



International Journal of ChemTech Research CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555 Vol.13 No.01, pp 206-216, 2020

Thermodynamic Studies of Complexes of Amlodipine Besylate with Ni²⁺, Mg²⁺, Co²⁺ and Ca²⁺ cations in pure and in mixed binary solvent systems at 303.15, 313.15 and 323.15 K by Conductometric Method

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Abstract : The present work relates to the complexation reaction between Amlodipine Besylate[AML] with Ni²⁺, Mg²⁺, Co²⁺ and Ca²⁺ cation in dimethylsulfoxide (DMSO), pure methanol (MeOH) and their binary mixtures(DMSO-MeOH and DMSO-Water) by conductometric method. The conductance data show that the stoichiometry of the complexes formed between AML with Ni²⁺, Mg²⁺, Co²⁺ and Ca²⁺ cation in pure DMSO, pure MeOHas well as in the binary solvent mixtures was 1:1. The stability of AML complexes with Ni²⁺, Mg²⁺, Co²⁺ and Ca²⁺ metal ion was observed to be sensitive to the nature of the solvent system. In case of DMSO-Water binary solvent systems there was a linear change in LogK_f values observed. The negative values of ΔG^0 show that the reaction is spontaneous and ability of the AML ligand to form stable complexes. However, the result shows positive value of ΔH^0 which indicates that enthalpy is not driving force for the formation of the complexes. Furthermore, the positive value of ΔS^0 indicates that entropy is a driving force for the complexation. 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, Formation constants, Thermodynamics, Amlodipine Besylate.

Introduction:

Many metals particularly transition metals have very important application in meditational biochemistry. The transition metal complexes are very important and are used as drugs in the treatment of diabetes, infection control, carcinonus etc. The d shells of the transition metal are under the process of filling. This property of the transition metals is the fundamental basis of the formation of coordinate compounds. Many researchers are attracted towards metal complexes of medicinal drug. Chemistry of drug and its medicinal

M. M. Maisuria et al / International Journal of ChemTech Research, 2020,13(1): 206-216.

DOI= <u>http://dx.doi.org/10.20902/IJCTR.2019.130125</u>

application is more useful now a day. The stability of complexes of metal ion with medicinal drug play most important role in the biological and chemical activity. Drug act as ligand which has many functional groups and can bind to metal ion or enzyme or receptor that present in the body to form complexes and enhance activity of drug. Metal complexes are widely used in various fields, such as biological processes pharmaceuticals, separation techniques, analytical processes etc.¹

Amlodipine besylate(AML),2-[(2-aminoethoxy)-methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5pyridine dicarboxylic acid 3-ethyl-5-methyl esterbenzenesulfonate, is antihypertensive calcium channel blocker agent.² It lowers the blood pressure, relaxes heart muscles and dilates the heart blood vessels to prevent spasm.The metal complexes of AML shows higher antimicrobial activity compared to the free AML ligand perhaps due to coordination and chelating tends to form more powerful and potent metal complexes that act as biological agents which inhibits the growth of the microorganisms.³ Moreover, chelating process enhancethe penetration of the complexes into lipid membranes by increasing the delocalization of π -electrons over the whole ring that blocks the binding site of the metal in the enzymes of microorganisms and also disturb therespiration process of the cell which restricts further growth of the organism.⁴

In present study we have reported for the first time conductometric method forthermodynamic studies of complex formation between AML and Ni²⁺, Mg²⁺, Co²⁺ and Ca²⁺cations in pure MeOH, DMSO and their binary solvent mixtures at 303.15 K, 313.15 K and 323.15 K temperature. The aim was to study the effect of solventproperties (pure solvents as well as their binary mixtures) and temperature on the selectivity and stoichiometry of the complexes formed and to understand the thermodynamic considerations of the complexation reactions. A large number of physico-chemical techniques such as spectrophotometry,⁵⁻ ⁷potentiometry,^{8,9}pHmetry,^{10,11}polarography¹² and conductometry¹³⁻¹⁷ have been used to study the complex formation between various drugs with metal ions. Among this various techniques, the conductometric technique is a very sensitive as well as inexpensive technique with a simple experimental arrangement for such kind of investigation.

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 bivalent metal ions, Mg (NO₃)₂·6H₂O, Ca (NO₃)₂·4H₂O, Co (NO₃)₂·3H₂O and Ni (NO₃)₂·6H₂O were procured from Central Drug House Pvt. Ltd. (New Delhi, India) having purity \geq 99.8 %. HPLC grade dimethylsulfoxide(DMSO)and 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 DMSO as well as 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 carried out using 856 Conductivity Module with touch control from METROHM AG (Herisau, Switzerland). A dip-type conductivity cell with a cell constant of 0.59 cm⁻¹ was used. The cell constant of the conductivity cell was determined by measuring the conductivity of aqueous potassium chloride solutions of different concentrations.¹⁸ A thermo stated water bath was used to maintain a constant solution temperature at the desired value having an accuracy of \pm 0.01 °C.

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

Results and Discussion:

Conductance study

In the present work, complex formation reaction between M^{2+} (Ni²⁺, Mg²⁺, Co²⁺ and Ca²⁺) and AML was studied by measuring the changes in molar conductance and the accompanying changes in the thermodynamic parameters like free energy (ΔG^0), enthalpy (ΔH^0) and entropy (ΔS^0) in pure DMSO, MeOH and the mixtures of DMSO with MeOH and water at different temperatures. The molar conductance (Λ_M) versus [L]/[M^{2+}] were recorded at three temperatures in pure DMSO as well as DMSO-Water(v/v % = 75/25, 50/50, 25/75) binary solvent mixtures shown in Fig.1-4. Such plots give direct evidence for the stoichiometry of the complex formed.







Fig. 3. Molar conductance (Λ_M) versus mole ratio $[L]/[Co^{2+}]$ plots for $[Co-AML]^+$ complex in pure DMSO and DMSO-Water binary solvent mixtures at different temperature:

<u>→</u> 303.15 K <u>→</u> 313.15 K → 323.15 K



Fig. 2. Molar conductance (Λ_M) versus mole ratio $[L]/[Mg^{2+}]$ plots for $[Mg-AML]^+$ complex in pure DMSO and DMSO-Water binary solvent mixtures at different temper



Fig. 4. Molar conductance (Λ_M) versus mole ratio $[L]/[Ca^{2+}]$ plots for $[Ca-AML]^+$ complex in pure DMSO and DMSO-Water binary solvent mixturesat different temperature:

The molar conductance (Λ_M) versus [L]/[M²⁺]were recorded at three temperatures in pure DMSO, pure MeOH and DMSO-MeOH(v/v % = 75/25, 50/50, 25/75) binary solvent mixtures shown in Fig. 5-8. Such plots give direct evidence for the stoichiometry of the complex formed.







Fig. 7. Molar conductance (Λ_M) versus mole ratio $[L]/[Co^{2+}]$ plots for $[Co-AML]^+$ complex in pure DMSO, pure MeOH and DMSO-MeOH binary solvent mixtures at different temperature:



As clear from these figures that there is a constant increase in the molar conductance of the solutions in pure MeOH and DMSO upon addition of AML. This complementary effect indicates that the complexed cations in pure MeOH and DMSO are more mobile compared to the free solvated M^{2+} cations. Further, the

corresponding slopes of these plots change at a point where the $[L]/[M^{2+}]$ mole ratio is 1 which indicates that the stochiometry of the formed complexes is 1:1.

Formation constants

The formation constant values in pure and binary solvent systems at different temperature are shown in Table 2. The values of formation constant $(\log K_f)$ increased with increase in temperature, in pure as well as binary solvent mixtures. In case of pure DMSO and pure MeOH, the value of LogK_f is higher in MeOH compare to DMSO, because MeOH with low DN(19.0)^{19,20} is poorly solvates the cation and thus can be easily remove to form the complex. In most of all the cases Log K_f value increases with increase in the concentration of DMSO. This is due to the high dielectric constant of DMSO which increases the electrostatic interaction between negative ions and the positive ions resulting in the high stability of the Mⁿ⁺-Ligand complexes. In case of DMSO-MeOH binary solvent system non linear behaviour is observed. This is due to the interaction between the solvent molecules in their mixtures due to H-bonding which alters the structure of the mixed solvent and thereby changing solvation behaviour towards M²⁺ (Ni²⁺, Mg²⁺, Co²⁺ and Ca²⁺) cations, ligand and complexes. This further emphasizes the critical role of non-aqueous solvent systems on the complexation reactions.

Table 1. The values of Log K_f of AML-Mⁿ⁺ complex in pure DMSO, pure MeOH, DMSO-Water and DMSO-MeOH binary mixtures at different temperatures.

Complex	Solvent Medium	$\log K_{f^{\pm}}SD^{a}$		
		At 303.15 K	At 313.15 K	At 323.15 K
AML- Ni ²⁺	Pure Water	b	b	b
	75 % Water-25 % DMSO	4.415±0.006	4.426±0.004	4.439±0.005
	50 % Water-50 % DMSO	4.420±0.005	4.439±0.003	4.457±0.004
	25 % Water-75 % DMSO	4.430±0.004	4.450±0.004	4.465±0.008
	Pure DMSO	4.469±0.004	4.488 ± 0.004	4.507±0.008
	75 % DMSO-25 % MeOH	4.497±0.007	4.517±0.003	4.540±0.006
	50 % DMSO-50 % MeOH	4.521±0.003	4.535±0.006	4.546±0.007
	25 % DMSO-75 % MeOH	4.509±0.005	4.521±0.005	4.531±0.005
	Pure MeOH	4.510±0.004	4.523±0.006	4.537±0.008
AML- Mg ²⁺	Pure Water	b	b	b
	75 % Water-25 % DMSO	4.388±0.006	4.412±0.004	4.436±0.005
	50 % Water-50 % DMSO	4.415±0.005	4.429±0.003	4.444 ± 0.004
	25 % Water-75 % DMSO	4.420±0.004	4.440±0.004	4.454±0.008
	Pure DMSO	4.446±0.004	4.466±0.004	4.487±0.008
	75 % DMSO-25 % MeOH	4.461±0.007	4.479±0.003	4.497±0.006
	50 % DMSO-50 % MeOH	4.516±0.003	4.525±0.006	4.533±0.007
	25 % DMSO-75 % MeOH	4.503±0.005	4.512±0.005	4.523±0.005
	Pure MeOH	4.501±0.004	4.513±0.006	4.524±0.008
AML- Co ²⁺	Pure Water	b	b	b
	75 % Water-25 % DMSO	4.367±0.006	4.387±0.004	4.408±0.005
	50 % Water-50 % DMSO	4.402±0.005	4.412±0.003	4.422±0.004
	25 % Water-75 % DMSO	4.405±0.004	4.426±0.004	4.447±0.008

	Pure DMSO	4.437±0.004	4.457±0.004	4.476±0.008
	75 % DMSO-25 % MeOH	4.451±0.007	4.466±0.003	4.481±0.006
	50 % DMSO-50 % MeOH	4.507±0.003	4.516±0.006	4.525±0.007
	25 % DMSO-75 % MeOH	4.492±0.005	4.504±0.005	4.515±0.005
	Pure MeOH	4.489±0.004	4.495±0.006	4.500±0.008
AML-Ca ²⁺	Pure Water	b	b	b
	75 % Water-25 % DMSO	4.349±0.006	4.370±0.004	4.394±0.005
	50 % Water-50 % DMSO	4.364±0.005	4.383±0.003	4.403±0.004
	25 % Water-75 % DMSO	4.390±0.004	4.405±0.004	4.418±0.008
	Pure DMSO	4.396±0.004	4.417±0.004	4.434±0.008
	75 % DMSO-25 % MeOH	4.404±0.007	4.441±0.003	4.483±0.006
	50 % DMSO-50 % MeOH	4.500±0.003	4.511±0.006	4.521±0.007
	25 % DMSO-75 % MeOH	4.470±0.005	4.485±0.005	4.500±0.005
	Pure MeOH	4.464±0.004	4.486±0.006	4.507±0.008

 $^{a}SD =$ standard deviation, b = The data cannot be fitted to equations

The formation constant for $[M^{2+}-AML]^+$ complex in DMSO-Waterand DMSO-MeOH binary solvent mixtures at different temperatures is presented in Supplementary Table 1. As there was very little change in the logK_f values with changes in binary composition compared to other solvent mixtures.

Effect of Ionic size on formation constant:

It is observed that in case of complexes of AML with Mg^{2+} and Ca^{2+} , Mg^{2+} forms more stable complex than AML-Ca²⁺ complexes. This is attributed to the ionic radii of Mg^{2+} and Ca^{2+} . As the ionic radii of Mg^{2+} is lower than the ionic radii of Ca^{2+} the specific charge per unit area increases. Hence, the metal's attraction for the ligand increases. So, Mg^{2+} form more stable complex than Ca^{2+} . In the case of Co^{2+} and Ni^{2+} complexes with AML, it is observed that the stability of AML-Ni²⁺ complex is higher than the AML-Co²⁺ complexes. This is due to the lower ionic radii of Ni²⁺.

It is observed that the AML form more stable complexes with Co^{2+} and Ni^{2+} compare to Ca^{2+} . This is due to the fact that Ca^{2+} has inert gas confirguration in the outermost shall whereas Co^{2+} and Ni^{2+} have pseudo inert gas confirguation(n-1) sp⁶d¹⁰ in the outer most shall. The latter confirguration much poorer in shielding the excess positive charges located on the nucleus than the former confirguration. So, the effective nuclear charge actually larger in case of Co^{2+} and Ni^{2+} , compare to Ca^{2+} . It means Co^{2+} and Ni^{2+} will behave as if is possesses grater nuclear charge. So Co^{2+} and Ni^{2+} have greater attraction for the electrons of AML. So, Co^{2+} and Ni^{2+} form more stable complexes with AML.



Fig. 9. Variation of log K_f for AML-Ni²⁺, AML-Mg²⁺, AML-Co²⁺ and AML-Ca²⁺ complexes versus cationic radius in pure DMSO and DMSO-Water binary systems at 303.15 K, 313.15K and 323.15K.



Fig. 10. Variation of log K_f for AML-Ni²⁺, AML-Mg²⁺, AML-Co²⁺ and AML-Ca²⁺ complexes versus cationic radius in pure DMSO, MeOH and DMSO-MeOH binary systems at 303.15 K, 313.15K and 323.15K.

Thermodynamic considerations

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 in the binary solvent mixtures. These thermodynamic quantities were evaluated from the corresponding slope and intercept of the van't Hoff plots of $\ln K_f$ vs. 1000 T⁻¹ respectively in the pure and binary solvent mixtures (Fig. 11,12).



Fig. 11: van't Hoff plots for [M–AML]⁺ complex in a pure DMSO and their binary solvent mixtures.



Fig. 12: van't Hoff plots for [M–AML]⁺ complex in a pure DMSO, pure MeOH and their binary solvent mixtures.

The thermodynamic data shown in Table 2clearly indicates that the values of ΔH^0 and ΔS^0 vary with change in solvent composition. In all the cases, the $[M^{2+}-AML]^+$ complexation reactions were enthalpydestabilized, where it was entropy stabilized. The change in entropy on account of complexation can be related to several factors like change in the conformation of the ligand due to complexation with the cation, its size and its ability to solvate free and complexed cation. The positive values for ΔS^0 can be explained based on increased flexibility of the ligand upon complexation due to the increase in degree of freedom as a result of desolvation of the cation and the ligand. The changes in enthalpy for complexation reactions can be attributed to difference in solvation, metal ion induced steric deformation of the ligand, intermolecular ligand-ligand repulsion and others.^{21,22}

Complex	Solvent Medium	$\Delta G^{o} \pm SD^{a}$ (kJ.mol ⁻¹)	$\frac{\Delta H^{o} \pm SD^{a}}{(kJ.mol^{-1})}$	$\Delta S^{o} \pm SD^{a}$ (J.mol ⁻¹ K ⁻¹)
AML- Ni ²⁺	Pure Water	b	b	b
	75 % Water-25 % DMSO	-25.63±0.09	2.24±0.1	91.86±7
	50 % Water-50 % DMSO	-25.65±0.1	3.46±0.09	96.02±5
	25 % Water-75 % DMSO	-25.71±0.09	3.27±0.11	95.61±6
	Pure DMSO	-25.94 ± 0.08	3.55±0.09	97.27±5
	75 % DMSO-25 % MeOH	-26.10±0.1	4.02±0.1	99.35±7
	50 % DMSO-50 % MeOH	-26.24±0.09	2.34±0.09	94.28±6
	25 % DMSO-75 % MeOH	-26.17±0.08	2.06 ±0.1	93.11±7
	Pure MeOH	-26.33±0.09	2.52±0.12	94.61±5
AML- Mg ²⁺	Pure Water	b	b	b
	75 % Water-25 % DMSO	-25.47 ± 0.08	4.48±0.09	98.85±5
	50 % Water-50 % DMSO	-25.63±0.09	2.71 ±0.1	93.45±7

Table 2. Thermodynamic parameters for AML-Mⁿ⁺ complexes in pure DMSO, pure MeOH, DMSO-Water and DMSO-MeOH binary systems at 303.15 K.

	25 % Water-75 % DMSO	-25.65±0.1	3.18±0.09	95.11±5
	Pure DMSO	-25.80±0.09	3.83±0.11	97.77±6
	75 % DMSO-25 % MeOH	-25.89±0.06	3.36±0.08	96.52±8
	50 % DMSO-50 % MeOH	-26.21±0.09	1.58 ± 0.08	91.70±5
	25 % DMSO-75 % MeOH	-26.14±0.1	1.87±0.1	92.36±7
	Pure MeOH	-26.13±0.09	2.16±0.09	93.28±6
AML- Co ²⁺	Pure Water	b	b	b
	75 % Water-25 % DMSO	-25.35±0.09	3.83±0.1	96.27±7
	50 % Water-50 % DMSO	-25.48±0.1	1.87±0.09	90.45±5
	25 % Water-75 % DMSO	-25.57±0.09	3.93±0.11	97.27±6
	Pure DMSO	-25.75±0.06	3.64±0.08	96.94±8
	75 % DMSO-25 % MeOH	-25.84±0.09	2.81±0.08	94.48±5
	50 % DMSO-50 % MeOH	-26.17±0.1	1.68±0.1	91.78±7
	25 % DMSO-75 % MeOH	-26.01±0.09	2.15±0.09	93.11±6
	Pure MeOH	-26.06±0.08	1.03±0.09	89.29±5
AML-Ca ²⁺	Pure Water	b	b	b
	75 % Water-25 % DMSO	-25.24±0.1	4.21±0.1	97.10±7
	50 % Water-50 % DMSO	-25.33±0.09	3.64±0.09	95.52±6
	25 % Water-75 % DMSO	-25.48±0.08	2.61±0.1	92.70±7
	Pure DMSO	-25.52±0.07	3.55±0.09	95.86±9
	75 % DMSO-25 % MeOH	-25.56±0.08	7.39±0.1	108.66±4
	50 % DMSO-50 % MeOH	-26.12±0.09	1.96±0.12	92.62±5
	25 % DMSO-75 % MeOH	-25.94±0.06	2.81±0.09	94.77±4
	Pure MeOH	-25.92±0.07	4.02±0.08	98.77±3

 $^{a}SD =$ standard deviation, b = The data cannot be fitted to equations.

Conclusion:

In the present work complexation reaction between $M^{2+}(Ni^{2+}, Mg^{2+}, Co^{2+} and Ca^{2+})$ cation and AML has been studied in pure DMSO, pure MeOH and their binary solvent mixtures(DMSO-MeOH and DMSO-Water) by conductometry. Results obtained indicate that the nature and composition of the solvent systems play very important role in the thermodynamic stability and selectivity of the M^{2+} cations complexes formed. The stoichiometry of the [M²⁺-AML]⁺ in pure as well as binary solvent mixtures was 1:1. The formation constant of $[M^{2+}-AML]$ complex in pure solvents was according to the reverse order of their solvating ability as per the Gutmann donor number (DN) concept. The observed order of selectivity was MeOH (DN 19.0) > DMSO (DN 29.8) > Water (DN 78.36). In addition to dielectric constant and donor ability of solvent, size of the metal ion may influence the complex formation. A monotonic behaviour was observed between the LogK_f values and the composition of the solvent systems in all the cases, except DMSO-MeOH binary mixtures. It is important to note that in DMSO-Water, the log K_f values increases with increase in v/v% of DMSO in the binary solvent mixtures. The non-linear behavior in DMSO-MeOH can be related to the interaction between the solvent molecules in their binary mixtures (due to H-bonding), which alters the structure of the mixed solvents and thereby changing the solvation behavior towards $M^{2+}(Ni^{2+}, Mg^{2+}, Co^{2+} and Ca^{2+})$ cations, ligand and the complex. Further, the complexation process was entropy driven in most of the solvent systems studied and the reactions were spontaneous.

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