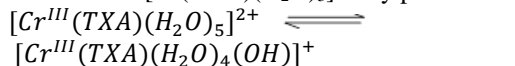
Over the studied pH range, I$^{VII}$ will be used to represent H$_4$IO$_6^-$. Coordination of periodate ion with complex occur through the hydroxy group of the complex [Cr(TXA)(H$_2$O)$_4$(OH)]$^+$ which act as a bridge between complex and I$^{VII}$.

In aqueous solution the complex may be involved in the equilibrium shown in Eq. (9):

$$[Cr(TXA)(H_2O)_5]^{2+} \rightleftharpoons [Cr(TXA)(H_2O)_4(OH)]^+ + H^+ \qquad K_4 \quad (9)$$
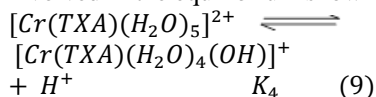
$K_4$ was measured potentiometrically and has the value of (7.009 x10$^{-4}$) at 298 K. The results obtained from the effect of [H$^+$] suggests that the deprotonated form of the complex is involved in the rate determining step.

The following mechanism is proposed for the oxidation of [Cr(TXA)(H$_2$O)$_5$] $^{2+}$ by periodate:

$$[Cr^{III}(TXA)(H_2O)_5]^{2+} \rightleftharpoons [Cr^{III}(TXA)(H_2O)_4(OH)]^+ + H^+ \qquad K_4 \quad (10)$$

$$[Cr^{III}(TXA)(H_2O)_4(OH)]^+ + I^{VII} \rightleftharpoons [(TXA)(H_2O)_4 Cr^{III}(OH)(I^{VII})] \qquad K_5 \quad (11)$$

$$[(TXA)(H_2O)_4 Cr^{III}(OH)(I^{VII})] \rightarrow [(TXA)(H_2O)_4 Cr^V(OH)] + I^V \qquad k \quad (12)$$

$$[Cr^V(TXA)(H_2O)_4(OH)] \xrightarrow{H^+} [Cr^V(TXA)(H_2O)_5] \qquad (13)$$

$$[Cr^V(TXA)(H_2O)_5] \longrightarrow Cr^V + TXA + 5 H_2O \qquad (14)$$

$$Cr^V + I^{VII} \longrightarrow Cr^{VI} + I^{VI} \qquad (15)$$

$$2I^{VI} \longrightarrow I^{VII} + I^V$$
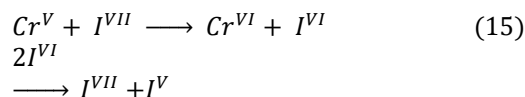
From the suggested mechanism, the rate of the reaction can be described as:

$$Rate = k \, [(TXA)(H_2O)_4 Cr^{III}(OH)(I^{VII})]$$

$$Rate = k \, K_5 \, [Cr^{III}(TXA)(H_2O)_4(OH)^+] \, [I^{VII}]$$

If [Cr$^{III}$]$_T$ represents all the chromium(III) species present in aqueous solution, then

$$[Cr^{III}]_T = [Cr^{III}(TXA)(H_2O)_4(OH)^+] \, [H^+]/K_4 + [Cr^{III}(TXA)(H_2O)_4(OH)^+] + K_5 \, [Cr^{III}(TXA)(H_2O)_4(OH)^+] \, [I^{VII}]$$

Substitution for [Cr$^{III}$(TXA)(H$_2$O)$_4$(OH)$^+$] from Eq. (19) into Eq. (18) then:

$$Rate = k \, K_4 \, K_5 \, [Cr^{III}]_T \, [I^{VII}]/([H^+] + K_4 + K_4 \, K_5 \, [I^{VII}]) \qquad (20)$$

$$k_{obs} = k \, K_4 \, K_5 \, [I^{VII}]/([H^+] + K_4 + K_4 \, K_5 \, [I^{VII}]) \qquad (21)$$

$$1/k_{obs} = ([H^+] + K_4 + K_4 \, K_5 \, [I^{VII}])/k \, K_4 \, K_5 \, [I^{VII}]$$

$$1/k_{obs} = ([H^+] + K_4)/k \, K_4 \, K_5 \, [I^{VII}] + 1/k$$

At constant [H$^+$] the derived rate law in Eq. (23) is consistent with the experimental rate law shown in Eq. (4), where $a = k \, K_4 \, K_5/([H^+] + K_4)$ and $b = K_4 \, K_5 /([H^+] + K_4)$.

From Eq. (23), it follows that the slopes of the plots can be represented by Eq. (24):

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$$slope = 1/a$$
$$= ( [H^+]/k \, K_4 \, K_5)$$
$$+ \; 1/k \, K_5 \qquad\qquad (24)$$

It is obvious from Eq. (24) that the slope is dependent on $[H^+]$. This is shown in Fig. 5 with correlation coefficient of 0.998, indicating the validity of our proposed mechanism.

Values of the intermolecular electron transfer rate constant, $10^3 \, k$ calculated from the reciprocal of the intercept of Eq. (23) plot, are 4.20, 4.64, 4.67,

5.10, and 5.55 s$^{-1}$ respectively at 293, 298, 303, 308, and 313 K. Value of the slope in Fig. 5 is 17.77 x 10$^2$ s and the intercept is 0.9871 M s at 298 K. $K_4$ value was calculated by dividing the intercept by the slope of Fig. 5 as 5.55x10$^{-4}$ M at 298K. The value of $K_5$ calculated by substituting the value of k from the intercept of Fig. 5 as 218.33 M. The calculated value of $K_4$ (5.55x10$^{-4}$ M) is in good agreement with the obtained potentiometrically ($K_4$ = 7.009 x10$^{-4}$) indicating the validity of our proposed mechanism.
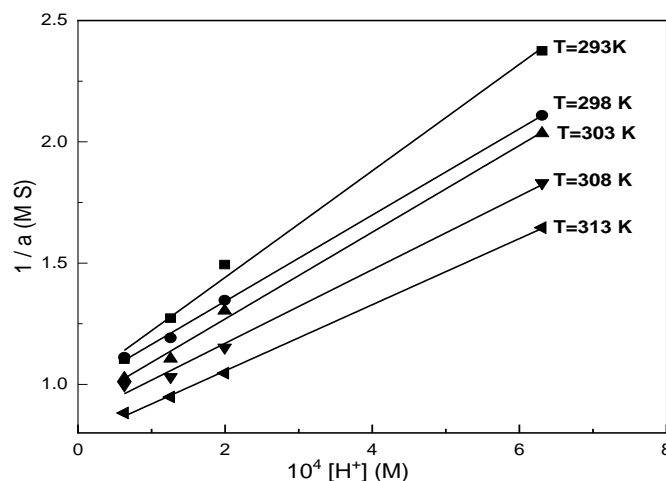


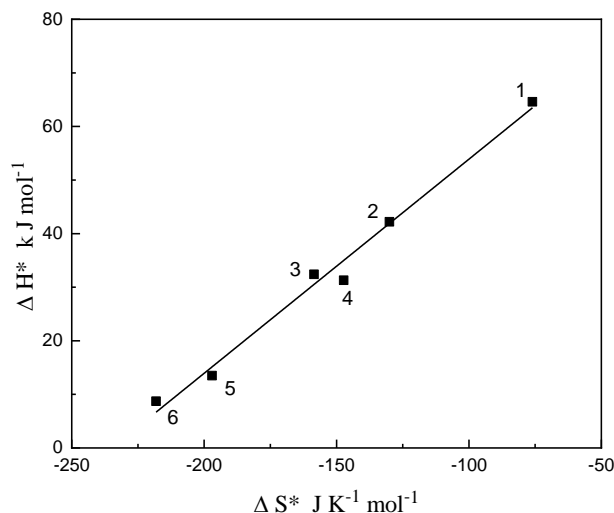**Fig. 5.** Plot of 1/a vs [H$^+$] at different temperatures



**Fig. 6.** Isokinetic plot for oxidation of chromium(III) complexes by periodate.

The thermodynamic activation parameters, $\Delta H^*$ and $\Delta S^*$ associated with the electron transfer step were achieved from the least-squares fit to transition state theory equation with correlation coefficient 0.9732 as 7.36 ± 0.09 kJ/mol and -220.08 ±0.2 J/ K mol, respectively. The high negative entropies of activation, $\Delta S^*$, is suggested to be as a result of charge concentration upon encounter complex formation, resulting in substantial mutual

ordering of the solvated water molecules. The small positive enthalpy of activation, ΔH*, can be explained as the intramolecular electron transfer steps are endothermic and the formation of a more solvated encounter complex. Enthalpies and entropies of activation for the oxidation of some chromium(III) complexes by periodate are collected in (Table 5). Plot of ΔH* vs ΔS* for the oxidation of hydroxochromium (III) complexes by periodate (Fig. 6) is linear, support the same inner sphere mechanism, an isokinetic relation probably exists for the oxidation of some chromium(III) complexes by periodate.

**Table 5.** Enthalpies and entropies of activation for the oxidation of some chromium(III) complexes by periodate

| Complex | $10^2 k_1$ (s$^{-1}$) | ΔH* kJ/mol | -ΔS*J/K mol | Ref. | Fig. 6 key |
|---|---|---|---|---|---|
| $[Cr(NTA)(Asp)(H_2O)]^{2-}$ | 0.39 | 64.5 | 76 | 34 | 1 |
| $[Cr (GMP)(H_2O)_4]^{3+}$ | 1.18 | 42.2 | 130 | 35 | 2 |
| $[Cr (G)(H_2O)_4]^{3+}$ | 2.73 | 32.4 | 158.5 | 36 | 3 |
| $[Cr(DPA)(IDA)(H_2O)]^-$ | 0.07 | 31.3 | 147.3 | 37 | 4 |
| $[Cr(2ABT)_3(Cl)_3]\cdot2H_2O$ | 0.69 | 13.5 | 197.01 | 38 | 5 |
| $[Cr(TXA)(H_2O)_5]^{2+}$ | 0.55 | 8.71 | 218.16 | This work | 6 |

**Conclusion**

An inner sphere mechanism is proposed for the oxidation of $[Cr(TXA)(H_2O)_5]^{2+}$ complex by periodate in which the deprotonated Cr$^{III}$ complex is formed rapidly in equilibrium steps preceding the rate determining step, in which the hydroxyl group act as a bridge between the complex and periodate. The reaction rate increase with increasing pH (3.20-4.20) and temperature (293-313) K, decrease with increasing ionic strength (0.1-0.6) M. A common mechanism for the oxidation of chromium(III) complex by periodate is proposed and is supported by the excellent isokinetic relationship between ΔH* and ΔS* values for these reactions.

**References**

[1] Lewicki, S., Zdanowski, R., Krzyzowska, M., Lewicka, A., Debski, B., Niemcewicz, M. and Goniewicz, M. The role of Chromium III in the organism and its possible use in diabetes and obesity treatment. *Annals of Agricultural and Environmental Medicine*, *21*(2), 331-335 (2014). https://doi.org/10.5604/1232-1966.1108599.

[2] Liu, L., Cui, W. M., Zhang, S. W., Kong, F. H., Pedersen, M. A., Wen, Y. and Lv, J. P. Effect of glucose tolerance factor (GTF) from high chromium yeast on glucose metabolism in insulin-resistant 3T3-L1 adipocytes. *Rsc Advances*, *5*(5), 3482-3490 (2015). https://doi.org/10.1039/C4RA10343B.

[3] Vincent, J. B. Is the pharmacological mode of action of chromium (III) as a second messenger? *Biological trace element research*, *166*(1), 7-12 (2015) . https://doi.org/10.1007/s12011-015-0231-9.

[4] Levina, A. and Lay, P. A. Chemical properties and toxicity of chromium (III) nutritional supplements. *Chemical research in toxicology*, *21*(3), 563-571(2008). https://doi.org/10.1021/tx700385t.

[5] Ackerley, D. F., Gonzalez, C. F., Park, C. H., Blake, R. 2., Keyhan, M. and Matin, A. Chromate-reducing properties of soluble flavoproteins from Pseudomonas putida and Escherichia coli. *Applied and environmental microbiology*, *70*(2), 873-882 (2004). https://dx.doi.org/10.1128%2FAEM.70.2.873-882.2004.

[6] Urrutia, C., Rudolph, A., Lermanda, M. P. and Ahumada, R. Assessment of EDTA in chromium (III–VI) toxicity on marine intertidal crab (Petrolisthes laevigatus). *Bulletin of Environmental Contamination and Toxicology*, *80*(6), 526-528 (2008). https://doi.org/10.1007/s00128-007-9310-8.

[7] Furtmüller, R., Schlag, M. G., Berger, M., Hopf, R., Huck, S., Sieghart, W. and Redl, H. Tranexamic acid, a widely used antifibrinolytic agent, causes convulsions by a γ-aminobutyric acid A receptor antagonistic effect. *Journal of Pharmacology and Experimental Therapeutics*, *301*(1), 168-173 (2002). https://doi.org/10.1124/jpet.301.1.168.

[8] Clevenger, B., Mallett, S. V., Klein, A. A., and Richards, T. Patient blood management to reduce surgical risk. *Journal of British Surgery*, *102*(11), 1325-1337 (2015). https://doi.org/10.1002/bjs.9898.

[9] Dai, Z., Chu, H., Wang, S. and Liang, Y. The effect of tranexamic acid to reduce blood loss and transfusion on off-pump coronary artery bypass surgery: a systematic review and cumulative meta-analysis. *Journal of Clinical Anesthesia*, *44*, 23-31(2018). https://doi.org/10.1016/j.jclinane.2017.10.004.

[10] Danninger, T. and Memtsoudis, S. G. Tranexamic acid and orthopedic surgery—the search for the holy grail of blood conservation. *Annals of Translational Medicine*, *3*(6), 1-4 (2015). http://dx.doi.org/10.3978/j.issn.2305-5839.2015.01.25.

[11] A. Abul-Azm and K. M. Abdullah, European Journal of Anaesthesiology 23.5 (2006) 380–384. Abul-Azm, A. and Abdullah, K. M. Effect of topical tranexamic acid in open heart surgery. *European journal of anaesthesiology*, *23*(5), 380-384 (2006). https://doi.org/10.1017/S0265021505001894.

[12] Longo, M. A., Cavalheiro, B. T. and de Oliveira Filho, G. R. Systematic review and meta-analyses of tranexamic acid use for bleeding reduction in prostate surgery. *Journal of Clinical Anesthesia*, *48*, 32-38 (2018). https://doi.org/10.1016/j.jclinane.2018.04.014.

[13] Jennings, J. D., Solarz, M. K., and Haydel, C. Application of tranexamic acid in trauma and orthopedic surgery. *Orthopedic Clinics*, *47*(1), 137-143 (2016). https://doi.org/10.1016/j.ocl.2015.08.014.

[14] Gausden, E. B., Garner, M. R., Warner, S. J., Levack, A., Nellestein, A. M., Tedore, T., Flores, E. and Lorich, D. G. Tranexamic acid in hip fracture patients: a protocol for a randomised, placebo controlled trial on the efficacy of tranexamic acid in reducing blood loss in hip fracture patients. *BMJ open*, *6*(6), e010676 (2016). http://dx.doi.org/10.1136/bmjopen-2015-010676.

[15] Ortmann, E., Besser, M. W. and Klein, A. A. Antifibrinolytic agents in current anaesthetic practice. *British journal of anaesthesia*, *111*(4), 549-563 (2013). https://doi.org/10.1093/bja/aet154.

[16] Peitsidis, P. and Kadir, R. A. Antifibrinolytic therapy with tranexamic acid in pregnancy and postpartum. *Expert opinion on pharmacotherapy*, *12*(4), 503-516 (2011). https://doi.org/10.1517/14656566.2011.545818.

[17] Lei, Y. T., Xie, J. W., Huang, Q., Huang, W. and Pei, F. X. The antifibrinolytic and anti-inflammatory effects of a high initial-dose tranexamic acid in total knee arthroplasty: a randomized controlled trial. *International Orthopaedics*, *44*(3), 477-486 (2020). https://doi.org/10.1007/s00264-019-04469-w.

[18] Tan, A. W. M., Sen, P., Chua, S. H. and Goh, B. K. Oral tranexamic acid lightens refractory melasma. *Australasian Journal of Dermatology*, *58*(3), e105-e108 (2017). https://doi.org/10.1111/ajd.12474.

[19] Hsieh, P. W., Chen, W. Y., Aljuffali, A., Chen, C. C. and Fang, J. Y. Co-drug strategy for promoting skin targeting and minimizing the transdermal diffusion of hydroquinone and tranexamic acid. *Current Medicinal Chemistry*, *20*(32), 4080-4092 (2013). https://doi.org/10.2174/15672050113109990202.

[20] El-Habeeb, A. A. and Refat, M. S. Synthesis, structure interpretation, antimicrobial and anticancer studies of tranexamic acid complexes towards Ga (III), W (VI), Y (III) and Si (IV) metal ions. *Journal of Molecular Structure*, *1175*, 65-72 (2019). https://doi.org/10.1016/j.molstruc.2018.07.099.

[21] Anwer, J., Ali, S., Shahzadi, S., Shahid, M., Sharma, S. K. and Qanungo, K. Synthesis, characterization, semi-empirical study and biological activities of homobimetallic complexes of tranexamic acid with organotin (IV). *Journal of Coordination Chemistry*, *66*(7), 1142-1152 (2013). https://doi.org/10.1080/00958972.2013.776678.

[22] Khan, M. F., Khan, M. F., Ashfaq, M. and Khan, G. M. Comparative evaluation of some new tranexamic acid derivatives and their copper (II) complexes for antitumor, analgesic, bactericidal and fungicidal activities. *Pakistan Journal of Pharmaceutical Sciences*, *15*(1), 55-62 (2002).

[23] Tiziani, S., Sussich, F. and Cesaro, A. The kinetics of periodate oxidation of carbohydrates 2. Polymeric substrates. *Carbohydrate Research*, *338*(10), 1083-1095 (2003). https://doi.org/10.1016/S0008-6215(03)00082-X.

[24] Mirkhani, V., Tangestaninejad, S., Moghadam, M. and Moghbel, M. Cytochrome P-450 dependent monooxygenases model system: rapid and efficient oxidation of primary aromatic amines to azo derivatives with sodium periodate catalyzed by manganese (III) Schiff base complexes. *Bioorganic & medicinal chemistry*, *12*(17), 4673-4677 (2004). https://doi.org/10.1016/j.bmc.2004.06.029.

[25] Bassil, D., Makris, D. P. and Kefalas, P. Oxidation of caffeic acid in the presence of L-cysteine: isolation of 2-S-cysteinylcaffeic acid and evaluation of its antioxidant properties. *Food research international*, *38*(4), 395-402 (2005). https://doi.org/10.1016/j.foodres.2004.10.009.

[26] Zhang, Y. and Fatehi, P. Periodate oxidation of carbohydrate-enriched hydrolysis lignin and its application as coagulant for aluminum oxide suspension. *Industrial Crops and Products*, *130*, 81-95 (2019). https://doi.org/10.1016/j.indcrop.2018.12.052.

[27] Prodanovic, O., Spasojevic, D., Prokopijevic, M., Radotic, K., Markovic, N., Blazic, M. and Prodanovic, R. Tyramine modified alginates via periodate oxidation for peroxidase induced hydrogel formation and immobilization. *Reactive and Functional Polymers*, *93*, 77-83 (2015). https://doi.org/10.1016/j.reactfunctpolym.2015.06.004.

_____

[28]    Gupta, M., Srivastava, A. and Srivastava, S. Kinetic, Mechanistic, and Thermodynamic Studies for Oxidation of L-Alanine by Alkaline Sodium Periodate in Presence of Os (VIII) in its Nano Concentration Range as Homogenous Catalyst. *Bulletin of Chemical Reaction Engineering & Catalysis*, *13*(2), 355-364 (2018). https://doi.org/10.9767/bcrec.13.2.1583.355-364.

[29]    Khaled, E. S. Inner-sphere oxidation of binary and ternary uridine chromium (III) complexes involving aspartate by periodate. *BioInorganic Reaction Mechanisms*, *6*(3), 247-256 (2007). https://doi.org/10.1515/IRM.2007.6.3.247.

[30]    Mahmoud, S. A., Taha, M., Mohamed, R. A., Khaled, E. S. and Abdel-khalek, A. A. Complexation of chromium (III) with the antifibrinolytic drug tranexamic acid: Formation, kinetics, and molecular modeling studies. *Journal of Molecular Liquids*, *329*, 115513 (2021). https://doi.org/10.1016/j.molliq.2021.115513.

[31]    Gans, P., Sabatini, A. and Vacca, A. Investigation of equilibria in solution. Determination of equilibrium constants with the HYPERQUAD suite of programs. *Talanta*, *43*(10), 1739-1753 (1996). https://doi.org/10.1016/0039-9140(96)01958-3.

[32]    Moore, J. W. and Pearson, R. G. *Kinetics and mechanism,* **3rd Edition,** John Wiley & Sons (1981). ISBN: 978-0-471-03558-9.

[33]    Levason, W. The coordination chemistry of periodate and tellurate ligands. *Coordination chemistry reviews*, *161*, 33-79 (1997). https://doi.org/10.1016/S0010-8545(97)90131-4.

[34]    Ewais, H. A., Habib, M. A. and Elroby, S. A. Kinetics and mechanism of periodate oxidation of two ternary nitrilotriacetatochromium (III) complexes involving histidine and aspartate co-ligands. *Transition Metal Chemistry*, *35*(1), 73-80 (2010). https://doi.org/10.1007/s11243-009-9297-6.

[35]    Ewais, H. A., Ahmed, S. A. and Abdel-Khalek, A. A. Kinetics and Mechanism of Oxidation of Chromium (III)-guanosine 5-Monophosphate Complex by Periodate. *Journal of the Chinese Chemical Society*, *51*(4), 713-718 (2004). https://doi.org/10.1002/jccs.200400108.

[36]    EWAIS, H. A., AHMED, S. A. and ABDEL-KHALEK, A. A. Kinetics and mechanism of oxidation of chromium (III)-guanosine complex by periodate. *BioInorganic Reaction Mechanisms*, *5*(2), 125-133 (2004). https://doi.org/10.1515/IRM.2004.5.2.125.

[37]    Ewais, H. A., Al-Orabi, R. O. and Obaid, A. Y. Manganese (II) catalyzed periodate oxidation of a ternary dipicolinatochromium (III) complex with iminodiacetate as co-ligand: mechanistic and kinetic study. *Transition Metal Chemistry*, *41*(4), 427-434 (2016). https://doi.org/10.1007/s11243-016-0038-3.

[38]    Abdel-Hady, A. E. M. Inner-sphere oxidation of 2-aminobenzothiazole chromium (III) complex by periodate. Evidence for the inhibiting effect of copper (II) and iron (II) ions. *Industrial & Engineering Chemistry Research*, *53*(15), 6268-6273 (2014). https://doi.org/10.1021/ie5001168.

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