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Thermodynamic Studies of Complexes of Amlodipine Besylate with Fe^{3+}, Ni^{2+}, Mg^{2+}, Co^{2+} and Ca^{2+} cations in pure Methanol and in the mixtures of Methanol-Water at 303.15, 313.15 and 323.15 K by Conductometric Method.

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Abstract

The complexation reaction between Amlodipine Besylate[AML] with Fe^{3+}, Ni^{2+}, Mg^{2+}, Co^{2+} and Ca^{2+} cation was studied in pure methanol (MeOH) and in the mixtures of MeOH-Water at various temperatures by conductometric method. The conductance data showed that the stoichiometry of the complexes formed in pure as well as in the binary solvent mixtures was 1:1 ($[M^{2+}]$:[AML]). In binary solvent mixtures, the values of log K_f increases with increase in temperature and with increase in the percentage of MeOH. The negative values of ΔG^0 show the spontaneous reaction and positive value of ΔH^0 which indicates that the complexation reaction is enthalpy destabilized. Furthermore, the positive value of ΔS^0 indicates that entropy is a driving force for the complexation reaction. The values of ΔH^0 and ΔS^0 for formation of the complexes were obtained from temperature dependence of the stability constants.

Keywords: Complexes, Conductance, Stability constants, Thermodynamics, Amlodipine Besylate.

INTRODUCTION

The task of transition metal complexes as therapeutic compounds is becoming more and more significant with the development in the medicinal chemistry. The use of transition metal complexes as therapeutic compounds has become progressively distinct in clinical use, and encourages further studies for new metallodrugs, such as metal mediated antibiotics, antibacterial, antiviral, antiparasitic, radio sensitizing agents and anticancer compounds [1]. Moreover, coordination complexes present a wide variety of coordination spheres, ligand designs, oxidation states and redox potentials, giving the ability to systematically alter the kinetic and thermodynamic properties of the complexes towards biological receptors [2]. Hence, study of interaction between drugs and metals may accidentally reduce or increase the drug effect, is an active research area in bioinorganic chemistry.

Amlodipine besylate(AML) is a widely used antihypertensive drug. It selectively inhibits calcium influx across cell membranes in cardiac and vascular smooth muscle [3].

The aim of the present investigation is to evaluate the thermodynamic studies of complex formation between AML and Fe^{3+}, Ni^{2+}, Mg^{2+}, Co^{2+} and Ca^{2+}cations in pure MeOH and their binary solvent systems at 303.15 K, 313.15 K and 323.15 K temperature and to study the effect of solvent and temperature on the selectivity and stoichiometry of the complexes formed and also to understand the thermodynamic considerations of the complexation reactions. The advantage of conductometry is that it can be done at very low solution concentrations with high sensitivity using a simple experimental set-up as well as an inexpensive technique and gives reliable results [4],[5].

EXPERIMENTAL

Reagents and solvents:

Reference standard of amlodipine besylate (99.27 %) was purchased from Clearsynth Labs Pvt. Ltd. (Mumbai, India). Analytical grade nitrate salts of, $Mg(NO_3)_2·6H_2O$, $Ca(NO_3)_2·4H_2O$, $Co(NO_3)_2·3H_2O$, $Fe(NO_3)_3·4H_2O$ and $Ni(NO_3)_2·6H_2O$ were procured from Central Drug House Pvt. Ltd. (New Delhi, India) having purity ≥ 99.8 %. HPLC grade methanol (MeOH) was purchased from spectrochem (Ahmedabad, India). Water was purified using Milli-Q water purification system from Millipore (Bangalore, India). All standard stock and working solutions of AML and metal ions were prepared by accurately weighing known amounts of the compounds in MeOH having conductivity less than 1.0×10^{-7} S/cm. Glassware used were thoroughly cleaned with freshly prepared aqua-regia and rinsed thoroughly with deionized water.

Apparatus:

The conductance measurements were performed on 856 Conductivity Module with touch control from METROHM AG (Herisau, Switzerland). A conductometric cell with a cell constant of 0.59 cm^{-1} was used throughout the studies by measuring the conductivity of aqueous potassium chloride solutions of different concentrations [6]. A thermo stated water bath was used to maintain a constant solution temperature at the desired value having an accuracy of ± 0.01 °C.

Sartorius GD503 (Bradford, MA, USA) analytical balance having a readability of 0.0001 g was employed for weighing of samples.

RESULTS

The changes of molar conductivity (Λ_M) versus the ligand to cation mole ratio $[L]_t/[M]_t$ for the complexation of AML with Fe^{3+}, Ni^{2+}, Mg^{2+}, Co^{2+} and Ca^{2+} cation in pure MeOH and in the mixtures of MeOH-H_2O were studied at different temperatures. The typical series of molar conductance values as a function of $[L]_t/[M]_t$ for AML-M^{n+} complex in pure MeOH and the mixtures of MeOH-H_2O (v/v % = 75/25, 50/50, 25/75) are shown in Figures 1-5.

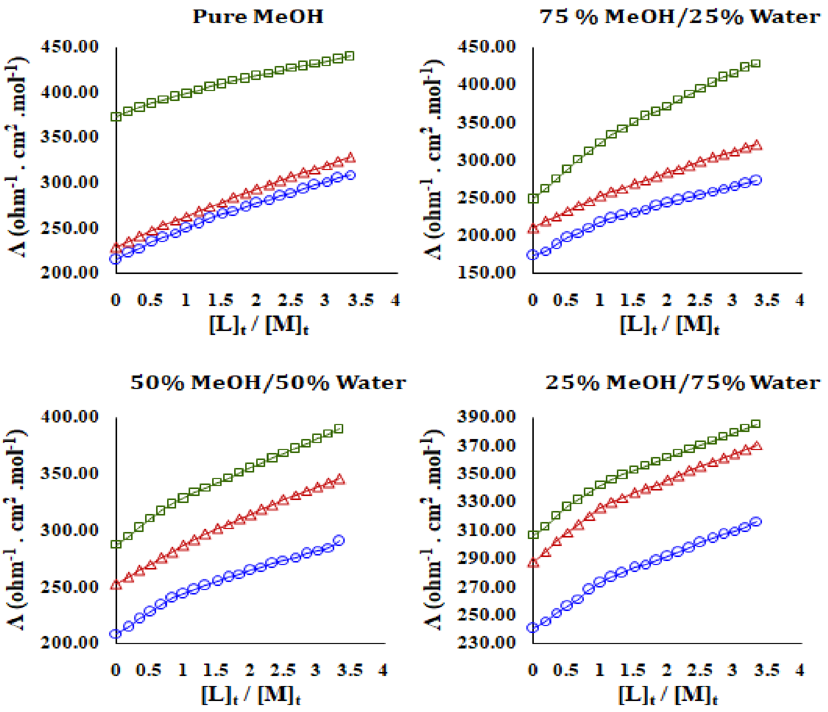

Fig. 1: Molar conductance (Λ_M) versus mole ratio $[L]/[Fe^{3+}]$ plots for AML-Fe^{3+} complex in pure MeOH and the mixtures of MeOH-Water at different temperature:

—○— 303.15 K —△— 313.15 K —□— 323.15 K

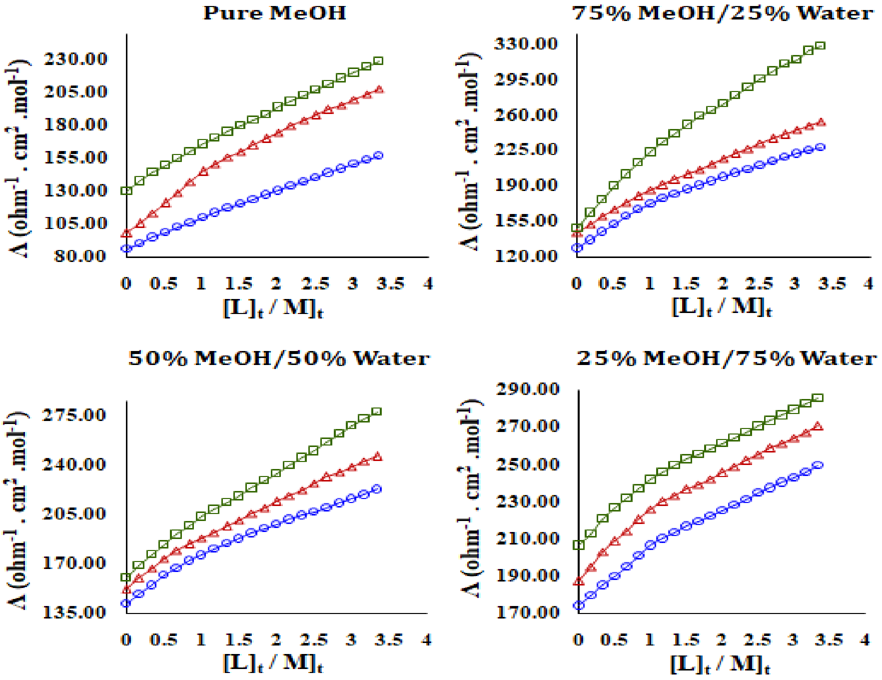

Fig. 2: Molar conductance (Λ_M) versus mole ratio [L]/[Ni^{2+}] plots for AML-Ni^{2+} complex in pure MeOH and the mixtures of MeOH-Water at different temperature:

○ 303.15 K △ 313.15 K □ 323.15 K

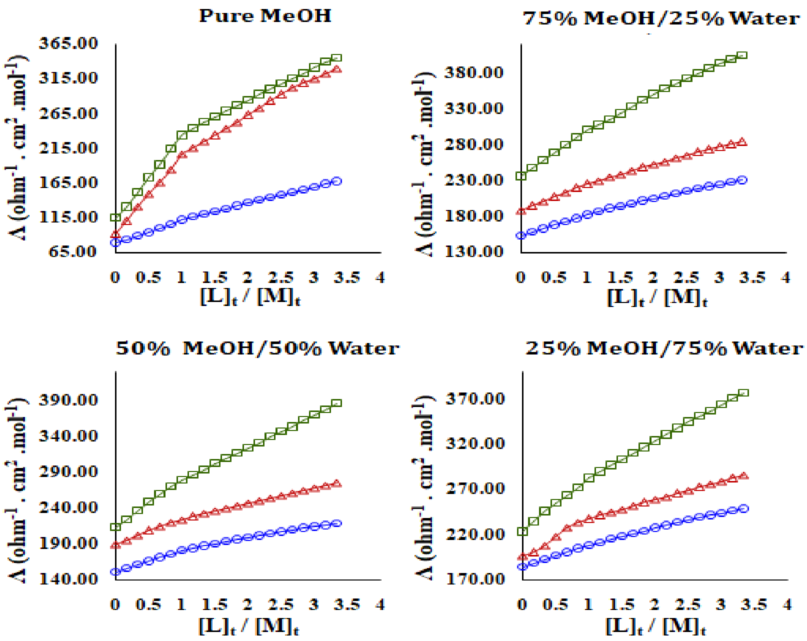

Fig. 3: Molar conductance (Λ_M) versus mole ratio [L]/[Mg^{2+}] plots for AML-Mg^{2+} complex in pure MeOH and the mixtures of MeOH-Water at different temperature:

○ 303.15 K △ 313.15 K □ 323.15 K

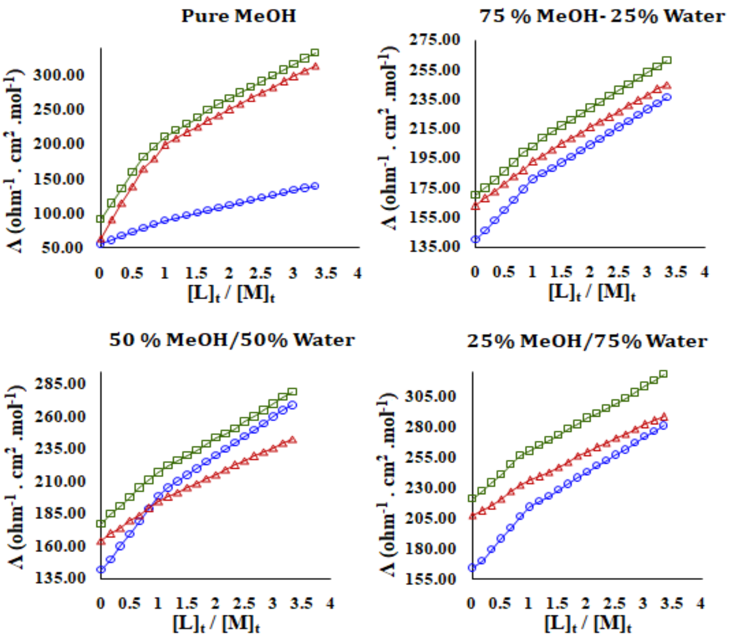

Fig. 4: Molar conductance (Λ_M) versus mole ratio [L]/[Co^{2+}] plots for AML-Co^{2+} complex in pure MeOH and the mixtures of MeOH-Water at different temperature:

—○—**303.15 K** —△—**313.15 K** —□—**323.15 K**

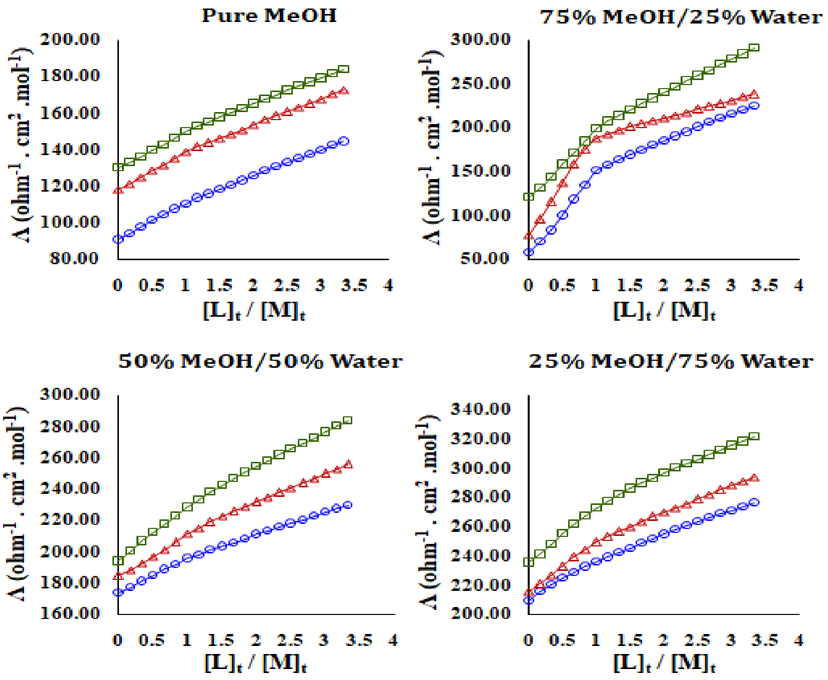

Fig. 5: Molar conductance (Λ_M) versus mole ratio [L]/[Ca^{2+}] plots for AML-Ca^{2+} complex in pure MeOH and the mixtures of MeOH-Water at different temperature:

—○—**303.15 K** —△—**313.15 K** —□—**323.15 K**

The stability constant of AML-M^{n+} complex at each temperature was obtained from variation of molar conductance as a function of $[L]_t/[M]_t$ molar ratio plots using a GENPLOT computer program. The values of the stability constant (log K_f) for the AML-M^{n+} complex in various solvent systems are listed in Table 1. Plots of LnK_f versus 1/T in all cases were linear and a typical example of these plots is shown in Figure 7. The changes in standard enthalpy (ΔH^0) for complexation reaction were determined from the slope of the van't Hoff plots assuming that ΔC_p is equal to zero over the entire temperature range investigated. The changes of standard entropy (ΔS^0) were calculated from the relationship: $\Delta G^0 = \Delta H^0 - T\Delta S^0$ and the results are summarized in Table 2.

Table 1. The values of Log K_f of AML-M^{n+} complex in pure MeOH and MeOH-H_2O binary systems at different temperatures.

Complex	**Solvent Medium**	**Log K_f ± SD[a]**		
		At 303.15 K	**At 313.15 K**	**At 323.15 K**
AML- Fe^{3+}	Pure MeOH	4.531±0.004	4.539±0.006	4.546±0.008
	75 % MeOH-25 % H_2O	4.492±0.004	4.504±0.004	4.516±0.008
	50 % MeOH-50 % H_2O	4.476±0.004	4.485±0.006	4.493±0.005
	25 % MeOH-75 % H_2O	4.461±0.006	4.474±0.004	4.485±0.003
	Pure H_2O	b	b	b
AML- Ni^{2+}	Pure MeOH	4.510±0.004	4.523±0.006	4.537±0.008
	75 % MeOH-25 % H_2O	4.486±0.004	4.498±0.004	4.508±0.008
	50 % MeOH-50 % H_2O	4.462±0.004	4.476±0.006	4.488±0.005
	25 % MeOH-75 % H_2O	4.447±0.006	4.466±0.004	4.485±0.003
	Pure H_2O	b	b	b
AML- Mg^{2+}	Pure MeOH	4.501±0.004	4.513±0.006	4.524±0.008
	75 % MeOH-25 % H_2O	4.448±0.004	4.460±0.004	4.471±0.008
	50 % MeOH-50 % H_2O	4.442±0.004	4.453±0.006	4.464±0.005
	25 % MeOH-75 % H_2O	4.414±0.006	4.422±0.004	4.430±0.003
	Pure H_2O	b	b	b
AML- Co^{2+}	Pure MeOH	4.489±0.004	4.495±0.006	4.500±0.008
	75 % MeOH-25 % H_2O	4.440±0.004	4.455±0.004	4.469±0.008
	50 % MeOH-50 % H_2O	4.437±0.004	4.452±0.006	4.463±0.005
	25 % MeOH-75 % H_2O	4.371±0.006	4.399±0.004	4.424±0.003
	Pure H_2O	b	b	b
AML-Ca^{2+}	Pure MeOH	4.464±0.004	4.486±0.006	4.507±0.008
	75 % MeOH-25 % H_2O	4.387±0.004	4.411±0.004	4.432±0.008
	50 % MeOH-50 % H_2O	4.377±0.004	4.400±0.006	4.425±0.005
	25 % MeOH-75 % H_2O	4.365±0.006	4.393±0.004	4.416±0.003
	Pure H_2O	b	b	b

[a]SD = standard deviation, b = The data cannot be fitted to equations

Table 2. Thermodynamic parameters for AML-M^{n+} complexes in pure MeOH and the mixtures of MeOH-H_2O at 303.15 K.

Complex	Solvent Medium	$\Delta G^o \pm SD^a$ (kJ.mol^{-1})	$\Delta H^o \pm SD^a$ (kJ.mol^{-1})	$\Delta S^o \pm SD^a$ (J.mol^{-1}K^{-1})
AML- Fe^{3+}	Pure MeOH	-26.30±0.09	1.40±0.08	91.37±5
	75 % MeOH-25 % H_2O	-26.08±0.1	2.25±0.1	93.36±7
	50 % MeOH-50 % H_2O	-25.98±0.09	1.59±0.09	90.95±6
	25 % MeOH-75 % H_2O	-25.89±0.08	2.24±0.1	92.78±7
	Pure H_2O	b	b	b
AML- Ni^{2+}	Pure MeOH	-26.33±0.09	2.52±0.12	94.61±5
	75 % MeOH-25 % H_2O	-26.03±0.09	2.06±0.12	92.70±5
	50 % MeOH-50 % H_2O	-25.90±0.06	2.43±0.09	93.44±4
	25 % MeOH-75 % H_2O	-25.81±0.07	3.55±0.08	96.85±3
	Pure H_2O	b	b	b
AML- Mg^{2+}	Pure MeOH	-26.13±0.09	2.16 ±0.09	93.28±6
	75 % MeOH-25 % H_2O	-25.82±0.08	2.15±0.1	92.20±7
	50 % MeOH-50 % H_2O	-25.78±0.07	2.04±0.09	91.78±9
	25 % MeOH-75 % H_2O	-25.62±0.08	1.50±0.1	89.46±4
	Pure H_2O	b	b	b
AML - Co^{2+}	Pure MeOH	-26.06±0.08	1.03±0.09	89.29±5
	75 % MeOH-25 % H_2O	-25.77±0.09	2.71±0.1	93.94±7
	50 % MeOH-50 % H_2O	-25.75±0.1	2.43±0.09	92.95±5
	25 % MeOH-75 % H_2O	-25.37±0.09	4.96±0.11	100.01±6
	Pure H_2O	b	b	b
AML-Ca^{2+}	Pure MeOH	-25.92±0.07	4.02±0.08	98.77±3
	75 % MeOH-25 % H_2O	-25.46±0.09	4.21±0.07	97.85±8
	50 % MeOH-50 % H_2O	-25.40±0.1	4.89±0.09	98.60±3
	25 % MeOH-75 % H_2O	-25.34±0.09	4.78±0.1	99.35±4
	Pure H_2O	b	b	b

[a]SD = standard deviation, b = The data cannot be fitted to equations

DISCUSSION:

It is obvious from Figure 1-5 that the molar conductivity of AML with M^{n+} (Fe^{3+}, Ni^{2+}, Mg^{2+}, Co^{2+} and Ca^{2+}) cations in pure MeOH as well as in the mixtures of MeOH-H_2O increase with increase in the temperature. The increase in the molar conductivity of AML- M^{n+} complexes in pure as well as in the mixtures of MeOH-

H_2O indicates that complex formed is more mobile than the free solvated corresponding cations. The slope of the corresponding Λ_M versus $[L]_t/[M]_t$ plot changes sharply at the point where $[L]_t/[M]_t$ is 1, which is a facts for formation of relatively stable 1:1 complex.

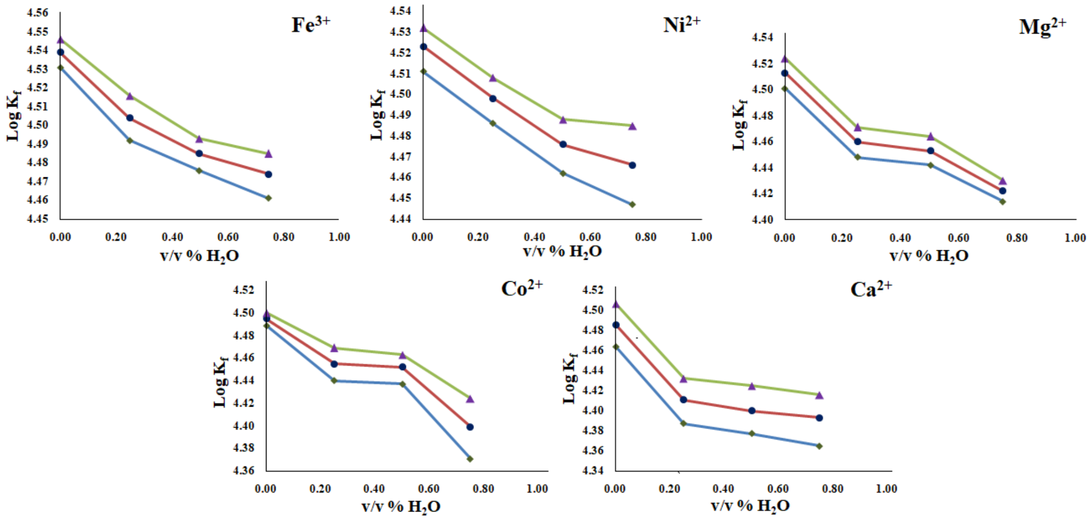

Fig. 6: Changes of the stability constant (log K_f) of AML-Fe^{3+}, AML-Ni^{2+}, AML-Mg^{2+}, AML-Co^{2+} and AML-Ca^{2+} complex with the mixtures of MeOH-Water at different temperatures.

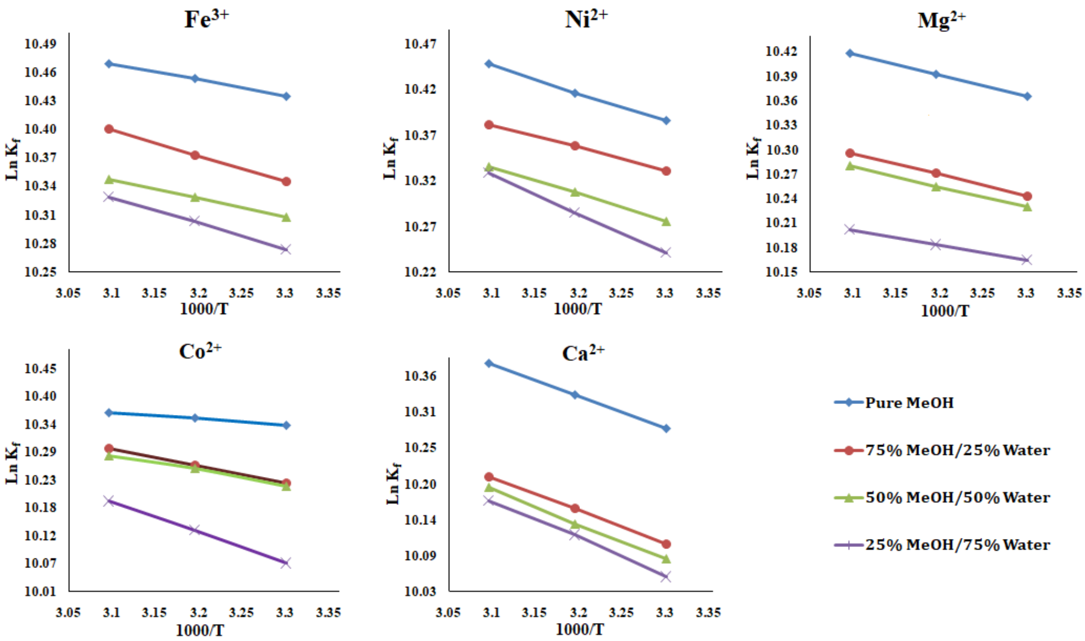

Fig. 7 van't Hoff plots for M^{n+}–AML complex in a pure MeOH and the mixtures of MeOH-H_2O.

It is observed from Table-1(Figure 6) that in most of all cases the stability of all the complexes decrease with increase in the concentration of H_2O in the mixtures of MeOH-H_2O. This is due to the strong solvation of metal ion with H_2O (DN-33.0) [8],[9] compared to MeOH (DN-19.0). The interaction between MeOH and H_2O does not have any significant effect and there was a linear relationship between Log K_f of the complexes. Further, the stability and selectivity of the complexes are influenced by several factors including the charge density and the polarizability of the cation, nature and composition of solvent and also the type of anion associated with the cation [7], [9].

From Figure 7, as the temperature increases, the slope of the plots of AML-M^{n+} complex increases, this is an evidence for formation of a stronger complex at high temperatures. Therefore, the complexation process between AML and M^{n+} cation in pure MeOH and in the mixtures of MeOH-H_2O is endothermic.

To have a better understanding about the thermodynamics of complexation reaction, the enthalpic (ΔH^0), and entropic (ΔS^0) contribution towards complex formation was evaluated in pure as well as binary solvent mixtures. As shown in the Table-2, the values of thermodynamic parameters for complexation reactions vary with the nature and composition of the mixed solvents, but they vary monotonically with the solvent

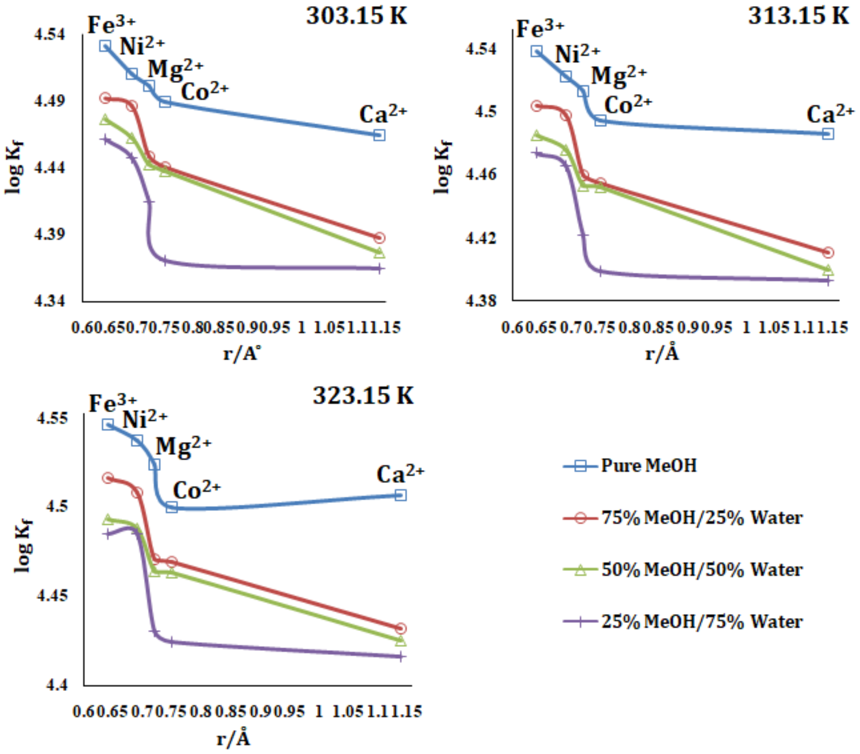

Fig. 8. Variation of log K_f for AML-Fe^{3+}, AML-Ni^{2+}, AML-Mg^{2+}, AML-Co^{2+} and AML-Ca^{2+} complexes versus cationic radius in the mixtures of MeOH-H_2O at 303.15 K, 313.15K and 323.15K.

composition. The negative values for free energy (ΔG^0) indicate that the complexation process is spontaneous. The experimental values of ΔH^0 and ΔS^0 show that in most of the cases, the complexation reaction is entropy stabilized while enthalpy destabilized, therefore, the entropy of complexation reaction are the principal driving forces for formation of the formed complexes in pure MeOH and in the mixtures of MeOH-H_2O. It seems reasonable to assume that the increase in entropy on complexation is due to the solvation of the cation and the ligand upon complexation [10].

It is observed from Figure 8 that the stability of the complexes increases with the decrease in the ionic size. As the ionic radii of cation decreases in the order: $Fe^{3+} < Ni^{2+} < Mg^{2+} < Co^{2+}$ and Ca^{2+}, the stability of the complexes increases in the order $Ca^{2+} < Co^{2+} < Mg^{2+} < Ni^{2+} < Fe^{3+}$.

CONCLUSIONS

In the present work complexation reaction between M^{n+}(Fe^{3+}, Ni^{2+}, Mg^{2+}, Co^{2+} and Ca^{2+}) cation and AML has been studied in pure MeOH and the mixtures of MeOH-H_2O by conductometry. The results obtained indicate that the nature and composition of solvent systems play a vital role in the thermodynamic stability and selectivity of the M^{n+} cations complexes formed. The stoichiometry of the AML-M^{n+} in pure as well as binary solvent mixtures was 1:1. Further, the complexation process was entropy driven in most of the solvent systems studied and the reactions were spontaneous. In most of all the cases, a monotonic behaviour was observed for variation of Log K_f of the complex versus the composition of the binary solvent systems.

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