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TBAB Influence on chemical speciation of binary complexes of L-glutamine and succinic acid with divalent metal ions of first transition series and Irving-Williams order

U. S. N. Prasad[1], R. K. Adhikamsetty[2*], V. S. Rao[3], G. N. Rao[4]
[1]*Department of Chemistry, AdikaviNannayya University, Rahamahendravaram, India*
[2]*Department of Chemistry, M.R.P.G.College, Vizianagaram, India*
[3]*Department of Chemistry, Govt. Arts College, Rajamahendravaram, India*
[4]*Honorary Professor & Former Vice Chancellor, Andhra University, Visakhapatnam, India*

Abstract: Tetrabutylammonium bromide (TBAB) influence on the binary complexes of divalent selected metal ions of first transition series;Manganese(II), Cobalt(II), Nickel(II), Copper(II) and Zinc(II) with L-glutamine (Gln) and succinic acid (Suc) has been studied pH metrically at an ionic strength of 0.16 mol dm^{-3} and temperature 303 K. Various models for the species of these ligands are refined by using the computer programs SCPHD and MINIQUAD75. The active species of the selected metal ions are MLH for succinic acid and ML_2H for L-glutamine. The trend in the variation of stability constants with atomic number is explained on the basis of ionic radii of metal ions, electrostatic and non-electrostatic interactions in solutions. The species distribution with pH, plausible equilibria and structures of the species are also presented.

Keywords: Complex equilibria,Speciation, L-glutamine, Succinic acid,Zinc, TBAB, MINIQUAD75.

1. Introduction

Metal ions like Mn(II), Fe(II), Co(II), Ni(II), Cu(II), Zn(II) in trace quantity plays vital role in biological functions. Metalloenzymes or metal activated enzymes participate in catalytic processes of the metabolic reactions [1]. The activity of these enzymes is due to the metal-enzyme-substrate complexes. Manganese performs a remarkable range of catalytic functions [2], especially in the Mn-clusters. For example, the unique redox properties of Mn are essential to the generation of dioxygen from water in the oxygen-evolving complex [3]. It is also useful in the production of the deoxyribonucleotide building blocks needed for DNA synthesis [4]. Mn(II) ions can be used as Lewis acid catalysts by numerous enzymes [5], including glutamine synthetase. The human body stores manganese in the liver, pancreas, bones, kidneys and brain [6]. It helps to support the bones by activating crucial enzymes involved in the formation of bone, cartilage and collagen.The soft tissue is concentrated in the liver and kidneys [6]. The human body contains about 12 mg of manganese, mostly in the bones.Along with vitamin K, manganese aids the formation of blood clots [7].

Cobalt is key constituent of cobalamin essential for the production of red blood cells. It acts as coenzyme in several biochemical processes. It speeds up ATP turnover. Cobalt is present in glutamate mutase, dialdehydase, methionine synthase and arginase. Excess cobalt leads to cardiomyopathi [8]. Urease is a Nickel dependent metallo enzyme [9], which is required in nucleic acid and lipid metabolism and iron absorption. Nickel deficiency causes [10] depressed growth and impaired iron absorption. Copper is essential [11] for maintaining the strength of the skin, blood vessels, epithelial and connective tissue throughout the body. It is useful in the production of hemoglobin, myelin and melanin and also keeps thyroid gland functioning normally. Deficiency of copper can produce an extensive range of symptoms, like in hernias, aneurysms, blood vessel breakage manifesting as bruising or nosebleeds, loss of pigment, weakness, fatigue, skin sores and poor thyroid function.Zinc is involved in numerous processes of cellular metabolism [12]. About 10% of human proteins potentially bind with zinc, in addition to hundreds which transport zinc. It is required for the catalytic activity of more than 200 enzymes [13,14]and it plays a role in immune function [15], wound healing, protein synthesis, DNA synthesis and cell division [16]. Zinc is required for proper sense of taste and smell [17,18] and supports normal growth and development during pregnancy, childhood, and adolescence [19]. It possesses antioxidant properties, which may protect against accelerated aging and helps speed up the healing process of injuries [20].

L-Glutamine (Gln) and succinic acid (Suc) are biologically important ligands [21]. Gln is a conditionally essential during inflammatory conditions such as infection and injury under appropriate conditions. Gln can act as a respiratory fuel and it can enhance the stimulation of immune cells [22]. Gln in the diet increased survival to bacterial challenge [23],is required to support optimal lymphocyte proliferation [24], production of cytokines by lymphocytes and macrophages [25] and it is highly conserved outer sphere residue in the active site of Escherichia coli (E. Coli) manganese superoxide dismutase [26]. Suc can be used for manufacture of medicaments or nutritional supplements effective for treating insulin resistance [27] in mammals.Suc is involved in citric acid cycle [28] and Glyoxalate cycle. Succinate is obtained by the oxidation of succinic semialdehyde. In neurotransmission, Gamma aminobutyric acid (GABA) is inactivated by transamination to succinic semi-aldehyde, which is then oxidized to succinate. The concentration of succinic acid in human blood plasma is 0.1-0.6 mg/dl. Succinatestimulates insulin secretion and pro-insulin biosynthesis [29]. Tetrabutylammonium bromide (TBAB) is a quaternary ammonium salt act as a cationic surfactant and has a positively charged head group with a bromide counter ion which plays important role in modifying the behavior of aqueous media. It is a commonly used as a phase transfer catalyst. It is used to prepare many other tetrabutylammonium salts via salt metathesis reactions [30].

Protonation and complexation equilibria of Gln and Suc in urea-water [31], dimethylformamide-water [31], ethyleneglycol-water [32], acetonitrile-water [21] and TBAB-water[33]media were studied to thoroughly understand the speciation of its complexes. The protonation constants of Gln and Suc are correlated [32] with the dielectric constant of the medium using various solvents. Effect of urea [34] and effect of DMF [35] on cobalt(II) and nickel(II) complexes of Gln and Suc have been studied.Similarly, speciation of cobalt(II) and nickel(II) ternary complexes of L-glutamine and succinic acid in urea-water [36] and DMF-water [37] mixtures were reported and no such studies are reported in the literature. Hence, the author has studied the influence of TBAB on speciation of selected metal ion complexes with Gln and Suc in 3.0 and 1.0%w/v of TBAB-water mixtures respectively in the present study.

2. Materials and Methods

A 99.5% pure TBAB (Sigma-Aldrich) was used without further purification. All the selected metal chlorides (Manganous chloride, Cobaltous chloride, Nickel chloride, Copper chloride and Zinc chloride), L-glutamine and succinic acid (E. Merck, Germany) solutions were prepared in triple distilled water. To assess the errors that might have crept into the determination of the concentrations of above solutions, the data were subjected to ANOVA [38]. The strength of alkali (NaOH) was determined using the Gran plot method [39]. Alkalimetric titrations were carried out in the medium containing 1.0% and 3.0% w/v of TBAB in water for both Suc and Gln respectively. The experiments were carried out in 1:2 and 1:3 metal-ligand ratios for both succinic acid and L-glutamine with the metal ion at an ionic strength of 0.16 mol dm^{-3} with NaCl at 303.0±0.1 K using a Control Dynamics-APX 175E/CpH meter.

The glass electrode was equilibrated in inert electrolyte. The correction factor, log F to correct the pH meter dial reading, was determined using the computer program SCPHD [40]. Other experimental details are given elsewhere [38]. The approximate protonation constants were calculated using SCPHD. By following some heuristics [41] in the refinement of the stability constants and using the statistical parameters of the least squares residuals, the best-fit chemical models for each system were arrived at using the computer program MINIQUAD75 [42].

3. Results and Discussion

The amino and carboxyl groups of L-glutamine and the two carboxyl groups of succinic acid are protonated. Alkalimetric titration curves in TBAB-water mixture revealed that the active forms of Gln and Suc are in the pH ranges 2.0–10.0 and 2.0-7.0, respectively [33].

Table 1. Best fit models for binary complexes of M(II) with Succinic acid in 1.0%w/vTBAB-water mixtures(pH 2.0 – 7.0, Temp = 303 K, ionic strength= 0.16mol.dm^{-3})

S.No	Metal ion, M(II)	logβ_{mlh}(SD) 111	NP	Skewness	Kurtosis	χ^2	Ucorr x 10^6	R-factor
1	Mn(II)	7.63(2)	128	0.02	2.70	29.46	2.99	0.0776
2	Co(II)	7.64(5)	89	0.75	3.73	90.28	4.43	0.0137
3	Ni(II)	7.75(2)	126	-0.09	2.99	19.54	2.38	0.0691
4	Cu(II)	7.89(1)	132	0.31	3.42	86.3	1.19	0.0596
5	Zn(II)	7.79(1)	135	1.49	5.51	19.6	1.96	0.0194

Note: No of titrations in each percentage is 6.

Models containing various numbers and combination of complexes of the selected metal ions with Gln and Suc are generated using an expert system package CEES [43]. These models were inputted to MINIQUAD75, along with the alkalimetric titration data and the best-fit models were obtained. The final models for the selected metal ions with Suc contain MLHand ML_2H for Gln as given in Tables 1 and 2, along with the statistical parameters.

Table 2. Best fit models for the binary complexes of M(II) with L-Glutamine in 3.0%w/v TBAB-water mixtures(pH 2.0 to 6.0, Temp = 303 K, ionic strength = 0.16mol.dm^{-3})

S.No	Metal ion, M(II)	logβ_{mlh} (SD) 121	NP	Skewness	Kurtosis	χ^2	Ucorr x 10^6	R-factor
1	Mn(II)	19.61(2)	49	-0.78	0.11	1.73	3.13	0.0149
2	Co(II)	22.56(1)	43	0.10	1.75	49.05	8.74	0.1064
3	Ni(II)	23.09(9)	46	-0.59	3.22	1.05	1.79	0.0297
4	Cu(II)	23.39(2)	38	0.29	1.19	11.30	1.38	0.0421
5	Zn(II)	23.38(8)	31	-0.69	3.22	2.05	1.05	0.0413

Note: No of titrations in each percentage is 6.

The skewness is between -0.19 to 1.49 for succinic acid and -0.78 to 0.10 for L-glutamine indicates that the residuals follow Gaussian distribution and so least squares technique can be applied. The low standard deviation in the model parameters (logβ) illustrates the adequacy of the models.

3.1. Influence of TBAB on speciation of binary complexes

TBAB acts as structure-breaker of water structure due to large hydrophobic group of TBAB and thus forming cages around itself, with empty spaces in the structure [44,45]. TBAB is a hydrotrope in presence of water [46]and CMC for TBAB is 0.2632mol/L at 303.16K in aqueous solutions [47]. The anisotropic water distribution within micellar structure causes non-uniform micropolarity, microviscosity and degree of hydration within the micellar media [48]. The degree of stability of complexes could be measured in terms of the magnitude of the overall stability constant of each species formed in metal ligand dynamic equilibria. The linear and non-linear variations in the magnitude of the stability constants of metal-ligand complexes are due to electrostatic and non-electrostatic opposing factors, respectively. The viscosity is strongly influenced by the ability of the liquid to transport the mass within the liquid, which is immensely responsible for any changes in the chemical reactions. The high viscosity of the TBAB causes the limited mobility of species within, which in turn causes a low conversion of products, especially in enzymatic reactions [49]. The linear variation of species with increasing % of TBAB indicates that electrostatic forces are dominating the equilibrium process under the present experimental conditions.

In the present study, results of the stability constants were found to be linearly increasing from atomic number 25 is Mn(II) to 29 is Cu(II) then decreased to atomic number 30 is Zn(II) in TBAB-water mixtures for both Suc and Gln complexes. This concept is in good agreement with the Irving-Williams order, but log β values are low in TBAB when compared to aqueous media. Dielectric constant(ε) is one of the most and prominent solvent properties that could be altered [50] by surfactants in the given titration mixtures. The dielectric constant of water is 78.4 and that for TBAB is 8.93 at 25°C is much lower than [51,52] aqueous media, but no data in the literature for corresponding percentages. Hence, the authors are taken %w/v TBAB on the abscissa. The destabilization of the metal ligand complexes could be attributed mainly to the low dielectric constant of the surfactant mediated solvent compared to aqueous medium. Moreover, the destabilization effect of the low dielectric constant is synergized by the cationic surfactant TBAB, which causes low logβ values as shown in Fig 1.

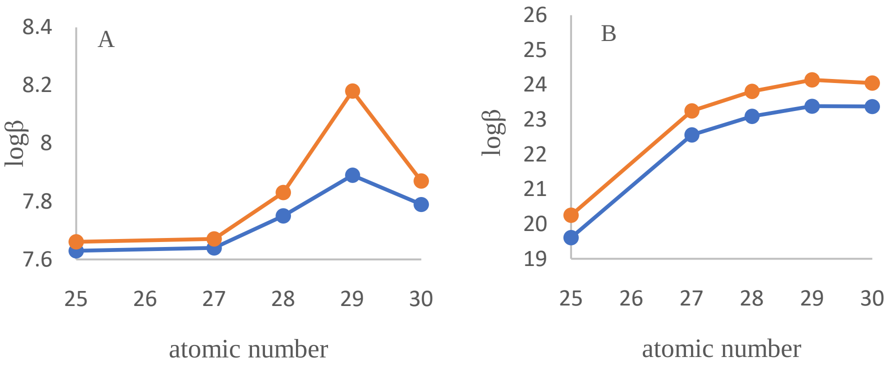


Fig 1: Variation of logβ Vs atomic number (A) MLH species of M-Suc in 1.0%w/v TBAB-water mixture and (B) ML_2H species of M-Gln in 3.0%w/v TBAB-water mixture. (●) in TBAB media and (●) in aqueous media.

The charges of species are omitted for clarity. Proton accepting ability of the ligand increases in acidic environment (in TBAB). Hear, the metal ion, protons and TBAB are competing to bind with the ligand. Hence, decreasing the availability of the electron pairs of the ligand made difficult to easily donate to vacant shell of the metal ion in the formation of complexes. As a result of these competing processes, the stability of the complex and values of the stability constants decreased in TBAB-water mixture.

The plausible equilibria for M(II) with succinic acid

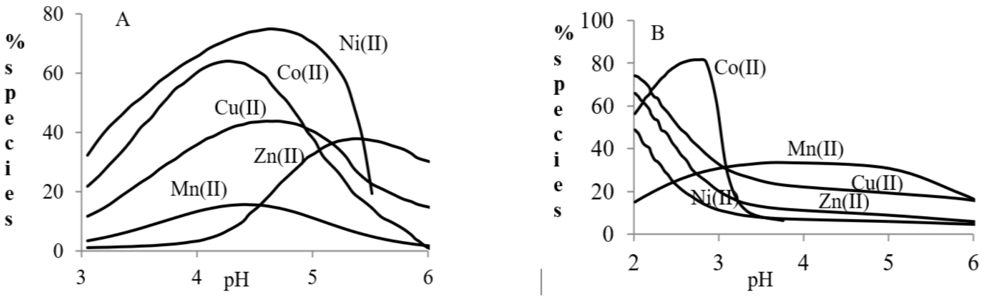
M(II) + LH	MLH (major)	….(a)
MLH	$ML + H^+$ (at higher pH)	….(b)

The plausible equilibria for M(II) with L-glutamine

M(II) + LH	MLH (minor)	….(c)
MLH + LH	$ML_2H + H^+$ (major)	….(d)
ML_2H	$ML_2 + H^+$(at higher pH)	….(e)

3.2. Distribution diagrams

Succinic acid has two carboxyl groups and both are protonated. The various forms of ligands exist in the pH range of study (2.0-10.0) are LH_2^+, LH and L^- for Gln and LH_2, LH^- and L^{2-} for Suc. L-glutamine has three functional groups (amino, carboxyl and amido) but only amino and carboxyl groups can associate with protons. Perusal of the models indicates that the species ML_2H for Gln and MLH for Suc are highly stable at lower pH are confirmed by MINIQUAD75 (Fig 2).



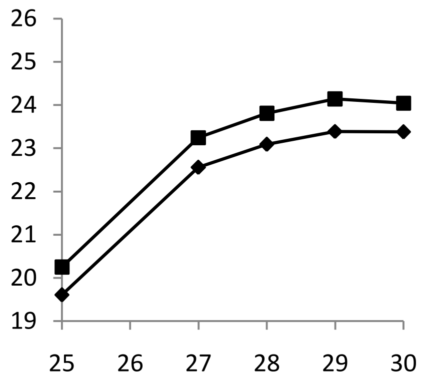
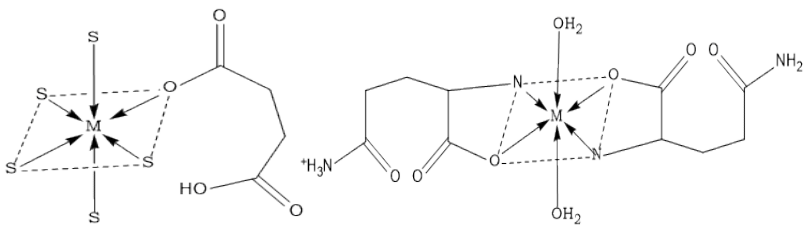


Fig 2: Distribution diagrams M(II) complexes of (A) Succinic acid in 1.0%w/vTBAB and (B) L-Glutamine in 3.0%w/v TBAB-water mixtures.

The plausible structures for succinic cid and L-glutamine complexes from the derived best fit models and equilibria are given in Fig 3.



MLH **ML_2H**

Fig. 3. Structures of binary complexes of succinic acid and L-glutamine with M(II). S is water or solvent.

3.3. Biological significance of the present study

The presence of TBAB in an aqueous solution considerably decreases the dielectric constant, and these solutions are expected to mimic the physiological conditions. The present study is helpful to understand the role played by the active site cavities in biological molecules and the bonding behavior of the protein residues with the metal ion in further studies. The refined species and relative concentrations under the present experimental conditions represent the possible forms of glutamine and succinate residues in the proteins.

4. Conclusions

The final models for M(II) with Sucis MLH, and for Glu is ML_2H at present experimental conditions.Stabilities of the species formed for selected metal ions obeying Irving-William's order with given ligands. In presence of TBAB, stabilities of the selected metal ligand complexes are low comparatively in aqueous media due to low dielectric constants but followed Irving-Williams order.

References

[1]. J.F. Riordan, Ann.Clinical Laboratory Sci.**7**, (1977).
[2]. R. J. P. Williams, FEBS Lett. **140**, 3–10 (1982).
[3]. D. J. Vinyard, G. M. Ananyev, G. C. Dismukes, Annu. Rev. Biochem. **82,** 577–606 (2013).
[4]. J. A. Cotruvo, J. Stubbe, Biochemistry. 2010, **49,** 1297–1309 (2010).

[5]. F. C. Wedler, R. B. Denman, W. G. Roby, Biochemistry. **21,** 6389–6396 (1982)
[6]. J. Emsley, "Manganese". Nature's Building Blocks: An A-Z Guide to the Elements. Oxford, UK: Oxford University Press. 249–253 (2001).
[7]. K. M. Erikson, M. Aschner, Neurochem. Int. **43,** 475-480 (2003).
[8]. Morin Y; Tětu A; Mercier G, Quebec beer-drinkers' cardiomyopathy: Clinical and hemodynamic aspects. Annals of the New York Academy of Sciences., **156 (1)**, 566–576 (1969).
[9]. MarilaAlfano,ChristineCavazza, Protein Science. **29(5)**, 1071-89 (2020).https://doi.org/10.1002/pro.3836

[10]. Nielsen, F.H., Zimmerman, T.J., Shuler, T.R., Brossart, B. and Uthus, E.O., Evidence for a Cooperative Metabolic Relationship Between Nickel and Vitamin. J.Tr.Elem Exp. Med. **2**, 21 (1989).
[11]. E. D. Harris, Nutr. Rev. **59,** 281 (2001). https://doi.org/10.1111/j.1753-4887.2001.tb07017.x
[12]. H. G. Classen, U. Gröber, D. Löw, J. Schmidt, and H. Stracke, Med. Monatsschr Pharm. **34**, 87 (2011).
[13]. H.H. Sandstead, J. Lab. Clin. Med. **124**, 322 (1994).
[14]. T.J. Mc Carthy, J.J. Zeelie, and D. Krause, J. Clin. Pharm. Therapeutics. **17**, 5 (1992). https://doi.org/10.1111/j.1365-2710.1992.tb01265.x
[15]. N.W. Solomons, Nutr. Rev. **56**, 27 (1998). https://doi.org/10.1111/j.1753-4887.1998.tb01656.x
[16]. A.S. Prasad, Nutrition.,**11,** 93 (1995).https://doi.org/10.1016/0026-0576(95)92106-0
[17]. C.A. Heyneman, Ann. Pharmacother. **30**, 186 (1996).https://doi.org/10.1177/106002809603000215
[18]. A.S. Prasad, F.W. Beck, S.M. Grabowski, J. Kaplan, and R.H. Mathog, Proc. Assoc. Am.Physicians, **109**, 68 (1997).
[19]. K. Simmer and R.P. Thompson, Acta. Paediatr. Scand. Suppl. **319**, 158 (1985). https://doi.org/10.1111/j.1651-2227.1985.tb10126.x
[20]. P.E. Milbury and A.C. Richer, Understanding the Antioxidant Controversy: Scrutinizing the "Fountain of Youth", (Greenwood Publishing Group, 2008)**99**.
[21]. G. N. Rao, and S.B. Ronald,J. Ind. Chem. Soc,**79**, 416 (2002).
[22]. E.A. Newsholme, Experientia, **52**, 455 (1996).https://doi.org/10.1007/BF01919315
[23]. A.A. Adjei, Y. Matsumoto, T. Oku,Y. Hiro, and S. Yamamoto, Nutr. Res. **14**,1591 (1994) . https://doi.org/10.1016/S0271-5317(05)80237-4
[24]. W.K. Chang, K.D. Yang, and M.F. Shaio, J. Clin. Exptl. Immunol. **117**, 482 (1999) . https://doi.org/10.1046/j.1365-2249.1999.01009.x
[25]. G.A. Duque and A. Descoteaux, Front. Immunol.**5**, 491 (2014). https://doi.org/10.3389/fimmu.2014.00491
[26]. R.A. Edwards, M.M. Whittaker, J.W.Whittaker, E.N. Baker, and G.B.Jameson, Biochemistry. **40**, 15 (2001)https://doi.org/10.1021/bi0018943
[27]. I.A. Pomytkin, O.E. Kolesova, and T.J. Ukhanova, PCT Int. Appl. Wo. **28**, 944 (2000).
[28]. E.T. Chouchani, V.R. Pell, E. Gaude, D.Ksentijević, S.Y. Sundier, E.L. Robb, A. Logan, S.M. Nadtochiy, E.N. Ord, A.C. Smith, F. Eyassu, R. Shirley, C.H. Hu, A.J. Dare, A.M. James, S. Rogatti, R.C.Hartley,S. Eaton, A.S. Costa, P.S. Brookes, S.M. Davidson,M.R. Duchen, K. Saeb-Parsy, M.J.Shattock, A.J. Robinson, L.M. Work, C. Frezza, T. Krieg, and M.P. Murphy, Nature. **515**, 431 (2014). https://doi.org/10.1038/nature13909
[29]. F. A. Kondrashov, E.V. Koonin, I.G. Morgunov, T.V. Finogenova, and M.N. Kondrashova, Biology Direct. **1**, 31 (2006).https://doi.org/10.1186/1745-6150-1-31
[30]. H.J. Ledon, Organic Syntheses. **6**, 414 (1988).
[31]. G.N. Rao and V.L.S.N. Murthy, J. Ind. Chem. Soc. **81**, 424 (2004).
[32]. G.N. Rao and R.B. Ronald, J. Ind.Chem. Soc. **79**, 796 (2002).
[33]. R.K. Adhikamsetty and U. S, N. Prasad, To Chem. J. 7, 15 (2020).

[34]. A. Ramakrishna and G. N. Rao, Chem. Speciation Bioavailability.**19**, 105 (2007). https://doi.org/10.3184/095422907X236263
[35]. A. Ramakrishna and G.N. Rao, J. Adv. Sci. **1**, 99 (2015).
[36]. G.N. Rao and A. Ramakrishna, J. Ind. Chem. Soc. **83**, 332 (2006).
[37]. A. Ramakrishna and G.N. Rao, Proc. Nat. Acad. Sci. India **77(A), I**, 21 (2007).
[38]. N. Padmaja, M. S. Babu, G.N. Rao, R.S. Rao, and K.V.Ramana, Polyhedron. **9**, 2497 (1990). https://doi.org/10.1016/S0277-5387(00)86784-4
[39]. G. Gran, Anal. Chim. Acta. **206**, 111 (1988).https://doi.org/10.1016/S0003-2670(00)80835-1
[40]. R.N. Sylva and M.R. Davidson, J. Chem. Soc. Dalton Trans. 465 (1979) .https://doi.org/10.1039/dt9790000465
[41]. G.N. Rao and R.S. Rao, J. Indian Council Chem. **8**, 12 (1992).
[42]. P. Gans, A. Sabatini, and A. Vacca, Inorg. Chim. Acta. **18**, 237 (1976).https://doi.org/10.1016/S0020-1693(00)95610-X
[43]. A. Braibanti, R.S. Rao, A.R. Babu, and G.N. Rao, Ann. Chim. (Italy), **85**, 17 (1995).
[44]. A. Losurdo and H. E. Wirth, J. Phys. Chem. **76**, 1333 (1972). https://doi.org/10.1021/j100653a020 39. S
[45]. Uzair, N. A. Malik, and A. Ali, J. Accoustical Soc. India. 430 (2013).
[46]. K. Kanan and A.-J. M. Kayali, Arabian J. Chem. **10**, 314 (2017). https://doi.org/10.1016/j.arabjc.2012.08.003
[47]. P. Saxena, Y. Singh, and P. Jain, Int. J. Eng. Sci. Comput. **18**, 213 (2018)
[48]. Y. Zhang, F. Liu, X. Li, and J. Liu, Talanta.**56**, 705 (2002). https://doi.org/10.5014/ajot.56.6.705
[49]. Y. Rizana, A. Emilia, S. Kamaliah, M. B. A. Rahman, Molecules **19**, ID 8011 (2014). https://doi.org/10.3390/molecules19068011
[50]. H. Sigel, R. B. Martin, R. Tribolet, U. K. Haring, and R. Malini Balakrishnan. Eur. J. Biochem. **152**, 187 (1985). https://doi.org/10.1111/j.1432-1033.1985.tb09180.x
[51]. R. Bernhard, M. M. Meier, R. Neueder, and W. Kunz, Acta Chim. Slov. 56, 30 (2009)
[52]. Y. Marcus, The Properties of Solvents (Wiley, New York, 1999).