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Research Paper

Kinetic and Mechanistic Studies of the Interaction of DL-methionine with cis-diaqua(cis-1,2-diaminocyclohexane)Platinum(II)Perchlorate in Aqueous Medium at pH 4.0

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Abstract: *The kinetics of the interaction of DL-methionine with cis-$[Pt(dach)(H_2O)_2](ClO_4)_2$ (dach=cis-diaminocyclohexane) have been studied spectrophotometrically as a function of $[Pt(dach)(H_2O)_2^{2+}]$, [DL-met] and temperature at a particular pH (4.0). The reaction proceeds via rapid outer sphere association complex formation followed by two consecutive slower steps (k_1 and k_2 of the order of $10^{-3}s^{-1}$ and $10^{-5}s^{-1}$ respectively).The first step involves the transformation of outer sphere complex into an inner sphere complex containing Pt-S bond and one aqua ligand, while the second step involves chelation when second aqua ligand is replaced. The equilibrium constant has been evaluated. The activation parameters for both the steps have been calculated ($\Delta H_1^{\#}$ = 13.73 ± 2.09 kJ mol^{-1} $\Delta S_1^{\#}$ = -251.68 ± 6.76 J $K^{-1}mol^{-1}$ $\Delta H_2^{\#}$ = 90.96 ± 1.26 kJ mol^{-1} $\Delta S_2^{\#}$ =-40.99 ± 4.06 J $K^{-1}mol^{-1}$). The low enthalpy of activation and negative entropy of activation suggest associative interchange mechanism. Also, from the thermodynamic consideration, this type of formation of outer sphere association complex is supported by the negative ΔG^0 (-16.60 kJ mol^{-1}).*

Keywords: Associative interchange, Bioactive ligands, Diaminocyclohexane, Pt(II) complex.

Introduction

The impact of cisplatin in cancer chemotherapy is unquestionable, but the drug has considerable adverse side-effects. Over the last 40 years much effort has been dedicated to discover new platinum based anticancer agents that are superior to cisplatin or its analogue. Platinum compounds bearing 1,2-diaminocyclohexane carrier ligand have resulted in novel anticancer agents capable of circumventing cisplatin resistance[1]. The complex L-[Pt(dach)(Glu)] (dach = trans(±)1,2-diaminocyclohexane, Glu = glutathione) was found to be 2-3 times more cytotoxic than cisplatin[2] and also Pt-dach complexes were found to have less nephrotoxicity. Earlier studies also indicated that aminoethylpyrrolidine-platinum complexes have considerable antitumor activity which is dependent on the leaving group of the complex[3]. Some Pt(II) complexes bearing thiourea is reported to have excellent cytotoxicity against leukemia cell line and ovarian cancer cell lines[4,5]. A full understanding of the mode of action of the metal based antitumoral drug requires the study of its interaction with all possible biological targets including amino acids, hormones, peptides and proteins. It is reasonable to expect that any injected metal drug will present some kind of interaction with these biomolecules which could crucially determine its bio-availability and toxicity. The Pt-dach complexes were reported to have strong affinity towards S-containing ligands[6]. In order to understand the specific and selective role of metal ions in biological systems, thermodynamic and kinetic investigations are of interest[7,8]. In this article I present the kinetic and mechanistic aspects of the interaction of $[Pt(dach)(H_2O)_2](ClO_4)_2$ with DL-methionine, a bioactive ligand, in aqueous medium at pH 4.0.

Material and Methods

The reactant complex (complex 1) $[Pt(dach)(H_2O)_2](ClO_4)_2$ was prepared from cis – dichlorodach platinum(II), prepared as per the literature method[9], by hydrolysis in presence of two molar equivalents of silver perchlorate. The diaqua complex was characterized spetrophotometrically. The product complex (complex 2) were prepared by mixing complex 1 and the ligand in the molar ratio 1:1, 1:2, 1:3, 1:5, and 1:10 ratio at pH 4.0 and equilibrating the mixture at 60^0C for 48 h. The absorption spectra of all the resultant solutions were recorded and it was found that all the solutions exhibit almost identical absorbance with λ_{max} 238 nm. The spectroscopic difference between complex 1 and complex 2 is shown in Figure 1.

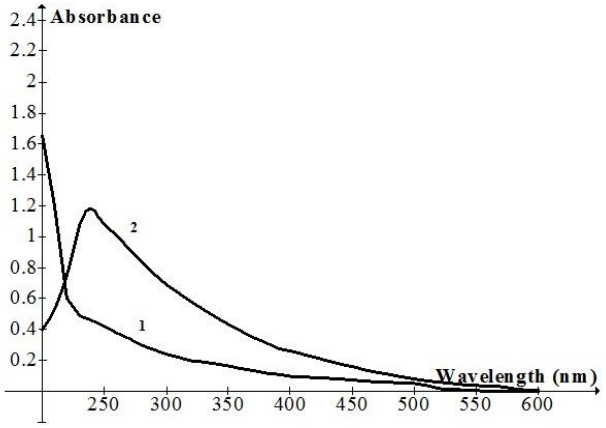

Figure 1: Spectral Difference between reactant complex and product complex 1 = $[Pt(dach)(H_2O)_2^{2+}]$ = 5.0×10^{-5} mol dm^{-3}, 2 = $[Pt(dach)(H_2O)_2^{2+}]$ = 5.0×10^{-5} mol dm^{-3}, [DL-met] = 5.0×10^{-4} mol dm^{-3}, pH = 4.0, cell used = 1 cm quartz cell

The composition in solution was determined by Job's method of continuous variation. The metal:ligand ratio was found to be 1:1. The pH of the solutions were adjusted by adding $NaOH/HClO_4$ and the measurements were carried out with the help of a Systronics digital pH-meter (Model No. 335) with an accuracy ± 0.01. Doubly distilled water was used to prepare all solutions. All other chemicals used were either AR grade or purified before use. The kinetic studies were performed at constant ionic strength 0.1 mol dm^{-3} $NaClO_4$.

The reactions were carried out either on a Shimadzu UV/VIS 2100 spectrophotometer attached to a thermoelectric cell temperature controller (Model No SPR 8, Accuracy ± 0.1 ^{0}C). The progress of the reactions was monitored by following the increase in absorbance at the wave length where the spectroscopic difference between the reactant complex (1) and the product complex (2) is maximum. The rate constants were determined from the plots of $\ln(A_\infty-A_t)$ vs. tine t where A_∞ and A_t are the absorbances at infinite time (or after the completion of the reaction) and at time t respectively. Conventional mixing techniques were followed and pseudo first order conditions were maintained throughout. The reported rate data represented as an average of duplicate runs were reproducible to within ± 4%.

Results and Discussion

At a fixed excess concentrations of the ligands, fixed temperature, fixed ionic strength and at fixed pH, the reactions were observed to first order with respect to concentration of complex 1.

$$\text{Rate} = d[(2)] / dt = k_{obs} \quad (1)$$

The reactant complex 1 at pH 4.0 is in diaqua form as the pK_1 and pK_2 values of the complex 1 are 6.25 and 7.80[10], so at pH 4.0 we can assume that the substrate is essentially in diaqua form, $[Pt(dach)(H_2O)_2]^{2+}$. The pK_1' and pK_2' values of DL-methionine are 2.24 and 9.07 at 25^0C[12]. So at pH 4.0 the zwitterionic form of the ligand predominates.

At constant ionic strength, temperature, pH, and at fixed concentration of complex 1, the $\ln(A_\infty-A_t)$ vs. tine (t) plot is curved at the initial stage and is subsequently of constant slope for different ligand concentrations (Figure 2).

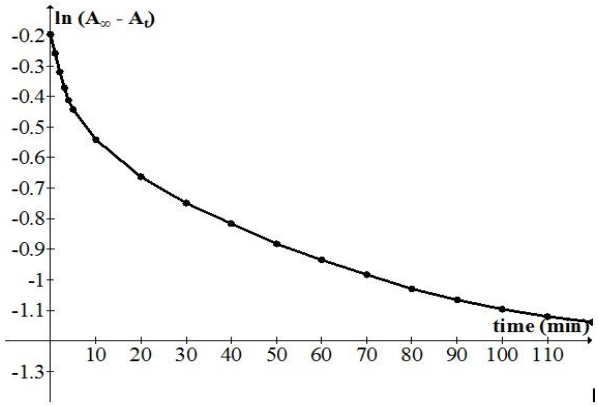

Figure 2: $\ln(A_\infty-A_t)$ vs. time (t) plot, 1 = 5.0×10^{-5} mol dm^{-3}, [DL-met] = 15.0×10^{-4} mol dm^{-3}, pH = 4.0, Temperature = 45^0C

This indicates that the process of substitution follows a two step consecutive path. The first is the displacement of one aqua ligand from $[Pt(dach)(H_2O)_2]^{2+}$ by the ligand, involving an outer sphere association complex formation, followed by an associative interchange. The second step is the slower step where another aqua ligand is replaced, and this is ring closure step. The anation rate constants for both the steps (k_1 and k_2) and outer sphere association equilibrium constants (K_E) for the first step have been calculated according to the following scheme A→B→C, where A is the diaqua species, B is the mono aqua species and C is the final product. The B→C step is the ring closure step and it is independent of the ligand concentration. The k_2 values were directly obtained from the slope of the linear

portion of the plots of $\ln(A_\infty - A_t)$ vs. tine t. The rate constants k_1 for A→B step can be evaluated by Weyh and Hamm[12] method using the usual consecutive rate law

$A_\infty - A_t = a_1 \exp(-k_{1(obs)}t) + a_2 \exp(-k_{2\,(obs)}t)$ ---------- (1)

Whence,

$A_\infty - A_t - a_2 \exp(-k_{2\,(obs)}t) = a_1 \exp(-k_{1(obs)}t)$---------- (2)

Where a_1 and a_2 are the constants dependent upon the rate constants and extinction coefficients, $a_2 \exp(-k_{2\,(obs)}t)$ is the value of $A_\infty - A_t$ for the second step only, hence, the difference

$\Delta = a_1 \exp(-k_{1(obs)}t)$ or,

$\ln \Delta = \text{constant} - k_{1(obs)}\, t$ ---------- (3)

The $k_{1(obs)}$ values were obtained from the slope of ln Δ vs. time (t) plot (Figure 3), when t is small.

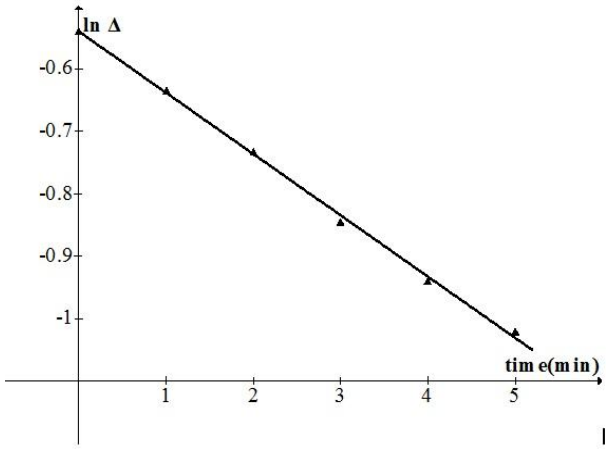

Figure 3: ln Δ vs. time (t) plot

A similar procedure is applied for each set of five different ligand concentrations in the range 5.0×10^{-4} mol dm^{-3} to 15.0×10^{-4} mol dm^{-3} at constant complex (1) concentration 5.0×10^{-5} mol dm^{-3}, at pH 4.0 and at four different temperatures 30, 35, 40 and 45^0C respectively. The $k_{1(obs)}$ values (Table 1) thus obtained increase with the increase in ligand concentration and temperature (Figure 4) and at high ligand concentration a limiting stage is reached at all temperature studied.

Table 1: 10^4 $k_{1(obs)}$ (s^{-1}) values at different concentration of DL-methionine at different temperatures. [Complex] = 5.0×10^{-5} mol dm^{-3}, pH = 4.0

[Ligand] $\times10^4$ mol dm^{-3}	T(^{0}C)			
	30	35	40	45
5.0	2.92	4.41	6.34	9.09
7.5	3.98	6.16	8.57	11.49
10.0	5.02	7.45	9.98	13.89
12.5	6.01	8.64	11.22	15.15
15.0	6.72	9.51	12.10	15.87

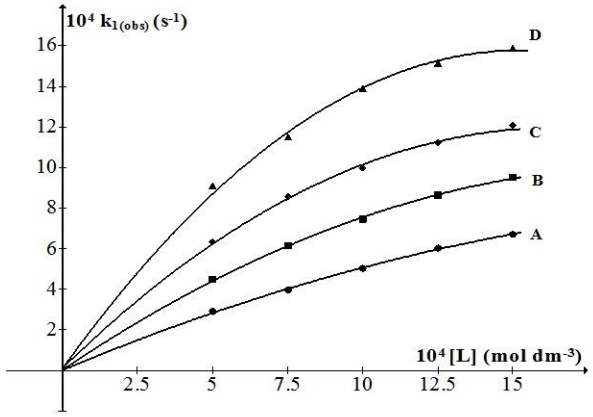

Figure 4: Variation of $k_{1(obs)}$ with [DL-met], A = 30, B = 35, C = 40 and D = 45^0C

The ligand concentration dependence of the $k_{1(obs)}$ values can be explained in terms of rapid outer sphere association complex formation between the reactant complex and the sulphur end of the DL-methionine in the A→B step. The following mechanism may be proposed.

$$[Pt(dach)(H_2O)_2]^{2+} + \text{DL-met} \underset{}{\overset{K_E}{\rightleftharpoons}} [Pt(dach)(H_2O)_2]^{2+}.\text{DL-met} \text{ ----------(4)}$$

$$[Pt(dach)(H_2O)_2]^{2+}.\text{DL-met} \xrightarrow{k_1,\ \text{slow anation}} [Pt(dach)(H_2O)(\text{DL-met})]^{2+} + H_2O \text{ ----------(5)}$$

$$[Pt(dach)(H_2O)(\text{DL-met})]^{2+} \xrightarrow{k_2,\ \text{chelation}} [Pt(dach)(\text{DL-met})]^{2+} + H_2O \text{ ----------(6)}$$

Based on the above scheme a rate expression (7) can be derived for A→B step

$k_{1(obs)} = k_1K_E[\text{DL-met}]/(1+K_E[\text{DL-met}])$ ----------(7)

where k_1 is the rate constant for the conversion of outer sphere complex to inner sphere complex and K_E is the outer sphere association equilibrium constant.

Equation (7) can be rearranged as

$1/k_{1(obs)} = 1/k_1 + 1/k_1K_E\,[\text{DL-met}]$ ----------(8)

Thus, a plot of $1/k_{1(obs)}$ vs. 1/[DL-met] should be linear (figure 5) with an intercept $1/k_1$ and slope $1/k_1K_E$ and this was found to be the case at all temperatures studied.

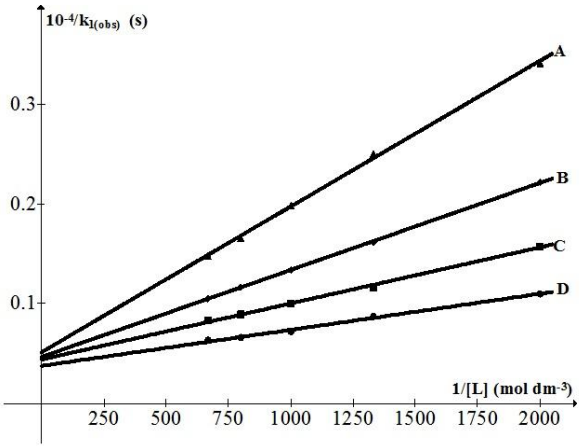

Figure 5: $1/k_{1(obs)}$ vs. 1/[DL-met} plot, A = 30, B = 35, C = 40 and D = 45^0C

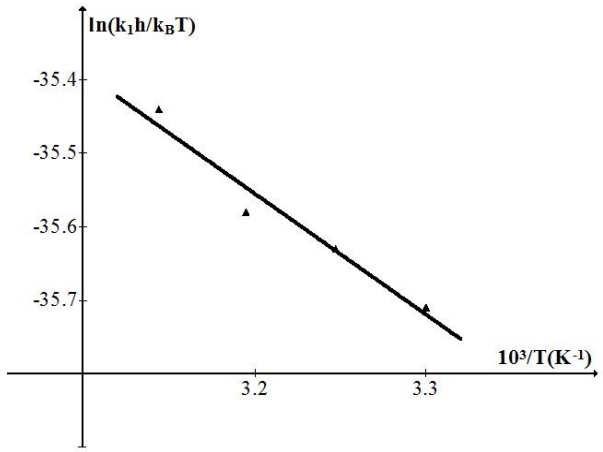

Figure 6: Eyring plot (Plot of ln (k_1h/k_BT) vs. 1/T)

The k_1 and K_E values are obtained from the intercept and from the slope to intercept ratio respectively and are included in Table 2. The B→C step is the ring closure step in which DL-methionine binds the metal center using the second N donor center. This step (chelation) is however independent of the ligand concentration. At a given temperature the k_2 values are directly obtained from the slope of the linear portion of $\ln(A_\infty-A_t)$ vs. tine (t) plot. The k_2 values are also included in Table 2.

The reactions were carried at four different temperatures for five different ligand concentrations and from the temperature dependence of the rate constants for both the steps A→B and B→C the activation parameters $\Delta H_1^{\#}$, $\Delta S_1^{\#}$, $\Delta H_2^{\#}$ and $\Delta S_2^{\#}$ have been calculated., using two Eyring equations, $\ln (k_1h/k_BT) = -\Delta H_1^{\#} / RT + \Delta S_1^{\#} / R$ (Figure 6) and $\ln (k_2h/k_BT) = -\Delta H_2^{\#} / RT + \Delta S_2^{\#} / R$ (Figure 7) where $\Delta H_1^{\#}$, $\Delta H_2^{\#}$ are the enthalpy of activation and $\Delta S_1^{\#}$, $\Delta S_2^{\#}$ are the entropy of activation for both the steps, respectively.

Table 2: k_1, k_2 and K_E values for the substitution reaction

Temperature (^{0}C)	$10^3k_1(s^{-1})$	$10^5k_2(s^{-1})$	K_E (dm^3mol^{-1})
30	1.95	0.92	349.53
35	2.15	1.73	531.84
40	2.28	3.07	777.99
45	2.67	5.37	1022.09

These values are summarized in Table 3 and can be compared with the activation parameters of the analogous systems involving the substitution in square planar Pt(II) complexes.

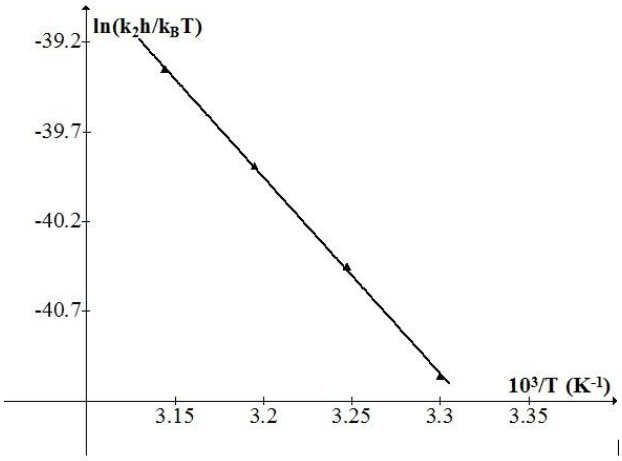

Figure 7: Eyring plot (Plot of ln (k_2h/k_BT) vs. 1/T)

Table 3: The activation parameters of the analogous systems

System	$\Delta H_1^{\#}$ (kJ mol^{-1})	$\Delta S_1^{\#}$ (J $K^{-1}mol^{-1}$)	$\Delta H_2^{\#}$ (kJ mol^{-1})	$\Delta S_2^{\#}$ (J $K^{-1}mol^{-1}$)	References
$[Pt(dach)(H_2O)2\}^{2+}$/Et_2DTC	66.8±3.7	-81±12	95.1±2.8	-34.4±9.1	13
/Glutathione	32.9±1.3	-187.2±4.2	30.5±0.1	-223.1±0.3	14
/2-thiouracil	14.1±1.0	-239±3	24.9±1.2	-248±4	15
/Glycine-L-leucine	51.9±2.8	-152±8	54.4±1.7	-162±5	16
/DL-penicillamine	36.1±4.1	-175±12	44.4±1.1	-189±3	17
/DL-methionine	13.73±2.09	-251.68± 6.76	90.96± 1.26	-40.99± 4.06	This work

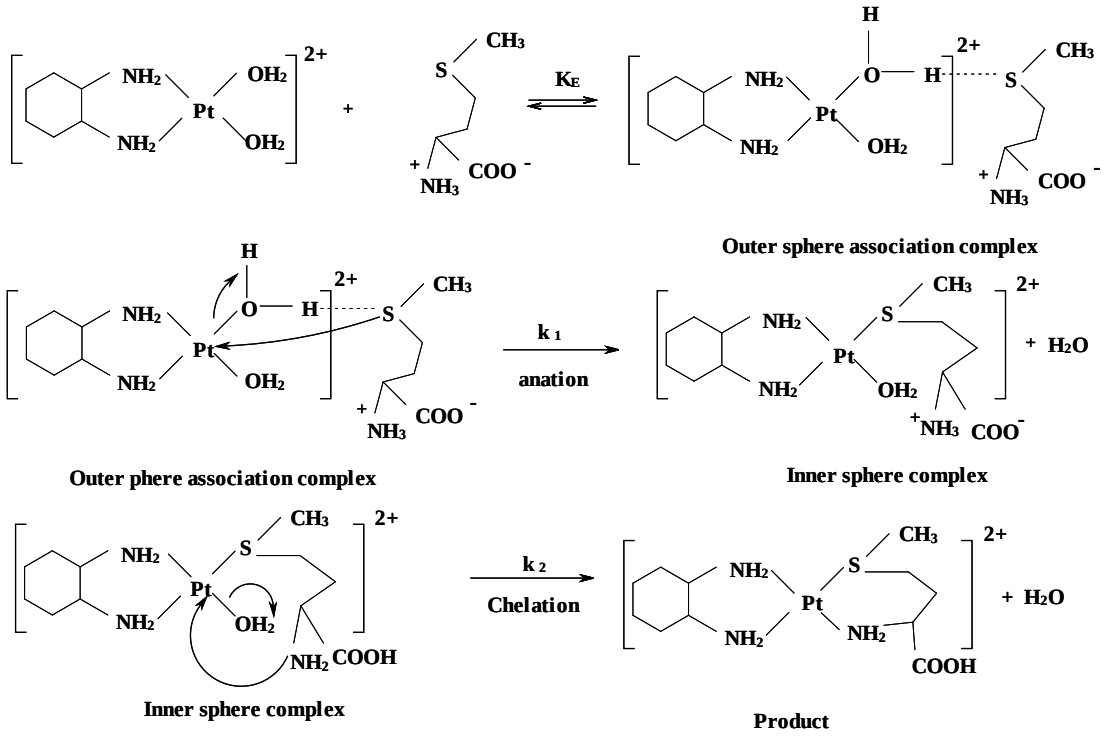

Figure 8. Plausible mechanism for the reaction

Mechanism and Conclusion

The solid product of the reaction could not be isolated (repeated attempts failed). Hence, bonding between the metal and ligand was not fully understood. DL-methionine has been reported to form chelate complex with Pt(II)[18] and the same type of binding mode with Pt(II) has been assumed in the present reaction condition. A plausible reaction sequence from reactant to product is shown in Figure 8.

The $\Delta H^{\#}$ values and negative $\Delta S^{\#}$ values suggest a good degree of ligand participation in the transition state and an associative interchange mechanism were proposed for the reaction. The positive enthalpy change for breaking the M—OH_2 bond is partly compensated by the formation of M—L bond in the transition state. A negative $\Delta S^{\#}$ indicates a more compact transition state. Further, $\Delta S_2^{\#}$ is less negative than $\Delta S_1^{\#}$, which suggests that the compactness has already been achieved in B the transformation from B to C is only the replacement of another aqua ligand through chelation.

Again, from the dependence of K_E on temperature (Figure 9), $\ln K_E = -\Delta H^0 / RT + \Delta S^0 / R$, the ΔH^0 and ΔS^0 have been evaluated as 57.92 ± 3.24 kJ mol^{-1} and 240.01 ± 10.47 J $K^{-1}mol^{-1}$ respectively. Thus, from the thermodynamic consideration, this type of formation of outer sphere association complex is supported by the negative ΔG^0 (-16.60 kJ mol^{-1}).

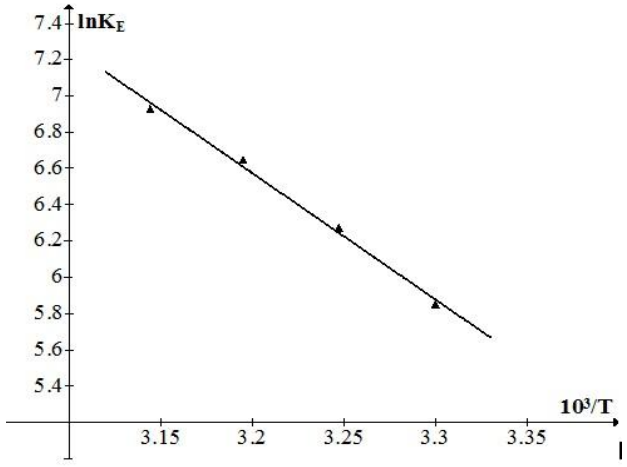

Figure 9: Plot of $\ln K_E$ vs.1/T

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