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Kinetics and Mechanism of Silver(I)-Catalyzed Oxidation of Tryptophan by Platinum(IV) in Perchlorate Solutions

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Abstract: The kinetics of oxidation of tryptophan by platinum(IV) was investigated in aqueous perchlorate solutions in the presence of silver(I) catalyst at a constant ionic strength of 2.0 mol dm^{-3} and at 25°C. The progress of the reaction was followed spectrophotometrically. The reaction did not proceed in the absence of the catalyst. The catalyzed reaction exhibited a first order dependence on both $[Pt^{IV}]$ and $[Ag^I]$ whereas the order with respect to tryptophan concentration was found to be less than unity. Increasing ionic strength and dielectric constant was found to decrease the oxidation rate. The suggested oxidation mechanism involves formation of a silver(I)-tryptophan intermediate complex in a pre-equilibrium step, which confirmed by both spectral and kinetic evidences. The complex reacts with the oxidant by an inner-sphere mechanism leading to decomposition of the complex in the rate-determining step. The final oxidation products of tryptophan were identified as the corresponding aldehyde (indole-3-acetaldehyde), ammonium ion and carbon dioxide.

Keywords: Tryptophan, Catalyzed-Oxidation, Silver(I), Platinum(IV), Kinetics, Mechanism

1. Introduction

Study of amino acids is one of the most exciting fields of organic chemistry. They play a significant role in a number of metabolic reactions like biosynthesis of polypeptide, protein and nucleotides. Thus, the mechanism of analogous non-enzymatic chemical processes in the oxidation of amino acids is a potential area for intensive investigation [1-18] in order to understand some aspects of enzyme kinetics. Tryptophan (Trp) is an essential amino acid in the human diet. It finds extensive application as a reducing agent in chemical and biochemical systems. Oxidation of tryptophan has previously been studied in acid media by few reagents, such as permanganate [4], vanadium [5], hexacyanoferrate(III) [8] and chromate [9], and in alkaline media by diperiodatocuprate(III) [6] and hexacyanoferrate(III) [7].

The chemistry of biologically active platinum(IV) complexes has increased interest in the last decades due to their remarkable anticancer properties [19-22]. Kinetic studies on the oxidation of inorganic and organic substrates using platinum(IV) complexes in the form of hexachloroplatinate(IV), $[PtCl_6]^{2-}$, are scarce and limited to a few cases [10-16, 23-25], in which $[PtCl_6]^{2-}$ may behave as one

or two electron oxidant, depending upon the substrate and experimental conditions. The knowledge of the reactivity of platinum(IV) compounds towards their reduction by potential bioreductant like tryptophan may be important for understanding the mechanism of where antitumor activity as well as for designing new compounds with the least side effect.

Kinetic investigations on the oxidation reactions of amino acids catalyzed by different metal ions are an important field of chemistry due to the role played by metals in biological systems. An extensive literature survey revealed no report on the mechanistic studies of oxidation of tryptophan by platinum(IV) in either absence or presence of a catalyst. The present study deals with the title reaction in attempt to explore the kinetics and mechanistic aspects of such catalyzed reaction in strong acid medium as well as the catalytic activity of Ag^I.

2. Experimental

2.1. Materials

Reagent grade chemicals and doubly distilled water were used throughout the work. A stock solution of tryptophan was prepared afresh by dissolving the amino acid sample (E. Merck) in bidistilled water. Chloroplatinic acid solution

(Johnson Matthey) was used without further purification. Required solution of the oxidant was freshly prepared before each experiment by proper dilution of its original solutionwhich is standardized spectrophotometrically [26]. The solution was stored in a bottle away from light and re-standardized periodically.

2.2. Kinetic Measurements

All kinetic investigations were conducted under pseudo-first-order conditions where tryptophan was present in a large excess over that of platinum(IV). The ionic strength, I, of the reaction mixture was adjusted to2.0moldm^{-3} using sodium perchlorate as an inert electrolyte.The reaction temperature (25°C) was controlled within ±0.1°C unless stated otherwise. The reaction was initiated by rapid addition of known amounts of the pre-equilibrated Pt^{IV} to the reaction mixture containing the required amounts of the amino acid, perchloric acid, silver(I) nitrate, sodium perchlorate and water, thermostated at the same temperature. The solutions were then mixed and transferred to a cell with a path length of 1 cm. The course of the reaction was followed spectrophotometrically by monitoring the decrease in the absorbance of Pt^{IV} at $\lambda = 261$ nm, its absorption maximum, as a function of time using Shimadzu UV-VIS-NIR-3600 double-beam spectrophotometer with a cell compartment kept at constant temperature. The applicability of Beer's law was verified at 261 nm under the reaction conditions. The molar extinction coefficient, ε, was determined ($\varepsilon = (1.32 \pm 0.04) \times 10^4$dm^{3}mol^{-1} cm^{-1}) and was found to be in a good agreement with that reported previously [26]. In addition, there is no interference from other reagents at this wavelength. It was observed that the oxidation reaction did not proceed in the absence of silver(I) catalyst. The pseudo-first order rate constant values of the catalyzed reaction (k_C) were obtained from the linear portion of ln (absorbance) versus time plots, which were the average of at least two independent kinetics runs and were reproducible to within ±4%. Double logarithmic plots were used to determine the order with respect to each reactant. The concentration of the particular species being examined was varied while the concentrations of the other species were held fixed.

Time-resolved spectra during the course of the reaction between tryptophan and platinum(IV) in the presence of silver(I) catalyst are shown in Figure 1. The scanned spectra indicate gradual disappearance of the Pt^{IV} absorption band with time as a result of its reduction. A hyposchromic shift in the Pt^{IV} band of about 5 nm from 261 to 256 nm as well as two isosbestic points located at 247 and 277 nm are apparent in the spectra.
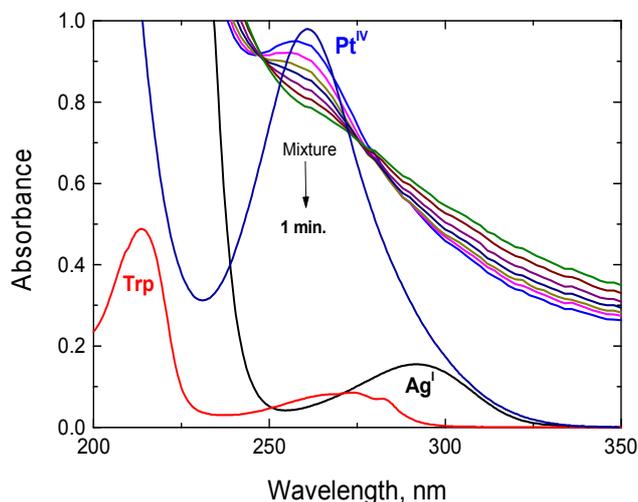
Figure 1. *Time-resolved spectra through silver(I)-catalyzed oxidation of tryptophan by platinum(IV) in perchlorate solution. [Trp] = 4.0x10^{-3}, [Pt^{IV}] = 8.0x10^{-5}, [H$^+$] = 1.0, [Ag^I] = 1.0x10^{-5} and I = 2.0 mol dm^{-3} at 25°C.*

3. Results

3.1. Stoichiometry and Product Identification

Different reaction mixtures with different sets of reactants containing various amounts of Pt^{IV} and tryptophan at fixed acidity, ionic strength, and temperature were allowed to react for 24 h in an inert atmosphere. After completion of the reactions, the unreacted [Pt^{IV}] was assayed spectrophotometrically. Results indicated that one mole of the amino acid consumed one mole of Pt^{IV} in the predominant reaction, as represented in the following stoichiometric equation:

The product aldehyde, indole-3-acetaldehyde, is tested by thin layer chromatography. One spot is obtained when the chromatogram is assayed with 2,4-dinitrophenylhydrazine. An aliquot (5 ml) is pipetted into 50 ml of 2.0 N HCl saturated with 2,4-dinitrophenylhydrazine, which is filtered, washed, dried and weighed. The product 2,4-dinitrophenyl-hydrazone was formed. Further proof of the formation of the aldehyde is obtained by isolating the aldehyde using the standard method [27]. The byproducts are identified as ammonia and carbon dioxide by Nessler's reagent [28] and lime water, respectively. Similar oxidation products with different experimental conditions have been reported earlier [7-9]. On the other hand, formation of [Pt^{II}Cl$_4$]$^{2-}$ was confirmed [29] by the observed black precipitate of platinum(II) hydroxide on addition of alkali to the reaction mixture, according to the reaction,

$$[PtCl_4]^{2-} + 2OH^- = Pt(OH)_2 + 4Cl^-$$
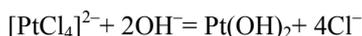
3.2. Effect of [Platinum(IV)] on the Oxidation Rate

The concentration of the oxidant, platinum(IV), was varied in the range of 2.0×10^{-5} to 14.0×10^{-5} mol dm^{-3} at constant [Trp], [Ag^I], [H$^+$], ionic strength and temperature. The non-variation in the observed first order rate constants at various concentrations of Pt^{IV} (Table 1) indicates that the order with respect to the oxidant is confirmed to be one.

Table 1. *Effect of variation of [Pt^{IV}], [Trp], [H$^+$], [Ag^I] and ionic strength, I, on the observed first order rate constant (k$_C$) in the silver(I)-catalyzed oxidation of tryptophan by platinum(IV) in perchlorate solutions at 25°C.*

10^5 [Pt^{IV}](mol dm^{-3})	10^3 [Trp](mol dm^{-3})	[H$^+$](mol dm^{-3})	10^5 [Ag^I](mol dm^{-3})	I(mol dm^{-3})	$10^5 k_C$(s^{-1})
2.0	4.0	1.0	1.0	2.0	33.1
4.0	4.0	1.0	1.0	2.0	33.9
6.0	4.0	1.0	1.0	2.0	34.3
8.0	4.0	1.0	1.0	2.0	33.2
10.0	4.0	1.0	1.0	2.0	32.7
12.0	4.0	1.0	1.0	2.0	31.9
14.0	4.0	1.0	1.0	2.0	33.4
8.0	1.0	1.0	1.0	2.0	16.3
8.0	2.0	1.0	1.0	2.0	23.1
8.0	4.0	1.0	1.0	2.0	33.2
8.0	6.0	1.0	1.0	2.0	42.0
8.0	8.0	1.0	1.0	2.0	49.8
8.0	10.0	1.0	1.0	2.0	56.2
8.0	12.0	1.0	1.0	2.0	63.9
8.0	4.0	0.4	1.0	2.0	19.2
8.0	4.0	0.6	1.0	2.0	24.1
8.0	4.0	0.8	1.0	2.0	28.8
8.0	4.0	1.0	1.0	2.0	33.2
8.0	4.0	1.3	1.0	2.0	40.2
8.0	4.0	1.6	1.0	2.0	46.7
8.0	4.0	2.0	1.0	2.0	52.4
8.0	4.0	1.0	0.2	2.0	7.8
8.0	4.0	1.0	0.5	2.0	17.4
8.0	4.0	1.0	1.0	2.0	33.2
8.0	4.0	1.0	1.5	2.0	46.2
8.0	4.0	1.0	2.0	2.0	59.8
8.0	4.0	1.0	2.5	2.0	60.7
8.0	4.0	1.0	3.0	2.0	81.0
8.0	4.0	1.0	1.0	2.0	33.2
8.0	4.0	1.0	1.0	2.4	30.7
8.0	4.0	1.0	1.0	2.8	28.4
8.0	4.0	1.0	1.0	3.2	25.0
8.0	4.0	1.0	1.0	3.6	22.7
8.0	4.0	1.0	1.0	4.0	19.2
8.0	4.0	1.0	1.0	4.5	17.8

Experimental Error ± 3%

3.3. Effect of [Tryptophan] on the Oxidation Rate

The observed first order rate constant (k_C) was determined at different initial concentrations of the reductant tryptophan keeping all other reactants concentration constant including sliver(I) catalyst. The results showed that the rate constant increased with increase in the tryptophan concentration as

listed in Table 1. A plot of k_C versus [Trp] was found to be linear with a positive intercept confirming fractional-first order dependence with respect to the amino acid (Figure not shown).

3.4. Effect of [H$^+$] on the Oxidation Rate

The reaction rate was measured at constant [Trp], [Pt^{IV}], [Ag^I], ionic strength and temperature but with various [H$^+$] (0.4 – 2.0 mol dm^{-3}). The rate of reaction was found to increase as [H$^+$] increased with less than unit order as found from the plot of log k_C versus log [H$^+$] (Figure not shown).

3.5. Effect of [Ag^I] Catalyst

The reaction rate was measured with various [Ag^I], (0.2–3.0) $\times 10^{-5}$ moldm^{-3} at constant other variables. The reaction rate increased with increase in [Ag^I] (Table 1). The order with respect to [Ag^I] was unity as found from the plot of log k_C versus log [Ag^I] (Figure 2).
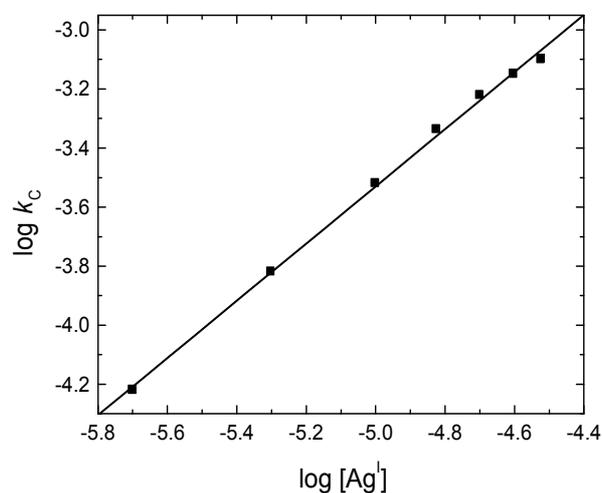
Figure 2. *Plot of log k$_C$ versus log [Ag^I] in the silver(I)-catalyzed oxidation of tryptophan by platinum(IV) in perchlorate solutions. [Trp] = 4.0 × 10^{-3}, [Pt^{IV}] = 8.0 × 10^{-5}, [H$^+$] = 1.0 and I = 2.0 moldm^{-3} at 25°C.*
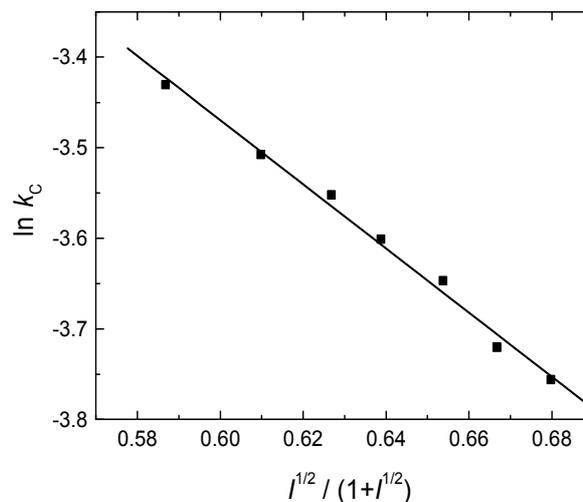

Figure 3. *Debye–Hückel plots in the silver(I)-catalyzed oxidation of tryptophan by platinum(IV) in perchlorate solutions. [Trp] = 4.0 × 10^{-3}, [Pt^{IV}] = 8.0 × 10^{-5} and [H$^+$] = 1.0 moldm^{-3} at 25°C.*

3.6. Effect of Ionic Strength and Dielectric Constant

The effect of ionic strength on the oxidation rate was studied by the addition of sodium perchlorate to the reaction medium at constant concentration of tryptophan, Pt^{IV} and Ag^{I}, and at constant pH and temperature. The results are presented in Table 1. These results showed that the rate constant decreased with increase in the ionic strength of the medium, and the Debye–Hückel plot was found to be linear with a negative slope as shown in Figure 3.

In order to determine the effect of the dielectric constant (D) of the medium on the oxidation rate, the oxidation of tryptophan by Pt^{IV} was studied at different solvent compositions (v/v) of acetic acid and water. The dielectric constant of the medium at different compositions was calculated using the dielectric constants of water and acetic acid as 78.5 and 6.15, respectively, at 25°C. The rate constant was found to increase with the decrease in dielectric constant of the solvent mixture, i.e., increase in acetic acid content. The plot of log k_C versus $1/D$ was found to be linear with a positive slope as shown in Figure 4.
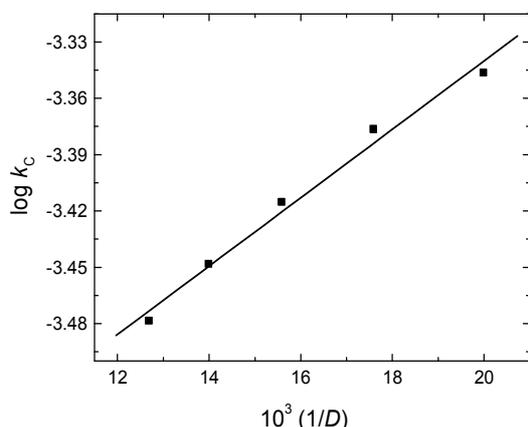
Figure 4. *Effect of solvent composition on the observed first order rate constant. Plot of log k_C versus $1/D$ for the silver(I)-catalyzed oxidation of tryptophan by platinum(IV) in perchlorate solutions. [Trp] = 4.0 × 10⁻³, [Pt^{IV}] = 8.0× 10⁻⁵, [H⁺] = 1.0 and I = 2.0 moldm⁻³ at 25°C.*

4. Discussion

Amino acids are known [30] to exist in zwitterionic forms in equilibrium with anionic and cationic forms, depending upon pH of the solution according to the following equilibria:
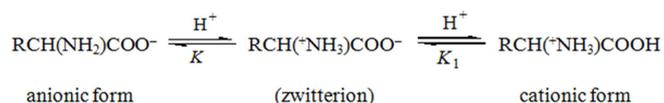
where K_1 is the protonation constant of the amino acid.

Under the present experimental conditions and the observed enhancement of the reaction rate upon increasing acid concentration, the protonated form of the amino acid may be the reactive species in the rate-determining step, which plays the main role in the reaction kinetics. On the other hand, amino acids form an adduct with Ag^{I} catalyst [12, 13, 16] owing to the availability of the electron pairs on both

oxygen atom of the carboxylate group and nitrogen atom of the amine group. Within the protolytic amino acid system, the carboxylate and amine groups may act as nucleophiles, depending on pH of the medium. The protolyticgroup with the highest basicity interacts with the silver(I) catalyst. Thus, at low pH where the amine group is protonated, the carboxylate group should be able to attack Ag^{I}.

It is also reported [31] that the platinum(IV) species in acid medium is present as $[PtCl_6]^{2-}$, which is assumed to be the principal reactive oxidant. The reduction of $[PtCl_6]^{2-}$ generally proceeds as follows:

$$[PtCl_6]^{2-} + 2e^- = [PtCl_4]^{2-} + 2Cl^-$$
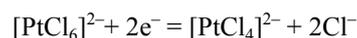
In this reduction process, octahedral Pt^{IV} is reduced to square planar Pt^{II} with release of two Cl^- ions. Therefore, this reaction is better classified as a reductive–elimination reaction [32, 33]. Because platinum(IV) complexes are generally substitution-inert [34], initial complex formation between platinum(IV) and reductant prior to electron transfer can be excluded in reductive–elimination reactions.

Two alternative reaction mechanisms for the oxidation of amino acids by platinum(IV) may be considered. The first mechanism involves a simultaneous two-electron transfer in a single step. The second mechanism involves two successive one-electron transfer steps. If the transition states of the reductant and/or oxidant are unstable, a simultaneous two-electron transfer mechanism may be suggested, such as that in the oxidation of uranium(IV) by $[PtCl_6]^{2-}$ [35]. In the present study, addition of acrylonitrile monomer to the reaction mixture failed to give polymerized products. It may be that a free radical such as the Pt^{III} species is too short-lived to interact with acrylonitrile to give the polymerized product under our experimental conditions. Consequently, the two-electron transfer mechanism seems plausible.

Reaction Mechanism

The reaction between platinum(IV) and tryptophan in the presence of small amounts of silver(I) catalyst has a stoichiometry of 1:1 with a first order dependence on both $[Pt^{IV}]$ and $[Ag^{I}]$, and less than unit order with respect to [Trp]. The rate of reduction of platinum(IV) increases with decreasing pH with fractional-first order dependence on [H⁺], suggesting that amino acid substrate is first subjected to protonation in a prior rate-determining step. The rate of reaction decreased on increasing the ionic strength and dielectric constant of the medium, suggesting that the reaction occurred between two ions with opposite charges [36-39].

The less than unit order with respect to [Trp] suggests formation of an intermediate complex between the catalyst silver(I) and amino acid substrate prior to the reaction with the oxidant. Complex formation was proved kinetically by a non-zero intercept of the plot of $[Ag^{I}]$ / k_C versus $1/[Trp]$ (Figure 5). Spectroscopic evidence to support complex formation between Ag^{I} and tryptophan which obtained from the UV-Vis spectra of platinum(IV) is the observed hypochromic shift in the wavelength with appearance of two isosbestic points as shown in Figure 1.

The experimental results suggested that the protonated amino acid combines with Ag^I to form an intermediate complex, $[Trp–Ag]^{2+}$ (C), which then reacts in a slow step with one mole of platinum(IV) to give rise to the products with regeneration of the catalyst Ag^I, as illustrated by the following sequence:

$$(1)$$

$$(2)$$

$$(3)$$

$$(4)$$

$$(5)$$
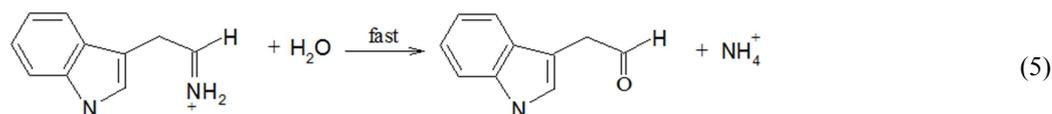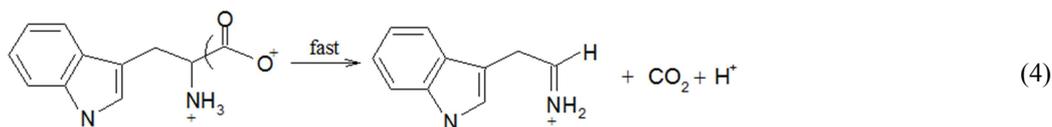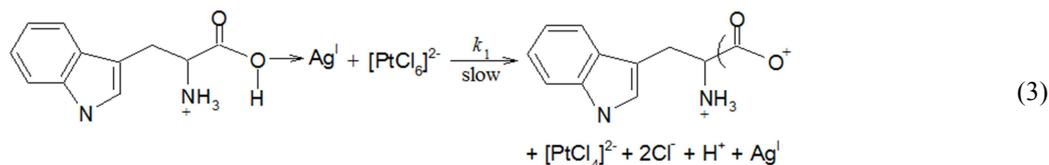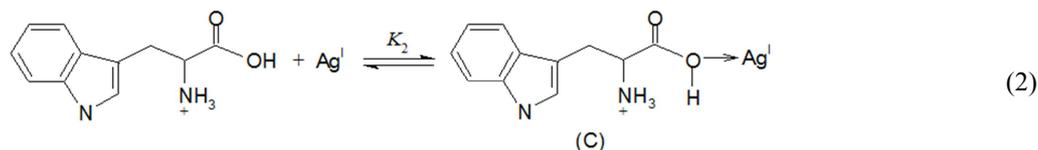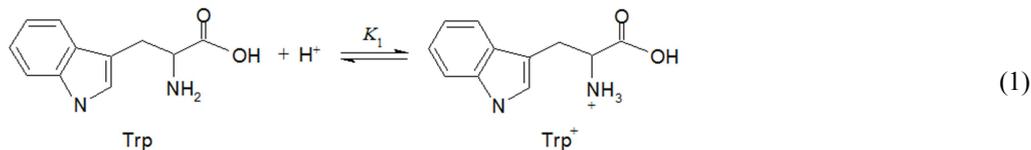
The suggested mechanism leads to the following rate law:

$$\text{Rate} = \frac{-d[Pt^{IV}]}{dt} = \frac{+d[C]}{dt} = k_1[C][Pt^{IV}] \qquad (6)$$

The relationship between the rate of complex formation and the substrate, hydrogen ion, catalyst and oxidant concentrations can be deduced to give the following rate-law expression:

$$\text{Rate} = \frac{k_1 K_1 K_2 [Trp][H^+][Ag^I][Pt^{IV}]}{(1 + K_1[H^+] + K_1 K_2[H^+][Ag^I])(1 + K_1 K_2[Trp][H^+])} \qquad (7)$$

In view of low concentration of $[Ag^I]$ used, the term $K_1 K_2[H^+][Ag^I]$ in the denominator can be neglected. Therefore, Eq. (7) becomes,

$$\text{Rate} = \frac{k_1 K_1 K_2 [Trp][H^+][Ag^I][Pt^{IV}]}{(1 + K_1[H^+])(1 + K_1 K_2[Trp][H^+])} \qquad (8)$$

Under pseudo-first order condition,

$$\text{Rate} = \frac{-d[Pt^{IV}]}{dt} = k_C[Pt^{IV}] \qquad (9)$$

Comparing Eqs. (8) and (9) and rearrangement, we obtain,

$$\frac{[Ag^I]}{k_C} = \left(\frac{1 + K_1[H^+]}{k_1 K_1 K_2[H^+]} \right) \frac{1}{[Trp]} + K' \qquad (10)$$

where, $K' = (1 + K_1[H^+]) / k_1$.

According to Eq. (10), the plots of $[Ag^I]/k_C$ against $1/[Trp]$, at constant $[H^+]$, and $[Ag^I]/k_C$ against $1/[H^+]$, at constant $[Trp]$, should be linear with positive intercepts on $[Ag^I]/k_C$ axes. The experimental results satisfied this requirement as shown in Figure 5.
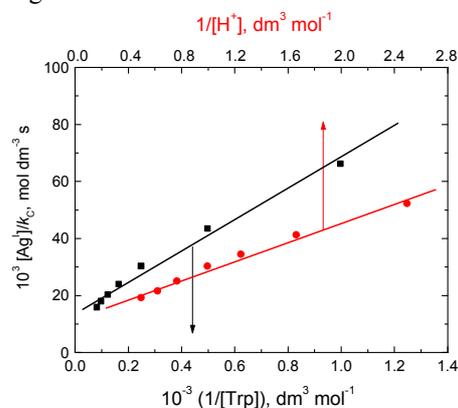

Figure 5. *Verification of the rate law (8) in the form of equation (10) in the silver(I)-catalyzed oxidation of tryptophan by platinum(IV) in perchlorate solutions. $[Pt^{IV}] = 8.0 \times 10^{-5}$ and $I = 2.0$ mol dm^{-3} at 25°C.*

5. Conclusion

The reaction between tryptophan and platinum(IV) in perchlorate solutions did not proceed in the absence of the catalyst. The suggested mechanism for oxidation involves formation of a silver(I)-tryptophan intermediate complex in a pre-equilibrium step, which reacts with the oxidant by an inner-sphere mechanism leading to decomposition of the complex in the rate-determining step. The final oxidation products of tryptophan were identified as indole-3-acetaldehyde, ammonium ion and carbon dioxide.

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