Pyrex Journals 2035-2789

Pyrex Journal of Research in Environmental Studies
Vol 2(2) pp. 006-014 March, 2015
http://www.pyrexjournals.org/pjres

Review Paper

Stability Constants of Rhenium (V) Metal Complexes with Selected Medicinal Drugs

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Accepted 20th December, 2014

Stability constants of rhenium (V) metal complexes with selected medicinal drugs Adenosine (ADE), isoniazid (ISO) and metformin hydrochloride (MET) have been determined using a pH metric titration technique in aqueous hydrochloric acid media at different temperature (293, 303, 313 and 323 K) and an ionic strength of 0.2 M. It is observed that rhenium (V) metal ion forms 1:1 and 1:2 complexes with these drugs. The proton-ligand and metal-ligand stability constants were determined by Calvin-Bjerrum pH titration technique as modified by Irving and Rossitti. The thermodynamic parameters such as, Gibb's free energy change (ΔG), entropy change (ΔS) and enthalpy change (ΔH) associated with the complexation reactions were calculated. The formations of metal complexes were found to be spontaneous, exothermic in nature and favorable at lower temperature.

Keywords: Medicinal drugs, Rhenium (V) complexes, Formation constants, Thermodynamic parameter.

INTRODUCTION

Chemistry of drugs attracts many researchers because of its application in medicinal study (Chaudhari et al., 2009; Jacob et al., 1984; Lehninger, 1950). Adenosine (2R,3R,4S,5R-2-(6-amino-9H-purin-9-yl)-5-(hydroxyl methyl) oxolane-3,4-diol), isoniazid (pyridine-4-carbohydrazide) and metformin hydrochloride (1,1-dimethylbiguanide hydrochloride) are an antidiabetic drugs (Mapari et al., 2011; Nair, 1999). These drugs used for treating non-insulin dependent diabetes mellitus (Thomas, 2003; Saladini et al., 2000; Mukharjee et al., 1996). The metal complexes of drugs play an important role in drug action and metabolism (Richards et al., 1970; Cotton et al., 1966; 1965).

Very few studies have been devoted to the composition and structure of oxocomplexes of Tc(V) and Re(V) with mercaptoamino acids and their derivatives despite a continuous interest in the biological behavior of ^{99m}Tc complexes of cysteine and derivatives (Lipowska et al., 2002, 1996). Recently, profound solution studies of the oxorhenium (V) penicillamine complex have been described, including the observation that the NH deprotonation does not occur in this system up to a very high pH value (Agarwal et al., 2011; Gielenet al., 2005). The complexation behavior of Tc(V) and Re(V) with cystamine as the simple N, S donor building block of the ligand of interest have been studied (Paulo et al., 2000). Kirch and his coworkers have extended their investigations to D-penicillamine methyl ester (Kirch et al., 1998).

They have by studying the reaction of oxorhenium (V) gluconate with D-penicillamine methyl ester (PME) which yielded three neutral 1:2 complexes. The complexation of rhenium (V) with 4-methyl-1,2,4-triazole-5-thiol in 7 M hydrobromic acid was potentiometrically studied (Aminjanov et al., 2014). The composition of complexes was determined, and their stepwise stability constants were calculated. The oxobromide rhenium (V) complexes were shown to have higher stability than similar oxochloride rhenium (V) complexes. The process of complex formation of rhenium (V) ions and 2-mercaptopyridine was investigated potentiometrically by evaluating the formation equilibrium, stability constants of the metal complex at a temperature range of 273-338 K (Okoronkwo, et al., 2005). These formation constants are used to derive the proportions of the various complex forms as a function of equilibrium ligand concentration. It was identified that for the temperature range of 273-328 K there are five complex forms and at 338 K, there

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are only four complex forms. Thermodynamic values for these complex forms were determined from the formation constants.

A new rhenium (V)-oxo, rhenium (III) and zinc (II) complexes [$ReOCl_2$ (L)], [$ReO(L)_2$]Cl and [$ZnCl_2$(HL)] (where; HL = 2-formylpyridine-N-(4)-phenylthiosemi carbazone) have been synthesized and characterized (Al-Jeboori, 2006). [$ReOCl_3$ (PPh_3)$_2$] and [ReO_4]$^-$ in the presence of PPh_3 have been used as a starting material to prepare rhenium (V)-oxo and rhenium (III) complexes, while $ZnCl_2$ is used to prepare the zinc complex.

The present paper describes studies of stability constants of selected medicinal drugs adenosine (ADE), isoniazid (ISO) and metformin hydrochloride (MET) with rhenium (V) metal ion in aqueous hydrochloric acid media at different temperature and an ionic strength of 0.2 M by pH metric study. Also, the thermodynamic parameters such as Gibb's free energy change (ΔG), entropy change (ΔS) and enthalpy change (ΔH) for formation of complexes are determined.

2. Experimental section

2.1. Materials and solution

The pure drug adenosine, isoniazid and metformin hydrochloride were dissolved in double distilled water. Metal ion solution (K_2ReOCl_5) was prepared as mentioned elsewhere (Jezowska-Trzebiatowska et al., 1966). The concentration of metal ion in the solution was determined spectrophoto-metrically at a wavelength (λ) of 480 nm. A standard carbonate-free KOH solution (0.1 M) was used in all titrations (Vogel, 1978). The ionic strength was adjusted to 0.2 M with KCl. Before an experimental point (pH) was measured, sufficient time was allowed for the establishment of equilibrium.

2.2. Potentiometric titrations

Potentiometric measurements were carried out using a Fischer Accumet 825MP pH-meter equipped with a Fischer combined glass electrode. The pH-meter was standardized with phthalate and phosphate buffers before titrations. Titrant solutions were added using a Fischer-455 automatic burette. Sample solutions were titrated in a double-walled glass cell maintained at different temperature using a Fischer Scientific Isotemp Refrigerated Circulating Bath. The following solutions were titrated:

(i) 5 ml 0.1 M HCl + 40 ml H_2O
(ii) 5 ml 0.0025 M Drug + 5 ml 0.1 M HCl + 35 ml H_2O
(iii) 5 ml 0.0025 M Drug + 5 ml 0.1 M HCl + 5 ml 0.00125 M Re(V) + 30 ml H_2O

The above mentioned sets prepared by keeping metal: drug ratio and the ionic strength were kept constant for all sets. The total volume of each mixture was adjusted to 50 ml and the ionic strength of the solutions was maintained constant at 0.2 M by adding appropriate amount of stock solution of KCl.

Equilibrium pH values were determined at every incremental addition of standard KOH to the solutions. The test solutions were magnetically stirred, KOH was added stepwise and pH reading was recorded until stable values, within ± 0.002 pH units were obtained.

2.3. Determination of stability constant of the binary complexes

The dissociation constant (pka) is one of the most important properties of a drug molecule, since it can be related to physiological activity, solubility and rate of absorption (Marshal, 1955; Fronaeus, 1953; Klotz et al., 1948). Moreover, it has a great value in preparative chemistry, since ionization constants indicate the conditions under which the substance can be isolated in maximal. The acid dissociation of the compounds understudying calculated from the titration curves of hydrochloric acid with potassium hydroxide solution in the absence and in the presence of the ligands at constant ionic strength adjusted by using potassium chloride. The proton-ligand equilibrium constant for the ligand under experimental conditions were determined by Calvin-Bjerrum pH-titration (Calvin et al., 1945; Bjerrum, 1941), which is modified by Irving and Rossotti (Sarin et al., 1972; Irving et al., 1953).

2.4. Calculation of pK and log K

From the titration curves, the average number of protons associated with the ligand ($\bar{n}_A$) at different pH values was calculated utilizing the acid, ligand. The proton-ligand formation ($\bar{n}_A$) were calculated by Irving and Rossotti expression:

$$\bar{n}_A = \gamma - \frac{(V_L - V_A)([N^o + E^o)}{(V_{total} + V_A)\, T_L^o}$$

Where, V_A and V_L are the volumes of alkali (ml) required to reach the same pH in acid and ligand titration curves, respectively, T_L^o is the total ligand concentration in 50 ml solution, γ is the total number of protons free attached to the ligand molecule, N^o is the normality of the alkali, E^o is the initial concentration of free acid and V_{total} is the total volume (ml) of the titration solution.

The average number of metal ion associated with the ligand ($\bar{n}$) at different pH values was calculated from the metal ion and ligand titration curve using the following equations:

$$\bar{n} = \frac{(V_M - V_L)(N^o + E^o)}{(V_{total} + V_L)\bar{n}_A T_M^o} \quad ,$$

$$pL = \log_{10}\left[\frac{\sum_{n=0}^{n=i} \beta_n^H \left(\frac{1}{anti\ log\ pH}\right)}{T_L^o - \bar{n}\, T_M^o} \cdot \frac{V_{total} + V_M}{V_{total}}\right]$$

Where, T_M^o denotes the total concentration of metal present in the solution, V_M is the volume (ml) of metal ions present in the solution and β_n^H is the overall proton ligand stability constant.

2.5. Determination of the thermodynamic parameters

The thermodynamic parameters such as Gibb's free energy change (ΔG), entropy change (ΔS) and enthalpy change (ΔH) for formation of complexes are determined from the slope of the plot pka or log K_i against 1 / T (Figs. 6, 7) using the graphical representation of Von't Hoff equations (Atkins et al., 2006). The change in Gibb's free energy (ΔG) of the ligands is calculated by using the following equations:

$d \log K_i / d T = \Delta H / RT^2$ (1)

$\Delta G = - 2.303\ RT \log K_i = \Delta H - T\Delta S$ (2)

$\log K_i = (- \Delta H / 2.303R)(1 / T) + (\Delta S + 2.303R)$ (3)

The change in enthalpy (ΔH) is calculated by plotting $\log K_i$ against 1 / T. The equation utilized for the calculation of changes in enthalpy (ΔH) is as:

$\text{Slope} = - \Delta H / 2.303\ R$ (4)

3. Results and discussion

The results obtained were analyzed by an Excel program using titration data and then stability constant values were calculated (Abdalazeem et al., 2014). The ligand undertaken to present study contains a hydroxyl group, so it can donate a proton and the remaining anion can act as a chelating agent. When any drug is mixed with metal ion in solution, there is a competition

Adenosine drug has N-atom at the binding site. The functional group ($–NH_2$) is mostly responsible for complexation, although there are atoms of nitrogen present in the coordinate bond formation. In addition, it contains three –OH groups, out of these, two are attached to cyclic ring and one is in the side chain. The deprotonation of side chain OH is easier compared to –OH directly attached to the ring (Thakur et al., 2013). Hence two deprotonation at 293 K in the acidic region (6.04) and the other proton-ligand stability constant (5.11) correspond to $–NH_2$ group.

Isoniazid drug shows two pKa values due to two dissociable protons. The pK_1 value (9.62) at 293 K can be assigned to the substituted amide (–CONHR) group which is near to the pKa value of nicotinamide. The pK_2 (4.97) value at the same temperature is assigned to the ($–RNHNH_2$) group which is attributed to the deprotonation of primary amino group. The low value of pK_2 may be attributed to the weak acidic nature of amide group.

Metformin hydrochloride has one free primary amino group and two terminal NH group. The structure of biguanide in solution is pH-dependent because of the strong basic character of the polar guanidine moiety. This results in its metal complexes also being pH–dependent in solution. Like biguanide, metformin (1,1-dimethyl biguanide) exists in various forms: diprotonated $(H_2MET)^{2+}$ in strong acidic solution, monoprotonated $(HMET)^{+}$ in weak acid, MET in neutral and deprotonated $(MET)^{-}$ in strong alkali solution (Zhu et al., 2002). Hence only one deprotonation in the acidic range (5.18) and the other proton-ligand stability constant (pKa) in the basic region correspond to –NH group only (9.81) at 293 K.

All the thermodynamic parameters of the stepwise stability constants of complexes are given in Table 5. The negative ΔG values indicate that both dissociation of the ligand and the complexation process are spontaneous (El-Sherbiny, 2005). A decrease in metal-ligand stability constant ($\log K_i$) with an increase in temperature and the negative values of enthalpy change (ΔH) for the complexation suggests that all the complexation reactions are exothermic, favorable at lower temperature and the metal-ligand binding process is enthalpy driven and metal-ligand bonds are fairly strong (Sharmeli et al., 2009; Perozzo et al., 2004). The negative change in entropy (ΔS) values indicated a highly solvated metal complex and

where R is ideal gas constant (8.314 JK^{-1} mol^{-1}), K_i is the dissociation constant for the ligand or the stability constant of the complex and T is the absolute Temperature in Kelvin (K). The evaluation of changes in entropy (ΔS) is done by the following equation:

$\Delta S = R * \text{intercept}$ (5)

between the metal ion and the protons for capturing the ligand. It is obvious that there would be a change in the pH of the solution in the formation of complex. Subsequently, the complexation reaction can be studied potentiometrically.

During the titration no precipitates were formed indicating that there is no tendency to form hydroxo complexes (Golcu et al., 2005). The some titration data were used to construct the curves between volumes of KOH against pH is represented in Tables 1 and 2.

indicated that the formation of these complexes was entropy favored (Al-Sarawy et al., 2006; Yang et al., 1996).

4. Conclusion

From the titration curves, it is observed that the departure between acid + ligand and acid + ligand + metal curves for all systems started from pH = 1.98 and 2.70. This indicated the commencement of complex formation. The less difference between $\log K_i$ values indicates the complex formation between rhenium (V) and ligands occurring simultaneously. The maximum value of was ≈ 2 indicating the rhenium (V) metal ion forms 1:1 and 1:2 complexes with these drugs. The metal ion solution used in the present study was very dilute (1.25×10^{-4} mol dm^{-3}), hence there was no possibility of formation of polynuclear complexes or hydrolysis of the rhenium (V) metal ion (Prakash et al., 1995). The metal titration curves were displaced to the right-hand side of the ligand titration curves along the volume axis, indicating proton release upon complex formation of the metal ion with the ligand. The large decrease in pH for the metal titration curves relative to ligand titration curve points to the formation of strong metal complexes (Athawale et al., 1996). In most cases, the color of the solution after complex formation was observed to be different from the color of the ligand at the same pH. For the same rhenium (V) metal ion at constant temperature, the stability of the chelates increases in rhenium (V)-isoniazid than rhenium (V)-metformin hydrochloride and rhenium (V)-adenosine complexes. This order largely reflects the changes in the heat of complex formation across the series from a combination of the influence of both the polarizing abilities of the metal ion and the crystal-field stabilization energies (Phillips et al., 1996; Bissantz et al., 2010). The negative values of change in enthalpy (ΔH) for the complexation suggest that all the complexation reactions are exothermic, favorable at lower temperature. The negative change in free energy (ΔG) values indicates that both dissociation of the ligand and the complication process are spontaneous. The negative change in entropy (ΔS) values indicated a highly solvated metal complex and indicated that the formation of these complexes was entropy favored.

Table 1: Calculation of various parameters for stability constant determination of Re (V)-ISO system at 293 K

pH	KOH (ml)			$\bar{n}_A$	$\bar{n}$	pISO
	V_A	V_L	V_M			
3.9	3.190	3.250	3.305	1.796	0.214	7.516
4.0	3.225	3.277	3.335	1.783	0.315	7.331
4.2	3.310	3.380	3.490	1.763	0.479	7.074
4.4	3.338	3.430	3.592	1.689	0.727	6.827
4.6	3.358	3.461	3.651	1.652	0.877	6.594
4.8	3.375	3.510	3.720	1.544	1.042	6.361
5.0	3.392	3.549	3.760	1.470	1.098	6.142
5.2	3.408	3.575	3.805	1.437	1.198	5.916
5.4	3.425	3.596	3.861	1.423	1.418	5.676
5.6	3.442	3.617	3.882	1.410	1.426	5.461
5.8	3.458	3.639	3.902	1.390	1.435	5.246
6.0	3.475	3.659	3.922	1.380	1.444	4.438
6.2	3.492	3.68	3.940	1.367	1.452	4.223
6.4	3.506	3.706	3.960	1.328	1.460	4.008
6.6	3.519	3.722	3.982	1.317	1.495	3.789
6.8	3.531	3.742	4.002	1.291	1.524	3.570
7.0	3.544	3.762	4.020	1.267	1.553	3.352
7.2	3.556	3.781	4.042	1.244	1.586	3.133
7.4	3.569	3.810	4.061	1.190	1.600	2.916
7.6	3.581	3.822	4.080	1.191	1.650	2.695
7.8	3.594	3.842	4.103	1.167	1.683	2.476
8.0	3.606	3.862	4.120	1.141	1.721	2.257
8.2	3.619	3.884	4.138	1.110	1.741	2.041
8.4	3.630	3.924	4.162	1.014	1.769	1.826
8.6	3.641	3.938	4.182	1.003	1.833	1.608
8.8	3.652	3.948	4.206	1.006	1.903	1.392
9.0	3.663	3.968	4.232	0.976	2.037	1.176
9.2	3.673	3.999	4.250	0.906	2.102	0.975
9.4	3.684	4.080	4.260	0.672	2.030	0.798
9.6	3.720	4.122	4.291	0.532	2.174	0.629
9.8	3.720	4.202	4.322	0.391	2.318	0.460

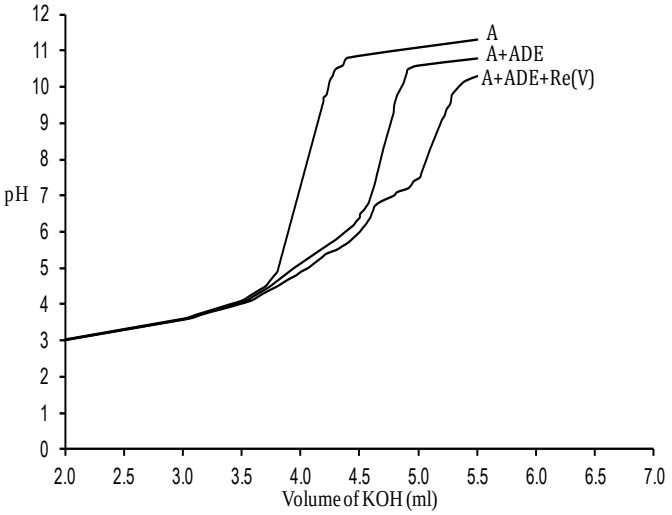

Fig. 1: pH metric titration curves for Re (V)-ADE system at 293 K, where A = free acid, ADE = Adenosine

Table 2: Calculation of various parameters for stability constant determination of Re (V)-MET system at 293 K

pH	KOH (ml)			$\bar{n}_A$	$\bar{n}$	pMET
	V_A	V_L	V_M			
4.7	3.367	3.479	3.786	1.664	1.104	6.939
4.9	3.383	3.520	3.843	1.589	1.215	6.793
5.1	3.402	3.560	3.902	1.521	1.336	6.662
5.3	3.417	3.602	3.930	1.452	1.357	6.466
5.5	3.433	3.650	3.970	1.350	1.414	6.298
5.7	3.450	3.702	3.997	1.252	1.414	6.085
5.9	3.467	3.748	4.025	1.159	1.423	5.880
6.0	3.474	3.759	4.037	1.121	1.426	5.776
6.1	3.483	3.790	4.049	1.082	1.430	5.671
6.3	3.502	3.810	4.068	1.073	1.435	5.462
6.5	3.513	3.832	4.084	1.052	1.440	5.251
6.8	3.531	3.862	4.107	1.018	1.445	4.933
7.0	3.543	3.883	4.128	0.994	4.462	4.743
7.2	3.556	3.903	4.145	0.973	1.500	4.552
7.4	3.569	3.922	4.165	0.952	1.530	4.367
7.6	3.581	3.940	4.186	0.929	1.575	4.199
7.8	3.594	3.968	4.211	0.883	1.631	4.050
8.1	3.613	3.986	4.233	0.887	1.651	3.753
8.4	3.630	4.022	4.255	0.838	1.665	3.449
8.6	3.641	4.042	4.290	0.810	1.827	3.546
8.8	3.652	4.063	4.293	0.783	1.762	3.178
9.0	3.663	4.086	4.297	0.748	1.693	2.859
9.2	3.674	4.108	4.301	0.713	1.623	2.542
9.4	3.684	4.131	4.305	0.671	1.542	2.222
9.6	3.695	4.182	4.321	0.555	1.490	1.958
9.7	3.705	4.205	4.332	0.525	1.461	1.826
9.9	3.735	4.250	4.351	0.467	1.264	1.473

The difference in the volume of KOH utilized for the ligand and metal titrations was a measure of extent of complexation. By plotting the observed pH against the volume of alkali, different trends in the titration curves obtained, the acid curve (A), the ligand curves (A+ADE, A+ISO, A+MET) and a metal complex titration curves (A+ADE+Re(V), A+ISO+Re(V), A+MET+Re(V)) see Figs. 1, 2 and 3.

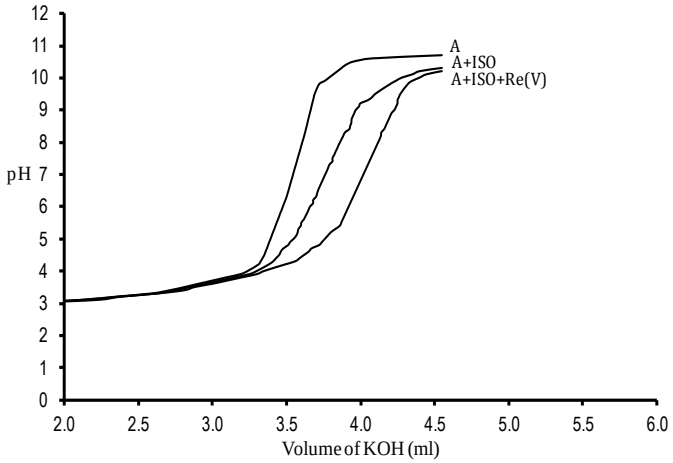

Fig. 2: pH metric titration curve for Re (V)-ISO system at 293 K, where ISO = Isoniazid

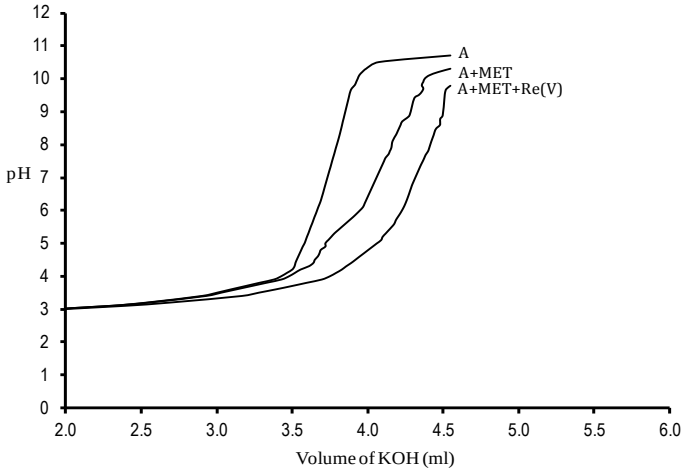

Fig. 3: pH metric titration curve for Re (V)-MET system at 313 K, where MET = metformin hydrochloride

The formation curves (Figs. 4 and 5) were obtained by plotting value of $\bar{n}_A$ against the pH value of the systems (ADE and ISO). An exact values of practical proton-ligand stability constant were calculated by Calvin-Bjerrum half integral method at $\bar{n}_A$ = 0.5 as modified by Irving and Rossitti pH titration techniques. When the maximum value of $\bar{n}_A$ obtained was more than one, the ligand is dibasic in nature.

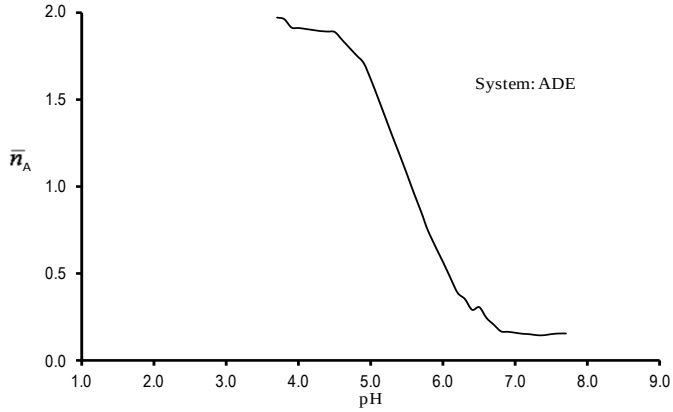

Fig. 4: Formation curve of system-ADE plotting of $\bar{n}_A$ against pH meter reading at 293 K

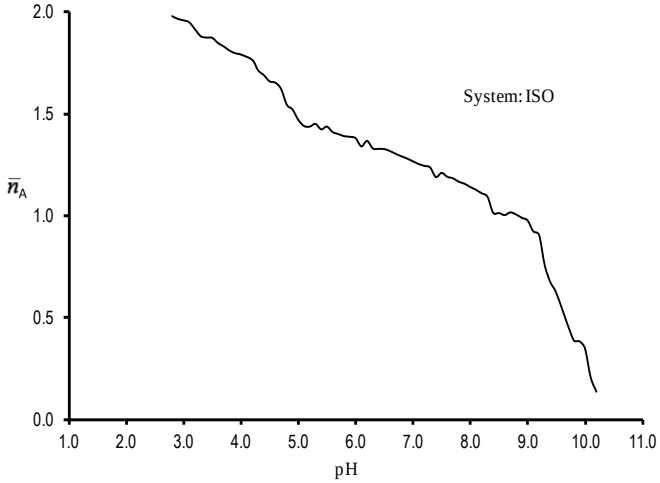

Fig. 5: Formation curve of system-ISO plotting of $\bar{n}_A$ against pH meter reading at 293 K

The dissociation constants (pka) for drugs, as well as the stability constants of its complexes with rhenium (V) have been evaluated at 293, 303, 313 and 323 K, and are given in Table 3.

Table 3: Proton-ligand stability constant of the drugs under study

Ligand	pK_1				pK_2			
	Temperature, K				Temperature, K			
	293	303	313	323	293	303	313	323
ADE	6.04	5.74	5.32	4.78	5.11	4.82	4.52	4.21
ISO	9.62	9.31	8.92	8.52	4.97	4.56	4.12	3.92
MET	9.81	9.38	8.31	7.85	5.18	4.62	4.39	4.01

The proton-ligand stability constant (pKa) values decrease with increase in temperature, i.e. the acidity of the ligands increases (El-Bindary et al., 2003). This suggests that the liberation of protons becomes easier at higher temperature (Figs. 6 and 7).

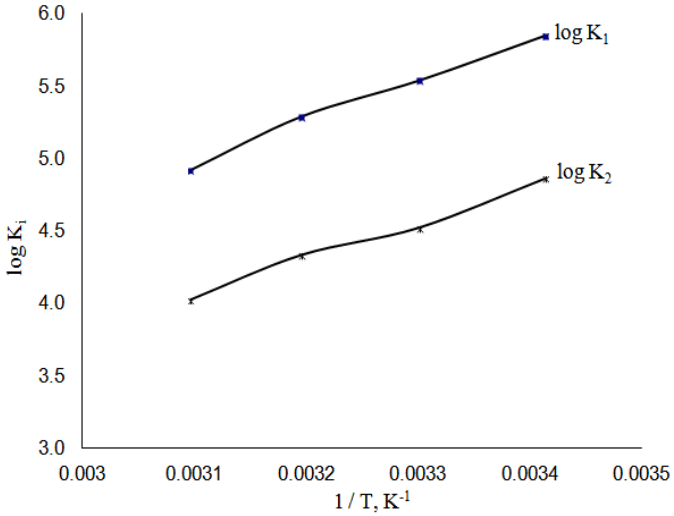

Fig. 6: Vant Hoff Plot log K_i of Re (V) complexes with ADE against 1 / T.

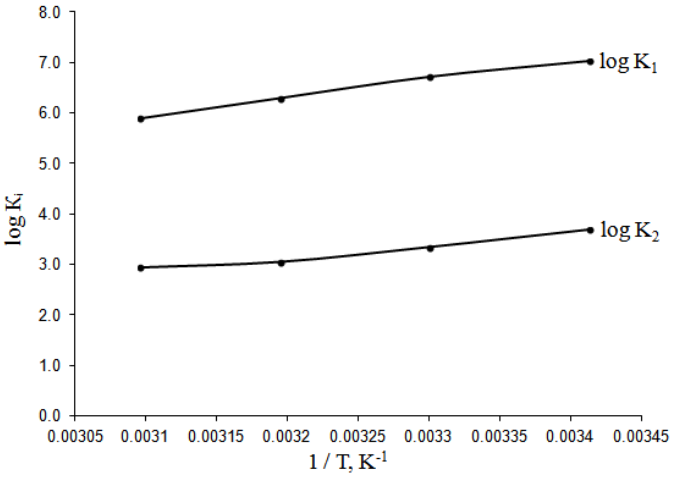

Fig. 7: Vant Hoff plot of log K_i of rhenium (V) complexes with ISO against 1 / T.

The complex titration curve was found to be well separated from the ligands titration curves indicating that the liberation of protons was due to chelation. The metal-ligand complex stability constants were obtained by analysis of formation curves (Figs. 8 and 9) plotting versus pL (where L = ADE and ISO).

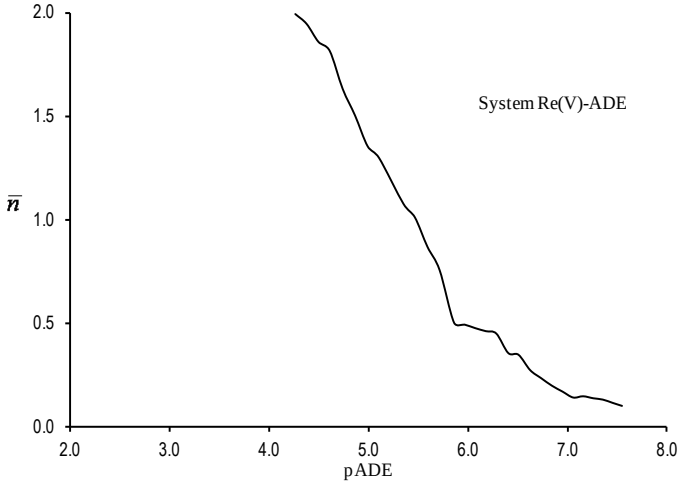

Fig. 8: Formation curve of system Re (V)-ADE plotting of versus pADE at 293 K.

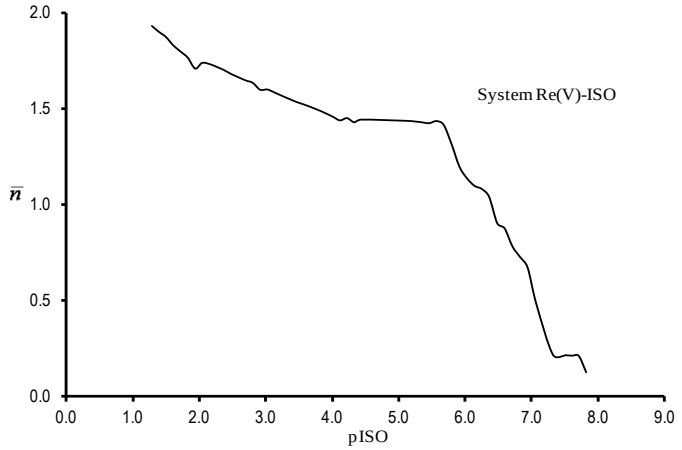

Fig. 9: Formation curve of system Re (V)-ISO plotting of versus pISO at 293 K

It is known that the rhenium (V) metal ion exists in solution as octahedral specie (Santos et al., 2004). Rhenium (V)-ligand stability constant log K_1 and log K_2 for 1:1 and 1:2 complexes respectively are summarized in Table 4 at different temperature. There is no such appreciable difference between log K_1 and log K_2 values. The order of log K_1 > log K_2 is observed. The reason is statistically effective, statistically coordination of a second molecule is difficult when compare to the first due to availability of less number of coordinating sites on the metal ion for the second ligand.

Table 4: Metal-ligand stability constant of selected drugs under study

System	log K_1				log K_2			
	Temperature, K				Temperature, K			
	293	303	313	323	293	303	313	323
Re(V)-ADE	5.85	5.54	5.29	4.92	4.86	4.52	4.33	4.02
Re(V)-ISO	7.02	6.71	6.29	5.89	3.68	3.34	3.05	2.94
Re(V)-MET	8.08	7.08	6.79	6.23	4.53	3.71	3.39	2.88

Table 5: Thermodynamic parameters of selected drug complexes formation with rhenium (V) metal ion

System	log K_i	- ΔG, kJ/mol	- ΔH, kJ/mol	- ΔS, J/mol K
Re(V)-ADE	log K_1	ΔG_1 = 32.52	ΔH_1 = 54.98	ΔS_1 = 72.36
	log K_2	ΔG_2 = 26.82	ΔH_2 = 49.11	ΔS_2 = 74.80
Re(V)-ISO	log K_1	ΔG_1 = 39.11	ΔH_1 = 68.69	ΔS_1 = 99.93
	log K_2	ΔG_2 = 19.98	ΔH_2 = 45.72	ΔS_2 = 99.93
Re(V)-MET	log K_1	ΔG_1 = 43.51	ΔH_1 = 106.3	ΔS_1 = 86.37
	log K_2	ΔG_2 = 23.96	ΔH_2 = 95.81	ΔS_2 = 242.0

Acknowledgment

The author wishes to express his gratitude to Professor Aminjanov Azimjon Alimovich, Research Institute, Tajik National University, and to Professor Ulmas Mirsaidov, Director, Nuclear and Radiation Safety Agency (State Regulatory Authority) Republic of Tajikistan for providing chemicals, some analytical equipment for this study.

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