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Research paper

Study of ternary association of anti-microbial drug 1, 10-phenanthroline and α - amino acid with copper salt, an ultrasonic investigation of competitive interaction

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Abstract

Molecular interaction studies using ultrasonic technique and spectroscopic investigation in ternary liquid mixture of drug 1,10-Phenanthroline, an α- amino acid Glycine and a transition metal salt like $CuCl_2$ in aqueous medium has been carried out at 300.15K and 2 MHz frequency. Using experimental values of density (ρ),ultrasonic velocity (U) and UV analysis, different acoustical parameters such as adiabatic compressibility (β),intermolecular free length (L_f), acoustic impedance (z),relative association (RA),apparent molar volume (V_ϕ), apparent molar adiabatic compressibility (K_ϕ) are evaluated for the mixture of drug, glycine and inorganic salt $CuCl_2$ at various concentrations. The ultrasonic and spectroscopic investigation clearly shows coordinative association of drug as a ligand with transition metal salt. Further interaction of glycine as an α- amino acid indicates a competitive association in the ternary system. The outcomes were expressed in terms of molecular interactions and the variation in parameters under varying solute concentrations providing conclusive remarks regarding the strength of intermolecular interactions in the ternary system with a bio-physical novelty.

Keywords: *1,10-Phenanthroline; α - Amino Acid; Adiabatic Compressibility; Acoustic Impedance; Apparent Molar Volume; Relative Association.*

1. Introduction

Drug-metal ion interaction plays a vital role in all the metabolic pathways of biological processes occurring inside the body which led to modern drug discovery. To interpret the physiochemistry of biological systems, it is essential to examine the properties of drug with metal ions. Transition metal salts interact with bioactive molecules like amino acids and form ternary liquid mixture with biocompatible drug 1,10-phenanthroline which provides a rich platform for design of novel antimicrobial drug (Kumar & Behal 2016). Ultrasonic technique has been employed to investigate the thermodynamic and physiochemical parameters of the liquid mixtures to understand solute-solute and solute-solvent interactions. Identification of interaction between metal ions with drug and amino acid through UV spectroscopic analysis also gives wealth of information regarding complex drug action results from various kinds of physicochemical interactions, e.g., ionic or covalent, charge transfer, hydrogen bonding, ion–dipole interactions, hydrophilic interactions (Iqbal & Chaudhry 2009).
Phenanthrolines (phens) are diazaphenanthrene analogs - polycyclic aromatic hydrocarbons present in sterols, sex hormones, cardiac glycosides, bile acids, and morphine alkaloids (Bencini & Lippolis 2010). Among nitrogen heterocycles, phens and their derivatives represent an important class of organic molecules that have attracted considerable interest from both synthetic and medicinal chemists, due to the presence of the phen ring system as a structural pattern in several natural biologically important products whose nitrogen atoms are beautifully placed to act cooperatively in cation binding. A wide range of biological and physiological activities are displayed by phen derivatives; thus, the synthesis of new compounds containing this core is currently an interesting research proposal (Nalle et al. 2016, Abebe et al. 2018). O-Phens haves attracted special interest from researchers due to their various structural and chemical properties like rigidity, planarity, aromaticity, basicity, hydrophobicity and chelating capability, which makes them versatile starting materials in the area of materials science and in many fields of chemistry such as analytical, organic, inorganic, bioorganic, supramolecular coordination, and catalysis chemistry. The complexes of metals with o-phens may be stabilized in DNA linked through a series of weak interactions (e.g. π-stacking) associated with intercalation between aromatic heterocyclic base pairs, hydrogen bonds, van der Waals interactions, and groups with hydrophobic effects (Cardozo et al. 2015).
Glycine is unique among the proteinogenic amino acids in that it is achiral. It can fit into hydrophilic or hydrophobic environments since it exists as zwitter ion at natural pH, due to its minimal side chain of only one hydrogen atom. It is the simplest amino acid, functions as a neurotransmitter and is one of the principle components of structural proteins, enzyme and hormones. It's essential for the production of

many different acids, including nucleic acids, bile acids, creatine phosphate and porphyrins. Glycine also has positive applications for individuals suffering from neurobehavioral disorders, diabetes, chronic fatigue and certain cancers (Berger et al. 1998, Aragon &Corcuera 2005).

Copper is an important component of many enzymes in the body and play an important role in cell energy production. In addition, enzymes that are responsible for connective tissue proteins formation (collagen and elastin) require copper. Copper is necessary for the development and maintenance of blood vessels, skin, bones and joints. Copper is a component of the enzyme copper-zinc superoxide dismutase, which serves as an antioxidant essential to preserve the body from damage caused by free radicals. Copper is also involved in the metabolism of fat and cholesterol, as well as the normal functioning of insulin (which regulates the metabolism of sugar) (Arredondo & Nunez 2005, Chohan et al. 2006).

It is involved in the synthesis of prostaglandins (substances that regulate many functions such as heart rate, blood pressure and wound healing). Moreover, a survey of literature has shown that no experimental ternary volumetric and sound speed data on the antimicrobial drug 1,10-phenanthroline and glycine with transition metal salt $CuCl_2$ were reported earlier. Therefore, the present study was undertaken in order to have deeper understanding of the intermolecular interactions when 1,10-phenanthroline and glycine are mixed with $CuCl_2$ at 300.15K

2. Experimental

2.1. Materials

The drug 1,10-Phenanthroline procured from Sigma Aldrich (minimum Assay mass fraction purity 0.995) .Glycine (mass fraction >0.99) was obtained from SD Fine chemicals Ltd, India. Inorganic salt $CuCl_2.2H_2O$ was purchased from High media Pvt. ltd. having purity of ≈ 99.9%. All the chemicals were used after drying thoroughly in a vacuum oven. Doubly distilled deionised water with a specific conductance < 10^{-6} $S.cm^{-1}$ was used in our experiments and was degassed prior to making solutions.

2.2. Methods

The densities of the solutions were measured using a single stem bicapillary Pycnometer (Borosil glass). An analytical balance (SHIMADZU AX- 200,Japan) with a precision of ±0.1 mg was used for all weight measurements. The uncertainty in the mole fraction was found to be ±0.0001. The ultrasonic speeds in solutions were measured using a single crystal variable path multifrequency ultrasonic interferometer [M-81S, Mittal Enterprises, India] operated at a fixed frequency of 2 MHz. All measurements were carried out in an automatic digital temperature controlled high precision water thermostat maintained at the temperature of (25.00 ± 0.02)^{0}C. UV -Visible spectra of the pure components and the ternary mixture was recorded through Agilent Cary 100 UV-Visible spectrophotometer.

Ultrasonic and volumetric parameters were determined applying following equations.

i) Apparent molar volume ($V_ø$)

The apparent molar volume was calculated by using equation (1)

$$V_ø = \frac{M}{d0} - \left[\frac{d-d0}{d0}\right]\frac{1000}{m} \quad (1)$$

m = Molality in (mol kg^{-1})

M = Molecular mass of the solute (mol kg^{-1})

d_0, d are density of solvent and solute (Kg m^{-3})

ii) Adiabatic compressibility is calculated by using the equation (2)

$$\beta = 1/u^2 d \quad (2)$$

U = Ultrasonic velocity

d = Density of solution

iii) The apparent molar compressibility is calculated by using the relation

$$K_\Phi = \frac{1000}{md0}[[\beta - \beta 0] + \beta\, \phi_v \quad (3)$$

iv) Intermolecular free length has been evaluated by formula

$$L_f = K\sqrt{\beta s} \quad (4)$$

K = Jacobson constant, β_s = Compressibility parameter of the solution

v) Acoustic impedance is evaluated from the formula

$$Z = d.\ U \quad (5)$$

d = Density of solution ,U = ultrasonic velocity

vi) The relative association is a measure of solute-solute or solute- solvent interaction. Relative association is measured by the equation.

$$R_A = (\ d0/d)\left(\frac{U0}{U}\right)^{1/2} \quad (6)$$

d_o = density of solvent, d = density of solution

U_0 = ultrasonic velocity of solvent, U = ultrasonic velocity of solution

3. Result and discussion

Fig.1 shows comparative spectra of 1,10-phenanthroline, Glycine and $CuCl_2$ in aqueous Medium. 1,10-phenanthroline showed two peaks with λ_{max} at 260 nm. and 230 nm.$CuCl_2$ showed a single peak at 210nm.while in Glycine there was a peak at 250 nm. But the UV spectra of ternary mixture shows a wavelength shift followed by appearance of new peak which indicates that there is a complex formation between the ligands drug 1,10-phenanthroline and glycine with transition metal centre (Venkatramana et al. 2015).
With increase in concentration ,adiabatic compressibility of 1,10- phenanthroline decreases more prominently as compared to $CuCl_2$ and Glycine as shown in Fig.2.This can be attributed to the fact that there is the possibility of formation of coordinated complex of the bidentated drug 1,10-phenanthroline with inorganic salt. (Rajagopal&Jayabalakrishnan2010, Syal et al. 2005, Sonar et al. 2011).

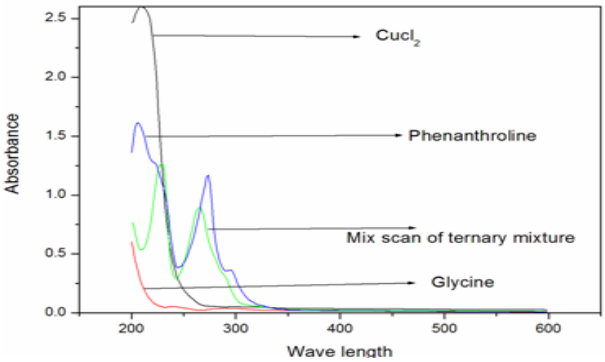

Fig. 1: Comparative UV – VIS Spectra of Ternary Mixture of 1, 10-Phenanthroline, Glycine and $CuCl_2$ Aqueous Medium.

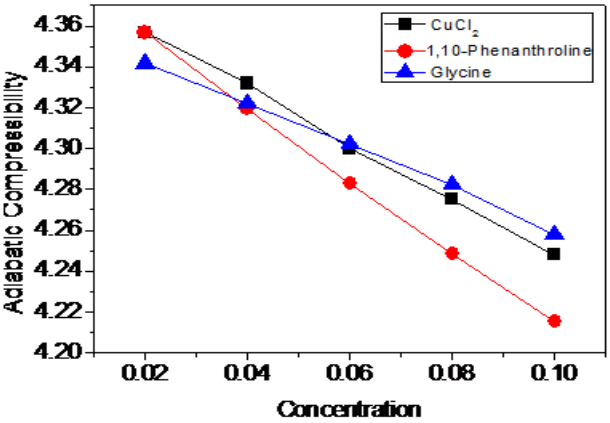

Fig. 2: Variation of Adiabatic Compressibility with Concentration.

Intermolecular free length of 1,10 -phenanthroline decreases appreciably (Fig.3) with increase in concentration as compared to $CuCl_2$ and Glycine. This signifies stronger association between the drug and glycine in polar protic solvent water and weaker drug-drug interaction. Decreased value of free length indicates the structure promoting behaviour and associative solvation of solute molecules (Tadkalkar et al. 2011, Eyring & Kincaud 1938).
With increase in concentration, acoustic impedance of 1,10- phenanthroline increases as represented in Fig.4.It may be due to stronger solute- solvent association. We all know that theoretical requirement of acoustic impedance is density and velocity which are increased with increase in concentration of solute in solution. It can be attributed to the effective solute- solvent association and weak solute-solute interaction. Z shows linear increasing variation with concentration of metal ion along with both the ligands i.e. 1,10- phenanthroline and glycine justify the formation of a coordinated complex (Naik et al. 2015, Naik et al. 2015).

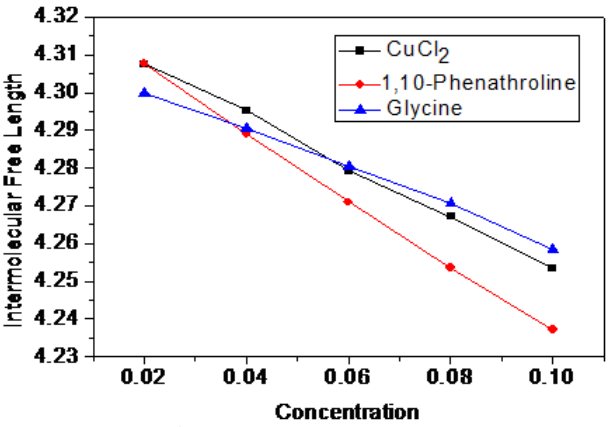

Fig. 3: Variation of Intermolecular Free Length with Concentration.

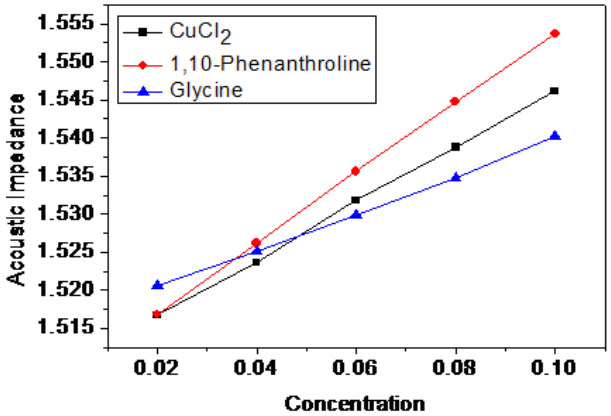

Fig. 4: Variation of Acoustic Impedance with Concentration.

Variation of apparent molar volume shows similar trend (Fig.5) in case of 1,10- phenanthroline and $CuCl_2$ i.e. with increase of concentration of the both, the positive value of partial molar volume decreases due to solute-solvent interaction indicating electrostatic solvation of ions. For glycine value of V_Φ shows a sudden decrease up to 0.04M concentration and then steadily decreases which indicates existence of weak glycine -solvent interaction. Evidently for the ternary system in aqueous medium the decreasing trend of V_Φ concludes strong drug-metal-amino acid interaction (Abdelkarim et al. 2015, Khan et al. 2015). Apparent molar adiabatic compressibility K_φ is a sensitive measure of solute solvent interactions existing in a solution. Here K_φ have high positive values for 1,10- phenanthroline (Fig.6) indicating strong association. The positive K_φ values indicate that the solute are loosely attached to solvent molecules and are more compressible. As the value slightly decreases, it indicates weak interaction for 1,10- phenanthroline -glycine- $CuCl_2$ system in aqueous medium (Gaba et al. 2016, Banik et al. 2012).

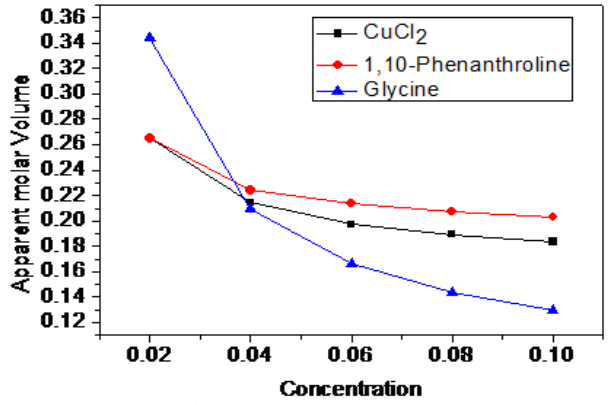

Fig. 5: Variation of Apparent Molar Volume with Concentration.

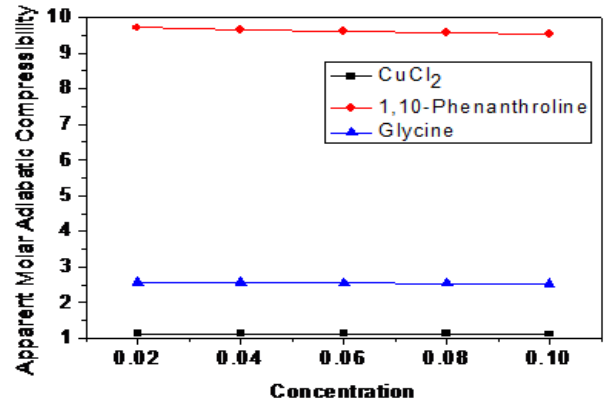

Fig. 6: Variation of Apparent Molar Adiabatic Compressibility with Concentration.

Relative association is the property of measure of extent of association of components in the medium. The relative association depends on either of breaking up of the solvent molecules on addition of solute to it or the solvation of ions that are present. At 2 MHz, RA increases which is due to the solvation of ions and significant solute-solvent interaction. All positive and steady increase in relative association in 1,10- phenanthroline -glycine- $CuCl_2$ system indicates high electrostatic dipole –induced dipole interaction between unlike molecules which result in contraction of volume.

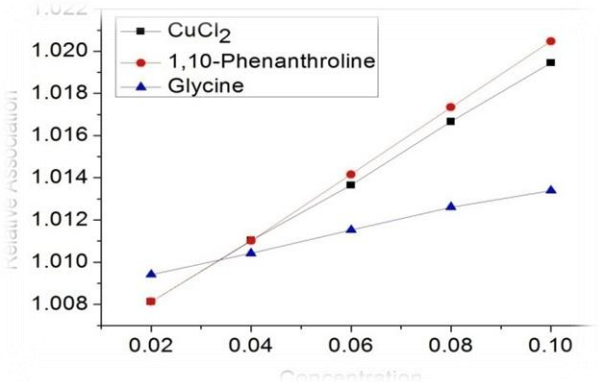

Fig. 7: Variation of Relative Association with Concentration.

Experimental data obtained for acoustical parameters at 300.15K are measured through ultrasonic interferometer are demonstrated in the following tables.

Table 1: Variation of [$CuCl_2$] with Fixed Concentration of Drug 1,10- Phenanthroline

[1,10-Phenanthroline]mol.L^{-1}	[$CuCl_2$]mol.L^{-1}	d kgm^{-3}	U (m/s)	β	Lf	Z	$V_ø$	$K_Φ$	R_A
0.02M	0.02M	1002.3	1513.264	4.35685E-10	4.30768E-11	1516744.51	-0.26502	1.13E-13	1.008128
0.02M	0.04M	1005.6	1515.128	4.33188E-10	4.29532E-11	1523612.72	-0.21428	1.13E-13	1.011032
0.02M	0.06M	1008.9	1518.276	4.29982E-10	4.27939E-11	1531788.66	-0.19701	1.12E-13	1.013648
0.02M	0.08M	1012.3	1520.092	4.27515E-10	4.2671E-11	1538789.13	-0.18933	1.12E-13	1.016659
0.02M	0.10M	1015.6	1522.456	4.24803E-10	4.25354E-11	1546206.31	-0.18353	1.12E-13	1.019445

Table 2: Variation of [1, 10-Phenolphthalein] with Fixed Concentration of $Cucl_2$

[1,10-Phenanthroline]mol.L^{-1}	[$CuCl_2$]mol.L^{-1}	Dkgm^{-3}	U (m/s)	β	Lf	Z	$V_ø$	$K_Φ$	R_A
0.02M	0.02M	1002.3	1513.264	4.35685E-10	4.30768E-11	1516744.51	-0.26499	9.72E-14	1.008128
0.04M	0.02M	1006	1517.024	4.31934E-10	4.28909E-11	1526126.14	-0.22413	9.67E-14	1.011013
0.06M	0.02M	1009.9	1520.52	4.28289E-10	4.27096E-11	1535573.15	-0.21334	9.62E-14	1.014154
0.08M	0.02M	1013.8	1523.772	4.24823E-10	4.25364E-11	1544800.05	-0.20757	9.58E-14	1.017345
0.10M	0.02M	1017.6	1526.856	4.21528E-10	4.23712E-11	1553728.67	-0.20285	9.54E-14	1.020471

Table 3: Variation of [Glycine] with Fixed Concentration of Phenolphthalein and $Cucl_2$

[1,10-Phenanthroline]mol.L^{-1}	[$CuCl_2$]mol.L^{-1}	[Gly]	d kgm^{-3}	U (m/s)	β	Lf	Z	$V_ø$	$K_Φ$	R_A
0.02M	0.02M	0.02M	1003.9	1514.73	4.34E-10	4.30E-11	1520643.47	-0.34462	2.56E-13	1.009410
0.02M	0.02M	0.04M	1005.4	1516.98	4.32E-10	4.2E-11	1525171.69	-0.20943	2.56E-13	1.010420
0.02M	0.02M	0.06M	1007	1519.27	4.30E-10	4.28E-11	1529910.93	-0.16593	2.55E-13	1.011517
0.02M	0.02M	0.08M	1008.6	1521.60	4.28E-10	4.27E-11	1534693.83	-0.14412	2.54E-13	1.012607
0.02M	0.02M	0.10M	1010.1	1524.85	4.25E-10	4.25E-11	1540253.01	-0.13001	2.53E-13	1.013393

4. Conclusion

Copper plays a vital role in activation of enzymes in our body and is responsible for connective tissue proteins formation (collagen and elastin). It is very important in creating the immune response during the inflammatory process or infection. Glycine is one of the principal components of structural proteins, enzyme and hormones.1,10-Phenanthroline is a dinitrogen polyheterocyclic aromatic derivative with a wide range of biological and physiological activities like antimicrobial properties. Molecular 1,10-phenanthroline has superb intercalation ability with DNA base pairs. However, it could not be used for medicinal applications. This is due to its toxicity caused by inhibiting metalloenzymes via its chelating nitrogen atoms. Moreover, the toxicity has been avoided for its attractive features of coordinating with transition metals.

Analysis of UV spectra indicates shifting of peaks in ternary mixture which concludes the formation of coordinate complex with bidentated drug phenanthroline and Glycine with transition metal copper.

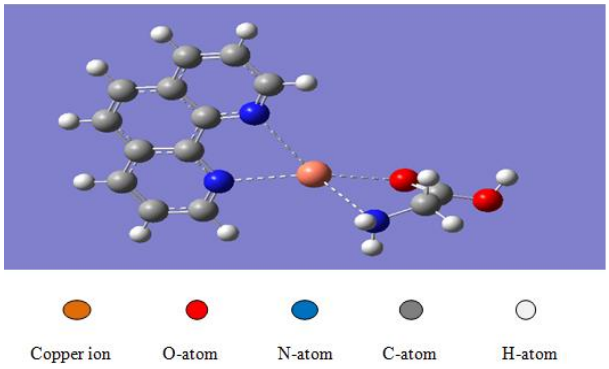

Fig. 8: Molecular Binding between the Drug, Amino Acid and Salt.

The trends of ultrasonic parameters like adiabatic compressibility, intermolecular free length, acoustic impedance, relative association, apparent molar volume, apparent molar adiabatic compressibility etc. shows the existence of strong competitive interactions between two active ligands (phenanthroline and Glycine) with a bioactive transition metal centre. Undoubtedly it will act as a superb alternative for antimicrobial and antioxidant solution in our biological system with versatile pharmacological applications.

5. Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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