



Kinetics and Mechanism of Reaction of cis -[Cr(C₂O₄)₂(H₂O)₂]⁻ with L-Dopa in Aqueous Medium: A Comparative Antiparkinsonian Studies

SUDHANSHU SEKHAR ROUT^{1,*}, DURGA MADHAB KAR¹, SOVAN PATTANAIK¹, SUDAM CHANDRA SI¹ and PRAKASH MOHANTY²

¹School of Pharmaceutical Sciences, Siksha 'O' Anusandhan University, Bhubaneswar-751 030, India

²Department of Chemistry, Ravenshaw University, Cuttack-753 003, India

*Corresponding author: E-mail: sudhanshurout@soauniversity.ac.in

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The substitution reaction of cis -[Cr(C₂O₄)₂(H₂O)₂]⁻ with L-Dopa in aqueous medium has been studied over the range 35 ≤ t ≤ 50 °C, 3.5 ≤ pH ≤ 6.0, 5.0 × 10⁻³ mol dm⁻³ ≤ [L-Dopa] ≤ 15 × 10⁻³ mol dm⁻³, I = 0.1 mol dm⁻³ (KNO₃). The reaction takes place *via* an outer sphere association between cis -[Cr(C₂O₄)₂(H₂O)₂]⁻ and L-Dopa followed by chelation. Characterization of the product was done by physico-chemical and infrared spectroscopic methods. The antiparkinsonian activity of L-Dopa was found to be less than that of the product chromium(III) complex.

Keywords: Kinetics and mechanism, Substitution, *cis*-Diaqua-bis(oxalato)chromate(III), L-Dopa, Antiparkinsonian drug.

INTRODUCTION

Parkinson disease is considered as the second most common neurodegenerative disorder [1]. The role of dopamine and its analogs in brain is significant and unquestionable. Dopamine is an important neurotransmitter and its deficiency is considered as a principal factor responsible for behavioural changes in neuro-disorder like Parkinson's disease. Levodopa [(*-*)-3-(3,4-dihydroxy)phenylalanine] is a precursor of both dopamine and norepinephrine in their biosynthetic pathways. These neurotransmitters and their derivatives regulate a variety of physiological functions in the human body. It has two binding sites, a catecholic and an alanine site [2].

According to several epidemiological studies some recent evidence indicates that there is a potential link between elevated blood sugar and neurodegeneration. Diabetic patients suffer from a variety of neurological disorders including dementia and peripheral neuropathy. In addition, patients with diabetes mellitus have a 36 % increased risk of developing Parkinson's disease. In light of recent findings, a hypothesis has emerged that suggests that mitochondrial dysfunction, endoplasmic reticulum stress, inflammation and alteration in metabolism may lead to insulin resistance and finally to diabetes and/or neurodegeneration. Especially in elderly population the increase in type 2 diabetes is expected to lead to a concomitant increase in neurodegeneration. Although the exact mechanisms that explain the coexistence of diabetes and Parkinson's disease

remain unknown, several studies have revealed potential mechanisms underlying this association [3]. Previous research has suggested that chromium in its trivalent form (Cr³⁺) is involved in the regulation of carbohydrate metabolism *via* an enhancement of insulin action [4]. Recent finding show that drugs to treat diabetic patients may elicit therapeutic effect in patients with Parkinson's disease [5]. It has been reported that metal chelators have an ability to reduce the symptoms of Parkinson [6]. Levodopa is the most commonly used antiparkinsonian drug. It may act as a chelator for chromium and is present in the different medications for clinical management of Parkinson disease. Hence, a cis -[Cr(C₂O₄)₂(H₂O)₂]⁻ complex of levodopa might act as a potentially antiparkinsonian agent. In the present study chelation ability of levodopa towards chromium ion has been explored. The studies on antiparkinsonian activity due to Cr(H₂O)₆³⁺ - L-Dopa complex was the first study of its kind reported from our laboratory [7].

The substitution reactions of cis -[Cr(C₂O₄)₂(OH)₂]⁻ [8-10] in aqueous medium have attracted continued attention because of the significant biological importance of chromium(III). The kinetics and mechanism of the substitution reactions of [Cr(H₂O)₆]³⁺ with various amino acids have been reported [11-24]. Recently the reaction between Cr(H₂O)₆³⁺ with 1,3-propanediamine-N,N-diacetate-N,N'-di-3-propionate has been reported [25]. These reactions generally take place at the metal center *via* a transition state showing a greater degree of bond formation with the incoming ligand than that of bond breaking

with the leaving ligand [26]. The current work describes the reaction of *cis*-[Cr(C₂O₄)₂(OH₂)₂]⁻ with L-Dopa [(*-*)-3-(3,4-dihydroxy)phenylalanine]. The aim of the study is to explore whether the reaction product show any antiparkinsonian activity or not. The negative $\Delta S^\ddagger$ (-68.6 JK⁻¹ mol⁻¹) and higher $10^4 k_{an}$ (50 °C) = 2.75 s⁻¹ with respect to $10^6 k_{ex}$ (25 °C) = 2.40 s⁻¹ supports I_a mechanism for the substitution reaction.

EXPERIMENTAL

K[Cr(C₂O₄)₂(H₂O)₂].3H₂O was prepared as described as reported [27]. An accurate amount of K[Cr(C₂O₄)₂(H₂O)₂].3H₂O was completely dissolved in a definite volume of water. The chromium(III) concentration was determined by iodometric method and AAS. A.R grade L-Dopa was collected from Dr Reddy's Laboratories, Hyderabad, India and used without further purification. Doubly distilled water was used throughout the reaction. pH of the solution was maintained using a SYSTRONICS digital pH meter 335 equipped with a combination of glass Ag/AgCl/Cl⁻ (3 mol dm⁻³ NaCl) electrode. It was calibrated with standard buffers of pH 4.0, 7.0 and 9.0 (Merck). Absorbances were recorded with a JASCO V-630 uv-visible spectrophotometer. 10 mm Quartz cuvettes were used. The IR spectra were taken with a JASCO FT-IR-4100 spectrophotometer.

Antiparkinsonian study

Acute haloperidol induced catalepsy test: The catalepsy test was performed as per the reported method [28]. The adult healthy mice of either sex were divided into eight groups of six animals each. Group I animals served as normal control group. Group II received solvent and served as solvent control group; group III-V received L-Dopa at dose level of (50, 100 and 200 mg/kg respectively p.o.) and group VI-VIII received *cis*-[Cr(C₂O₄)₂(OH₂)₂]⁻-L-Dopa complex at dose level of (50, 100 and 200 mg/kg respectively p.o.), 60 min after pretreatment with haloperidol (1 mg/kg i.p.). The duration of catalepsy was measured at 15, 30, 60, 90 and 120 min. using the bar test.

The catalepsy was assessed as the time during which the mouse maintained an imposed position with both forelimb extended and rested on a 4 cm high wooden bar (1 cm in diameter). The end point of catalepsy was considered to occur when both fore paws were removed from the bar or if the animal moved its head in an exploratory manner. A cut-off time of 300 s was applied. Between the 2 determinations, the animals were returned to their home cage. All the observations were made in a quiet room at 23-25 °C.

As per the scoring method, if the animal maintained the imposed posture for at least 20 s, it was considered to be cataleptic and the time was recorded in seconds.

Chronic haloperidol induced catalepsy test: Solvent (10 mL/kg p.o.), L-Dopa (50, 100 and 200 mg/kg p.o.) and *cis*-[Cr(C₂O₄)₂(OH₂)₂]⁻-L-Dopa complex (50, 100 and 200 mg/kg p.o.) were administered daily for 1 h prior to intraperitoneal injection of haloperidol (1 mg/kg) for 21 days. Catalepsy test was carried out on days 5, 9, 13, 17 and 21. The catalepsy was measured by the scoring method, if the animal maintained the imposed posture for at least 22 s, it was considered to be cataleptic and the time was recorded in seconds.

The experimental protocol (Approval No. 09/09/IAEC/SOAU) was approved by the Institutional Animal Ethics Committee (IAEC), SOA University (Regd. No. 1171/C/08/CPCSEA).

Kinetic measurements: Potassium nitrate solution was used to maintain ionic strength of the solution. The solution of L-Dopa at the desired pH was thermally equilibrated at a given temperature. Then, the required amount of thermally equilibrated chromium(III) oxalato complex solution was added to the L-Dopa solution and the change in absorbance was monitored at 413 nm. Pseudo-first-order conditions were maintained throughout these experiments by using a large excess of L-Dopa. [Chromium(III)]:[L-Dopa] was 1:15, 1:12.5, 1:10, 1:7.5, 1:5. The rate constant k_{obs} were obtained from the slopes of $\ln(A_\infty - A_t)$ versus time plot;

$$\ln(A_\infty - A_t) = \ln(A_\infty - A_0) - k_{obs}t$$

where A_0 , A_t , A_∞ are the absorbances of the solution at the beginning, at time t and at equilibrium respectively. The reported rate data are an average of duplicate runs and were reproducible to within ± 3 %. The correlation coefficients of plots used to determine k_{obs} were found to be 0.98 in most cases.

RESULTS AND DISCUSSION

Substitution products and stoichiometry: Addition of acidic solution of K[Cr(C₂O₄)₂(H₂O)₂].3H₂O to a solution of L-Dopa resulted in an increase in absorbance in the visible range. The absorption spectra of mixture of chromium(III) oxalato complex and L-Dopa indicate the formation of a new complex (Fig. 1), due to the blue shift of λ_{max} from 472 to 413 nm. The jobs plot indicates the formation of a 1:1 metal ligand complex. The tentative structure of the product is shown in Fig. 2.

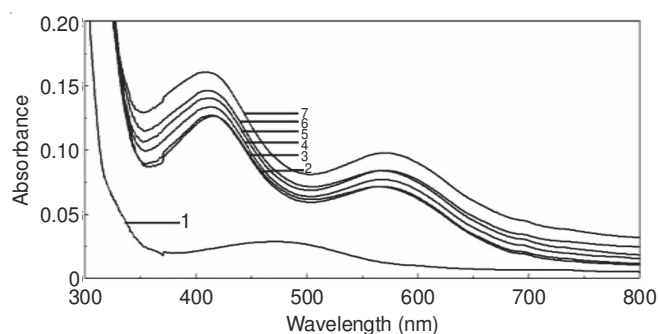


Fig. 1. An overlay scanning plot of Cr(III) + L-Dopa at different time intervals. 1. [L-Dopa] = 1×10^{-3} mol dm⁻³ 2. [Cr(III)]_T = 1×10^{-3} mol dm⁻³, [L-Dopa] = 5×10^{-3} mol dm⁻³, mole ratio = 1:5, pH = 5.3, I = 0.1 mol dm⁻³, 10 min after mixing. 3. After 20 min 4. After 30 min 5. After 40 min 6. After 50 min 7. After 60 min

Effect of variables on the reaction rate: The reaction was studied at varying pH (3.5-6.0), keeping I = 0.1 mol dm⁻³ and *cis*-[Cr(C₂O₄)₂(OH₂)₂]⁻ = 1.0×10^{-3} mol dm⁻³ at 50 °C. With the decrease in [H⁺], the k_{obs} values increased (Table-1). To explain the [H⁺] dependence on the reaction rate, it is necessary to consider the protonation equilibria of L-Dopa, as shown in Scheme-I.

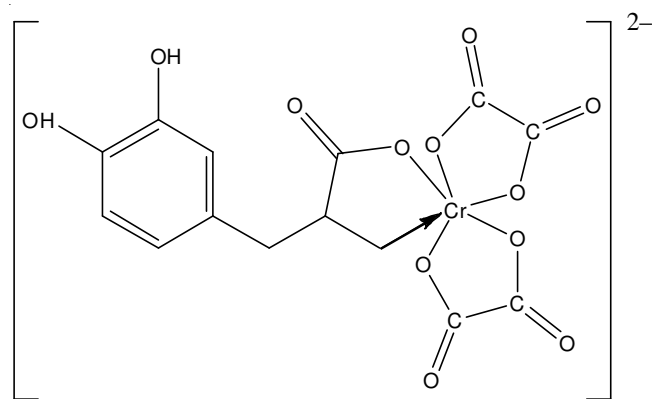
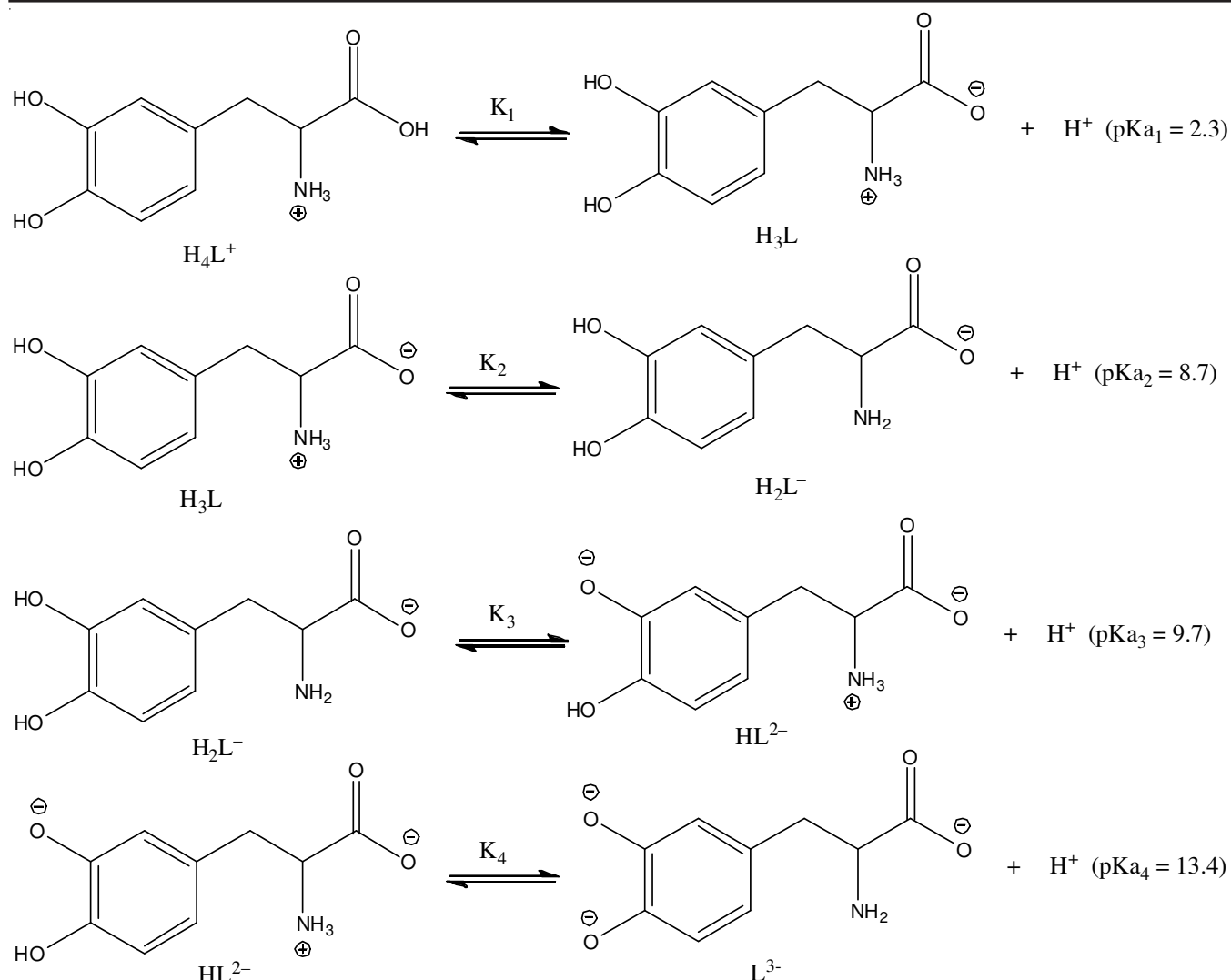


Fig. 2. Tentative structure of chromium(III) product complex

When pH is varied from 3.5 to 6.0, the most active species involved in the substitution reaction is likely to be [H₃L] (**Scheme-I**). The K_1 , K_2 , K_3 and K_4 values [29] of L-Dopa at 25 °C are 5.01×10^{-3} , 2×10^{-9} , 2×10^{-10} , 3.98×10^{-14} , respectively. The hydrolysis constant K_H at 25 °C for *cis*-[Cr(C₂O₄)₂(H₂O)₂]⁻ is 1.94×10^{-8} [30]. Hence the amount of *cis*-[Cr(C₂O₄)₂(H₂O)(OH)]²⁻ will be negligibly small at pH 3.5.

[L-Dopa]_T dependence on the rate was studied at fixed [H⁺] and at 50 °C. [L-Dopa]_T was varied from 5×10^{-3} to 15×10^{-3} mol dm⁻³ at constant [*cis*-[Cr(C₂O₄)₂(OH₂)₂]] = 1.0×10^{-3} mol dm⁻³. As [L-Dopa]_T was increased, k_{obs} increased in a nonlinear fashion, indicating outer sphere complex formation between *cis*-[Cr(C₂O₄)₂(OH₂)₂]⁻ and L-Dopa (Fig. 3). The order of the reaction with respect to [L-Dopa] is unity up to 7.5×10^{-3} and at higher [L-Dopa]_T the order is fractional. A Michaelis-Menton type plot (Fig. 3) also indicates complex formation between *cis*-[Cr(C₂O₄)₂(OH₂)₂]⁻ and L-Dopa.

To study the effect variation of concentration of chromium(III) complexes, *cis*-[Cr(C₂O₄)₂(OH₂)₂]_T was varied at constant concentration of L-Dopa. The pseudo-first order rate constant remain almost constant, giving $10^5 k_{\text{obs}} = (14.7 \pm 0.1)$ s⁻¹ when [*cis*-[Cr(C₂O₄)₂(OH₂)₂]] was varied from 0.001 to 0.003 mol dm⁻³. The independence of k_{obs} at 50 °C under the conditions [L-Dopa]_T = 15.0×10^{-3} mol dm⁻³, $I = 0.1$ mol dm⁻³ and pH = 3.5 is in agreement with first-order dependence of rate on [*cis*-[Cr(C₂O₄)₂(OH₂)₂]]_T.

The substitution reaction of *cis*-[Cr(C₂O₄)₂(H₂O)₂]⁻ with L-Dopa has been carried out at four different temperatures from 35 to 50 °C at different pH range from 3.5 to 6.0. The values of k_{obs} were found to increase by increasing temperature.

TABLE-1
RATE CONSTANTS FOR SUBSTITUTION OF L-Dopa
IN $cis-[Cr(C_2O_4)_2(H_2O)_2]^-$ AT 50 °C, $I = 0.1 \text{ mol dm}^{-3}$
AND $[cis-[Cr(C_2O_4)_2(H_2O)_2]^-] = 1.0 \times 10^{-3} \text{ mol dm}^{-3}$

pH	$10^3 [L-Dopa]_T$ (mol dm ⁻³)	$10^5 k_{obs} \text{ (s}^{-1}\text{)}$			
		35 °C	40 °C	45 °C	50 °C
3.50	5.0	6.03	7.12	8.17	8.60
	7.5	6.70	8.22	9.58	10.30
	10.0	7.19	9.15	10.78	11.62
	12.5	7.61	9.86	11.97	12.86
	15.0	7.79	10.31	12.61	13.96
4.00	5.0	6.61	7.71	9.34	9.80
	7.5	7.31	8.94	10.93	11.80
	10.0	7.81	9.88	12.12	13.33
	12.5	8.25	10.50	13.40	14.79
	15.0	8.59	10.89	14.05	16.09
4.50	5.0	7.15	8.28	10.30	11.10
	7.5	7.86	9.56	12.29	13.51
	10.0	8.54	10.60	13.50	15.15
	12.5	9.01	11.21	15.03	16.86
	15.0	9.44	11.66	15.80	18.36
5.30	5.0	7.98	9.24	12.12	13.30
	7.5	8.70	10.53	14.38	15.80
	10.0	9.41	11.50	15.40	18.18
	12.5	9.88	12.05	17.02	20.12
	15.0	10.29	12.43	17.72	21.93
6.00	5.0	8.70	10.13	14.20	15.20
	7.5	9.61	11.42	16.27	18.10
	10.0	10.20	12.36	17.10	21.30
	12.5	10.73	12.85	18.50	23.69
	15.0	11.16	13.18	18.95	25.98

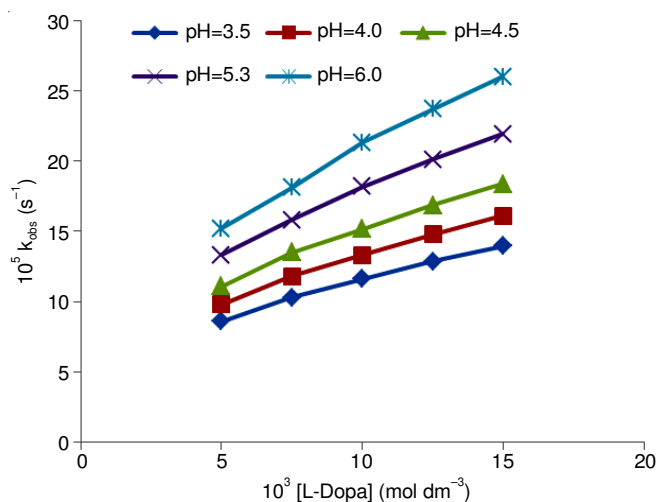
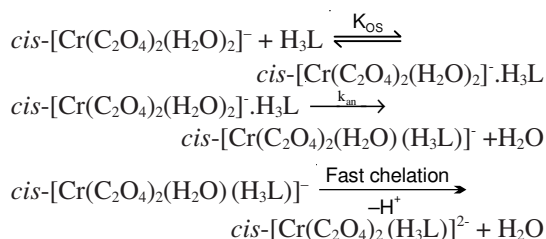


Fig. 3. Plot of $10^5 k_{obs}/s^{-1}$ versus $10^3 [H_4L^+]_T/\text{mol dm}^{-3}$ at different pH $[cis-[Cr(C_2O_4)_2(H_2O)_2]^-]_T = 1.0 \times 10^{-3} \text{ mol dm}^{-3}$, $I = 0.1 \text{ mol/dm}^{-3}$ (KNO₃), Temp. = 50 °C pH is varied from 3.5 to 6.0

The reaction sequence delineated below (**Scheme-II**) is consistent with the experimental data.



Scheme-II: Mechanism of reaction between $[Cr(III) \text{ complex}]$ and L-Dopa

The rate law for the substitution reaction can be derived in the following manner

$$\text{Rate} = k_{an} [O.S]_e = k_{an} K_{OS} [Cr(III) \text{ complex}]_e [H_3L]_e \quad (1)$$

$$= k_{an} K_{OS} K_1 [Cr(III) \text{ complex}]_e [H_4L^+]_e / [H^+] \quad (2)$$

$$\begin{aligned}
 [Cr(III) \text{ complex}]_T &= [Cr(III) \text{ complex}]_e + [O.S] \\
 &= [Cr(III) \text{ complex}]_e \{ [H^+] + K_{OS} K_1 [H_4L^+]_e \} / [H^+] \\
 [Cr(III) \text{ complex}]_e &= [Cr(III) \text{ complex}]_T [H^+] / \{ [H^+] + K_{OS} K_1 [H_4L^+]_e \} \quad (3)
 \end{aligned}$$

$$\begin{aligned}
 [H_4L^+]_T &= [H_4L^+]_e + [H_3L]_e \\
 &= [H_4L^+]_e + K_1 [H_4L^+]_e / [H^+] \\
 &= [H_4L^+]_e \{ ([H^+] + K_1) / [H^+] \} \quad (4)
 \end{aligned}$$

$$[H_4L^+]_e = [H_4L^+]_T [H^+] / \{ [H^+] + K_1 \}$$

Substituting the value of $[Cr(III) \text{ complex}]_e$ and $[H_4L^+]_e$ in eqn. 2, we get:

$$\text{Rate} = \frac{k_{an} K_{OS} K_1 [Cr(III) \text{ complex}]_T [H_4L^+]_T [H^+]}{[H^+]^2 + K_1 [H^+] + K_{OS} K_1 [H_4L^+]_T [H^+]} \quad (5)$$

$$= \frac{k_{an} K_{OS} K_1 [Cr(III) \text{ complex}]_T [H_4L^+]_T}{[H^+] + K_1 + K_{OS} K_1 [H_4L^+]_T}$$

Since we know that

$$\text{Rate} = k_{obs} [Cr(III) \text{ complex}]_T$$

$$k_{obs} = \frac{k_{an} K_{OS} K_1 [H_4L^+]_T}{\{ [H^+] + K_1 \} + K_{OS} K_1 [H_4L^+]_T} \quad (6)$$

$$1/k_{obs} = 1/k_{an} + \{ [H^+] + K_1 \} / \{ (k_{an} K_{OS} K_1) \times [H_4L^+]_T \} \quad (7)$$

where, O.S = outer sphere complex; K_{OS} = outer sphere complex formation constant.

The above mentioned rate law was tested by plotting k_{obs}^{-1} versus $[L-Dopa]^{-1}_T$. The plots (Fig. 4) are linear with $R^2 = 0.98$ for the anation reaction at all pH values from 3.5 to 6.0 at 50 °C. The value of k_{an} was calculated from the reciprocal of the intercept and K_{OS} (the outer sphere association constant) was calculated from the slope of the plot. k_{an} and K_{OS} are collected in Table-2. It is generally accepted that complex formation proceeds by a mechanism in which the rate determining step is the change from an outer sphere to an inner sphere complex. The value for k_{an} at 50 °C is $2.75 \times 10^{-4} \text{ s}^{-1}$. The far greater value of k_{an} compared to that of k_{ex} (2.40×10^{-6}) (25 °C) [32] supports the fact that the anation follows an I_a mechanism.

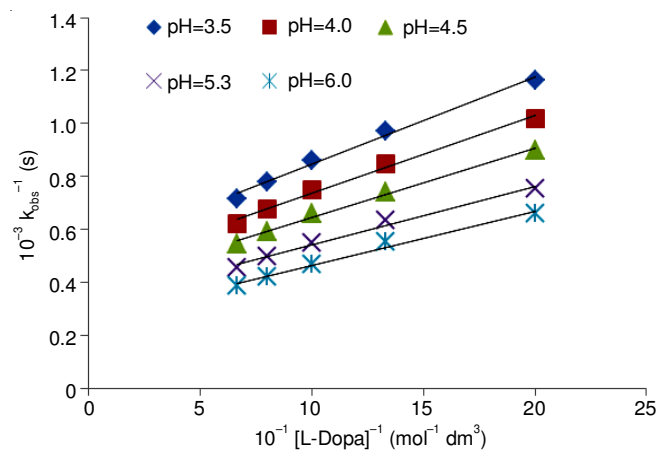


Fig. 4. Plot of $10^4 k_{obs}^{-1}/s$ versus $10^{-1} [H_4L^+]_T^{-1}/\text{mol}^{-1} \text{ dm}^3$ at different pH $[cis-[Cr(C_2O_4)_2(H_2O)_2]^-]_T = 1.0 \times 10^{-3} \text{ mol dm}^{-3}$, $I = 0.1 \text{ mol/dm}^{-3}$ (KNO₃), Temp. = 50 °C pH is varied from 3.5 to 6.0

TABLE-2
COMPARISON OF ANATION RATE CONSTANTS (k_{an}), OUTER SPHERE COMPLEX FORMATION
CONSTANTS (K_{OS}) AND ACTIVATION PARAMETERS FOR THE SUBSTITUTION REACTION OF
cis-DIAQUA-BIS(OXALATO)CHROMATE(III) WITH OTHER AQUA Cr(III) SYSTEMS

Systems (metal center/nucleophile)	k_{an} (s ⁻¹)	K_{OS}	$\Delta H^\ddagger$ (kJ mol ⁻¹)	$\Delta S^\ddagger$ (J K ⁻¹ mol ⁻¹)	Ref.
Cr(H ₂ O) ₆ ³⁺ /H ₂ O*	2.40×10^{-6} (25 °C)	-	108.6	11.6	[31]
Cr(H ₂ O) ₆ ³⁺ /gly	$(3.34-6.8) \times 10^{-6}$ (25 °C)	-	51.9	-42.7	[32]
Cr(H ₂ O) ₆ ³⁺ /ala	0.58×10^{-4} (35 °C)	-	64.9	-113.6	[15,16,18,33]
Cr(H ₂ O) ₆ ³⁺ /val	2.34×10^{-4} (25 °C)	3.29 ± 0.1	90.4	-21.0	[15,16,18,33]
Cr(H ₂ O) ₆ ³⁺ /L-ornithine	1.70×10^{-6} (40 °C)	18.9	55.8	-138 ± 17	[34,35]
Cr(H ₂ O) ₆ ³⁺ /hydroxyproline	1.00×10^{-4} (40 °C)	-	72.9	-98.2	[15,16,18,33]
Cr(H ₂ O) ₆ ³⁺ /tryptophan	1.17×10^{-4} (40 °C)	-	65.6	-112.4	[15,16,18,33]
Cr(H ₂ O) ₆ ³⁺ /methionine	2.22×10^{-4} (35 °C)	-	61.1	-116.3	[15,16,18,33]
Cr(H ₂ O) ₆ ³⁺ /glutamine	1.81×10^{-4} (40 °C)	-	52.0	-150.6	[15,16,18,33]
Cr(H ₂ O) ₆ ³⁺ /pyc-3	10.24×10^{-4} (35 °C)	5.42	-	-	[36]
Cr(H ₂ O) ₆ ³⁺ /phenylalanine	1.85×10^{-4} (35 °C)	-	53.6	-141.7	[15,16,18,33]
[Cr(Salm)(H ₂ O) ₂] ⁺ /pyc-2	17.6×10^{-4} (25 °C)	8.75	28.3 ± 0.2	-201 ± 0.6	[36]
[Cr(Salm)(H ₂ O) ₂] ⁺ /pyc-3	18.76×10^{-4} (25 °C)	3.00	38.33 ± 6.5	-172 ± 19	[36]
Cr(H ₂ O) ₆ ³⁺ /L-Dopa	1.43×10^{-4} (50 °C)	2.18	-	-	[7]
<i>cis</i> -[Cr(C ₂ O ₄) ₂ (OH ₂) ₂] ⁻ /L-Dopa	2.75×10^{-4} (50 °C)	0.104	50.13	-68.6	This work

gly glycine, ala alanine, val valine, pyc-2 pyridine-2-carboxylic acid, pyc-3 pyridine-3-carboxylic acid, H₂O* H₂O¹⁸, $\Delta H^\ddagger$ activation enthalpy, $\Delta S^\ddagger$ activation entropy

Characterization of the product complex: A mixture of solution of 0.002 mol dm⁻³ K[Cr(C₂O₄)₂(H₂O)₂] 3H₂O and 0.001 mol dm⁻³ L-Dopa at pH 5.3 were heated at 50 °C for 5 h and then transferred to a desiccator for drying. The resulting product was recrystallized and then it was washed with ethanol and diethyl ether. The product retained most of the peaks of L-Dopa. However, the carboxylate $\nu(C=O)$ for the product complex is observed at 1541 cm⁻¹ a 29 cm⁻¹ downshift compared to the free L-Dopa. A 142 cm⁻¹ downshift to 3232 cm⁻¹ for $\nu(N-H)$ is consistent with bonding through the N atom.

Assessment of catalepsy

Acute haloperidol induced catalepsy: The result of the study is given in Table-3. The *cis*-[Cr(C₂O₄)₂(OH₂)₂]⁻-L-Dopa complex showed a significant ($p < 0.05$) decrease in cataleptic score that peaked at 30 min of post treatment. The % decrease of cataleptic score is registered as 81.4 at the end of 2 h in *cis*-[Cr(C₂O₄)₂(OH₂)₂]⁻-L-Dopa complex whereas L-Dopa demonstrated 73.1 at the same time interval. The % reduction of catalepsy was dose and time dependent in both test drugs at all tested dose levels. However the extent of reduction of catalepsy was reported more in *cis*-[Cr(C₂O₄)₂(OH₂)₂]⁻-L-Dopa complex when compared with treatment of L-Dopa alone in all tested dose level and time interval. The comparatively

more decrease in catalepsy score of *cis*-[Cr(C₂O₄)₂(OH₂)₂]⁻-L-Dopa complex treated animals may be due to inhibition of peripheral degradation of L-Dopa to dopamine in the presence of dopa decarboxylase enzyme, thereby comparatively increase the availability of dopamine in the brain and hence the more response.

Chronic haloperidol induced catalepsy: The test result of chronic haloperidol induced catalepsy is given in Table-4. The test result revealed that *cis*-[Cr(C₂O₄)₂(OH₂)₂]⁻-L-Dopa complex registered progressive fall of catalepsy with respect to increasing dose and advanced days of treatment. The % fall of catalepsy of *cis*-[Cr(C₂O₄)₂(OH₂)₂]⁻-L-Dopa complex at 200 mg/kg, was calculated as 91.8 on 21st day of the study, whereas at the same time the L-Dopa possess 83.8. It is interesting that the treatment of complex of *cis*-[Cr(C₂O₄)₂(OH₂)₂]⁻-L-Dopa has more degree of fall of catalepsy in less quantity of L-Dopa, than L-Dopa alone. The more potentiality of the said complex may be due to decrease in peripheral degradation of L-Dopa to dopamine, thereby elevate the brain level of L-Dopa.

Conclusion

The kinetic and pharmaceutical study of *cis*-[Cr(C₂O₄)₂(OH₂)₂]⁻ complex with antiparkinsonian drug L-Dopa has been reported in this research work. L-Dopa is bound to Cr(III) ion *via* carboxylate

TABLE-3
EFFECT OF *cis*-[Cr(C₂O₄)₂(H₂O)₂]⁻-L-Dopa COMPLEX ON ACUTE HALOPERIDOL INDUCED CATALEPSY IN MICE

Treatment	Dose (mg/kg)	Catalepsy scores				
		15 min	30 min	60 min	90 min	120 min
Normal control	10 mL/kg	1 ± 0.0	1.30 ± 0.08	1.43 ± 0.12	1.39 ± 0.22	1.46 ± 0.31
Solvent control	1	28 ± 0.98	69 ± 2.79	85 ± 1.21	110 ± 1.09	145 ± 1.12
L-Dopa	50	24 ± 1.52 (14.2)	51 ± 1.52 ^a (26.1)	55 ± 1.07 ^b (35.2)	61 ± 1.22 ^b (44.5)	69 ± 1.87 ^b (52.4)
	100	22 ± 1.21 ^b (21.4)	36 ± 1.52 ^b (47.8)	40 ± 1.76 ^b (52.9)	49 ± 1.39 ^b (55.5)	55 ± 1.91 ^b (62.1)
	200	14 ± 1.25 ^b (50.0)	22 ± 1.43 ^b (68.1)	28 ± 1.33 ^b (67.1)	32 ± 1.18 ^b (70.9)	39 ± 1.52 ^b (73.1)
<i>cis</i> -[Cr(C ₂ O ₄) ₂ (H ₂ O) ₂] ⁻ -L-Dopa	50	21 ± 0.96 ^b (25)	41 ± 2.29 ^b (40.6)	42 ± 1.41 ^b (50.6)	46 ± 1.36 ^b (58.1)	51 ± 1.78 ^b (64.8)
	100	17 ± 1.29 ^b (39.2)	20 ± 2.11 ^b (71.0)	24 ± 1.31 ^b (71.8)	26 ± 1.12 ^b (76.4)	31 ± 1.49 ^b (78.6)
	200	11 ± 1.44 ^b (60.7)	18 ± 2.06 ^b (73.9)	21 ± 1.07 ^b (75.3)	23 ± 1.34 ^b (79.1)	27 ± 1.22 ^b (81.4)

Results are expressed in mean ± SEM (n = 6) & applied in one way analysis of variance followed by Dunnet t test, where the parenthesis indicates % protection of catalepsy, ^ap < 0.01 and ^bp < 0.001.

TABLE-4
EFFECT OF *cis*-[Cr(C₂O₄)₂(H₂O)₂]⁻-L-Dopa COMPLEX ON CHRONIC HALOPERIDOL INDUCED CATALEPSY IN MICE

Treatment	Dose (mg/kg)	Catalepsy scores				
		5 th day	9 th day	13 th day	17 th day	21 st day
Normal control	10 mL/kg	1.03±0.11	1.27 ±	1.00±0.19	1.25±0.23	1.09±0.44
Solvent control	1	24.89±2.69	72.29±2.05	119.06±1.09	198.70±1.67	243.83±1.19
L-Dopa	50	16.1±2.99 (35.3)	41.1±2.56 ^a (43.1)	57±1.71 ^b (52.1)	89.8±1.05 ^b (54.8)	100.9±0.51 ^b (58.6)
	100	12.7±1.72 ^b (49.0)	32.4±1.74 ^b (55.2)	44±1.48 ^b (63.0)	66.4±1.76 ^b (66.6)	72.4±0.59 ^b (70.3)
	200	9.5±0.91 ^b (61.8)	22.1±1.61 ^b (69.4)	30.6±1.01 ^b (74.3)	41.5±0.97 ^b (79.1)	39.5±0.33 ^b (83.8)
<i>cis</i> -[Cr(C ₂ O ₄) ₂ (H ₂ O) ₂] ⁻ -L-Dopa	50	13.6±0.56 ^b (49.1)	34.5±1.69 ^b (52.3)	46.8±1.23 ^b (60.7)	71.1±0.89 ^b (64.2)	73.3±1.05 ^b (68.3)
	100	10.8±0.89 ^b (62.5)	25.6±1.31 ^b (64.6)	33.5±0.89 ^b (71.9)	46.9±0.98 ^b (76.4)	49.7±1.02 ^b (79.6)
	200	7.9±1.21 ^b (68.4)	16.2±1.92 ^b (77.6)	19.2±1.25 ^b (83.9)	22.5±1.32 ^b (88.7)	22.4±1.77 ^b (91.8)

Results are expressed in mean ± SEM (n = 6) & applied in one way analysis of variance followed by Dunnet t test, where the parenthesis indicates % protection of catalepsy, ^ap < 0.01 and ^bp < 0.001.

oxygen, which is established from the IR spectrum of the product. The kinetic aspects of the study revealed that the complex formation proceeds by a mechanism in which the rate determining step is the change from an outer sphere to inner sphere complex. The antiparkinsonian studies of the product complex show the effectiveness of the drug, as a reduced dose compared to free L-Dopa produced significant recovery from catalepsy.

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