Journal of Physical Chemistry and Electrochemistry Vol.2 No.1(2013) 13-19

Islamic Azad University
Marvdasht Branch

Journal of Physical Chemistry and Electrochemistry

Journal homepage: http://journals.miau.ac.ir/jpe

Spectrophotometric Study of Stability Constants of Metal Complexes of Promethazine at Different Temperatures

Azar Bagheri Ghomi[a,*] and Fereshte Mazinani[a]

[a] Department of Chemistry, Center Tehran Branch, Islamic Azad University, Tehran, Iran

Abstract

The complexation reactions between Cu^{2+}, Pd^{2+} and Ni^{2+} metal ions with promethazine (PM) in water or DMF were studied by the spectrophotometric methods at [(15, 25,35 and 45±0.1) °C]. The complexation process was optimized in terms of pH, temperature and contact time. The stoichiometry of the complex was found to be 1:1 (metal ion/ligand). The formation constants of the resulting complexes were determined from computer fitting absorbance-mole ratio data. The values of the thermodynamic parameters for complexation reactions were obtained from the temperature dependence of the stability constants. The proposed method was successfully applied for the determination of PM in their dosage forms.

Keywords: Promethazine; Metal ions; Complexation; Thermodynamic; KINFIT

1. Introduction

Phenothiazines are widely used as tranquillizers antihistamines and hypnotics. The N-alkylamine side chain is considered to be responsible for the aforesaid pharmacological activities [1-3]. Metal-based drugs have been used as therapeutic agents since ages [4]. They are being used for the treatment of a variety of ailments viz. cancer, diabetes, rheumatoid arthritis, inflammatory and cardiovascular diseases as well as diagnostic agents [5-9].

The metal complexing effect of the phenothiazines derivatives may constitute the common cause of their action at the molecular level and, over the last thirty years the interaction between phenothiazine and metal ions has been extensively studied [10-18]. For example, it has been shown in literature that the antitumoral and antipsyhotic activities of phenothiazine (NAPTZ)may occur by formation of Cu(II) (from enzimes) charge transfer complexes with phenothiazine derivatives [19, 20]. Previously, some studies of transition metal-NAPTZ complexes have been reported by several workers [21-24]. PM may behave as a ligand and chelation of this bio-ligand with metal ions can disturb metal homeostasis in the human body. Literature survey reveals that a very few researchers have done such type of work using medicinal drug as a ligand. The detail study of complex under identical set of experimental condition is still lacking. Therefore we decide to study the effect of temperature on thermodynamic parameters ΔG, ΔH and ΔS of complexes of PM drug with Pd (II), Cu(II) or Ni(II). For evaluation of the formation constants of complexes, K_f, from the absorbance-mole ratio data, the nonlinear least-squares curve-

---

[*] Correspondig Author
E-mail address: azar.bagheri@iauctb.ac.ir

fitting program KINFIT was used [25].

2. Experimental

2.1. Apparatus

A JASCO model V-530 UV–Vis spectrophotometer with 1 cm matched cell was used for electronic spectral measurements. SPECTRA MANAGER software was used for all absorbance measurements. A Horiba D-14 pH meter was employed for pH measurements.

2.2. Solutions

A standard palladium (II) chloride solution (2×10−3 M) was prepared as described previously [26] and then standardized gravimetrically [27]. Walpole,s acetate buffer 22 was prepared by mixing appropriate quantities of 0.2 M acetic acid with 0.2 M sodium acetate to get the desired pH. A 0.2% (w/v) of sodium lauryl sulfate in DMF.

2.3. Procedure for calibration curve

Metal ions standard solution was pipetted into a 10 ml volumetric flask and then the specified volumes of Walpole’s acetate buffer and SLS (for copper nitrate) were added. Aliquots of PM (Fig. 1) within the concentration range cited in Table 1, were transferred each into its corresponding set. The solutions, were diluted in a 10 ml standard flask with water or DMF. The absorbance of the complex was measured at corresponding λmax for the studied drugs, against a reagent blank similarly prepared without drug solution.

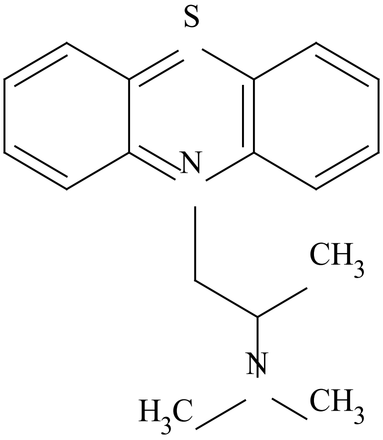

Fig. 1. Structure of promethazine

2.4. Procedure for the determination of PM in pharmaceutical formulations

Twenty tablets of PM were weighed and powdered and transferred to a 100 ml conical flask and extracted by shaking with 60 ml water for 20 min. Prepared solution was filtered and the filtrate was made up to 100 ml with water. An aliquot of this solution was treated by the same procedure as described for the calibration curve. Final estimated concentration of 100 ppm.

3. Results and Discussion

The reaction of PM with palladium (II) chloride, copper(II) nitrate and nickel (II) chloride were investigated over different PHs in acetate buffer solutions at [(15, 25,35 and 45±0.1) °C]. It was found that PM with the metals, water-soluble (Palladium (II) and Nickel (II) chloride) or DMF-soluble (copper nitrate) complexes. The complexes gave an absorption peak at 472, 672 and 579 nm, respectively, which were used for the analytical determination. Under the same conditions, PM and Pd (II), Cu(II) or Ni(II) does not absorb significantly over the investigated wavelength range. Formation of stable complexes depends largely on the reaction conditions. For evaluation of the formation constants of complexes, was used from KINFIT program.

3.1 palladium (II) – PM complex

The absorption spectrum PM–Pd was recorded over the wavelength range 400–800 nm and the absorption maxima are recorded in Table 1. It was found that PM with palladium (II) chloride form water-soluble 1:1 complex (Fig.2). The complex gave an absorption peak at 472 which were used for the analytical determination. Under the same conditions, PM and Pd (II) does not absorb significantly over the investigated wavelength range. Formation of stable complex depends largely on the reaction conditions.

The most suitable pH for formation of palladium(II) – PM complex was determined by mixing 3 ml 3 $\times10^{-4}$ M drug and 2 ml 2 $\times10^{-3}$ M palladium(II) chloride, 4 mL 0.2 M acetate buffer solutions of pH 2.5-6.5.

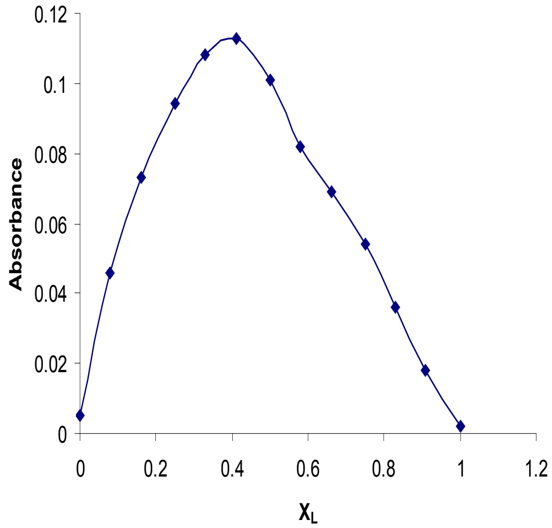

Fig. 2. Continuous variation graph of PM–palladium (II) chloride.

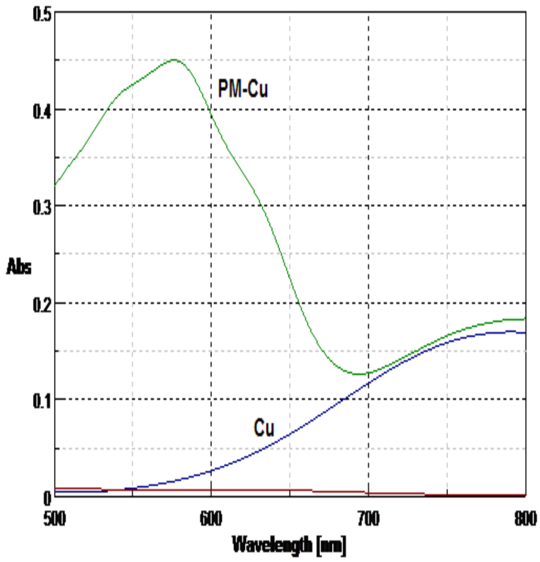

Fig. 4. Absorption spectra of Copper nitrate , complex of PM and Cu(II) in the range of 500-800 nm

The contents were diluted to volume in a 10-ml standard flask with water. The spectra of the formed coloured complex were scanned over the range of 400-600 nm against a reagent blank.

An investigation of the effect of palladium(II) chloride concentration on the complex formation showed that the drug (3 ×10^{-4} M) was converted quantitatively into the complex in the presence of a relatively large excess of palladium(II) chloride (2×10^{-3}M), i.e. an increasing concentration of palladium(II) chloride produced an increase in the absorbance of the complex. A suitable volume was selected, in which the absorbance of the complex reached a maximum (Fig. 3).

With further increasing the effect of palladium(II) concentration the absorbance remained constant. The complex formation is in stantaneous at room temperature.

3.2 Cu(II)- PM complex

The electronic absorption spectra of PM ligand and its Cu^{2+} complexes in DMF is shown in Fig. 4. As it is shown in Fig. 4, the maximum absorption is at 579 nm. and was used for the analytical measurements.

The stoichimetry of the complex was obtained 1:1. Maximum absorbance was

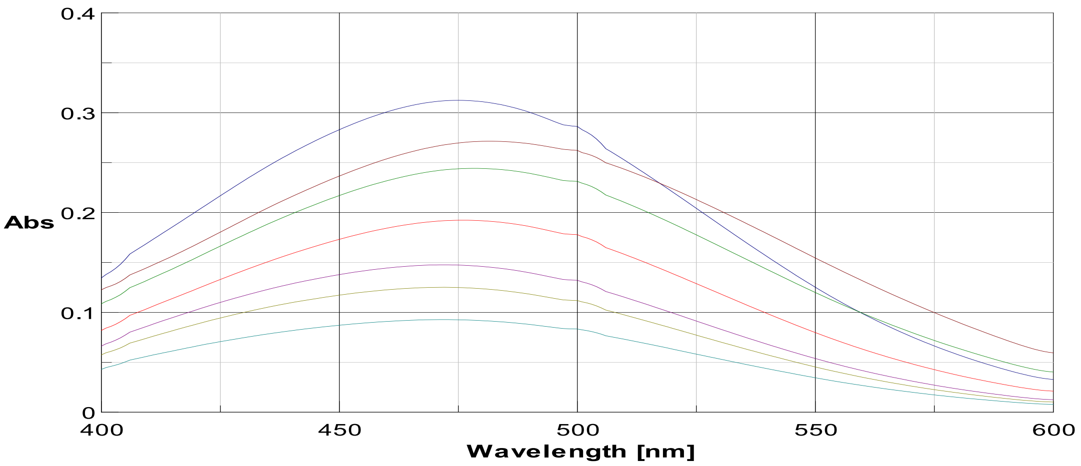

Fig. 3. Absorption spectra of the complex of 0. 5-35µg ml−1 PM with Pd (II).

achieved with volume of 2.5 mL of 2×10^{-3}M copper (II) nitrate, larger volumes of the metal ion has no effect on the absorbance. 2.5 mL of the metal ion solution was chosen to ensure maximum absorbance.

The reaction rate and the amount of the complex produced are considerably influenced by the mixture temperature and the heating time. Maximum color intensity was attained at 50 ºC after 20 min. The colour of the formed complexes is stable for more than 1 h.

3.3 Ni(II) - PM complex

The reaction of PM with nickel(II) chloride hexahydrate was investigated at four different temperatures, and at pH 5.0. The absorption spectra were recorded over the wavelength range of 400–800 nm. In solution, nickel was present as $[Ni(H2O)6]^{2+}$, which has an absorption maximum at 722 nm. It was found that PM with nickel (II) chloride hexahydrate formed a water soluble complex. The complex gave an absorption peak at 672 nm (Fig. 5). Under the same conditions, pure PM does not absorb significantly over the investigated wavelength range (Figure 5). Complex formation takes place in acidic medium at room temperature and is independent of temperature variation up to 50 °C.

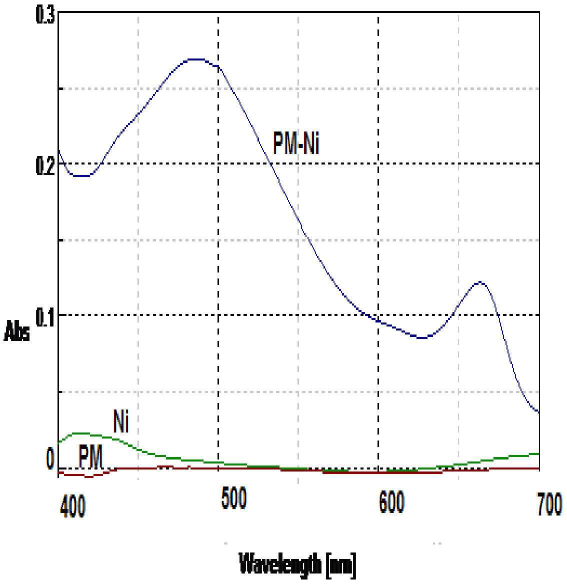

Fig. 5. Absorption spectra of nickel(II) chloride hexahydrate, complex of PM and Ni(II) in the range of 400-700 nm

3.4 The composition of the complex and conditional stability constant

Job's method of analysis corresponds well with the analogous values obtained using mole ratio method of analysis. When PM reacts with metal ions, in solution, it forms a 1:1 complex [28].

The mass balance equation for formation of ML, should be solved in order to calculation of the free ligand concentration [L][29].

$$M + L \rightleftharpoons ML$$

$$K = [ML]/ [M][L]$$

$$CM = [M] + [ML],\ CL = [L] + [ML] \qquad (1)$$

$$K[L]2 + (1 + K(CM - CL)[L] - CL = 0 \qquad (2)$$

The observed absorbance of solution is also given by the following equation:

$$Aobs = \varepsilon L[L] + \varepsilon ML[ML] \qquad (3)$$

where ε values are the molar absorptivities of the species denoted. To obtain the formation constants of the above molecular complexes, K_f, from the absorbance-mole ratio data, a non-linear least square curve-fitting program KINFIT was used [25]. The program is based on the iterative adjustment of the calculated values of absorbance to the observed values by using either the Wentworth matrix technique [30] or the Powell procedure [31].

The free ligand concentration, [L], was calculated bye means of a Newton–Raphson procedure. Once the value of [L] had been obtained, the concentrations of all other species involved are calculated from the corresponding mass-balance equation (1), by using the estimated value of the formation constantan the iteration step of the program. The output of program KINFIT comprises the refined parameters, the sum-of-squares and the standard deviation of the data.

A sample computer fit of the absorbance- mole ratio data for metal ion and PM at 25°C is shown in (Fig. 6).

3.5. Thermodynamic parameters

The thermodynamic parameters were calculated from the temperatures dependence

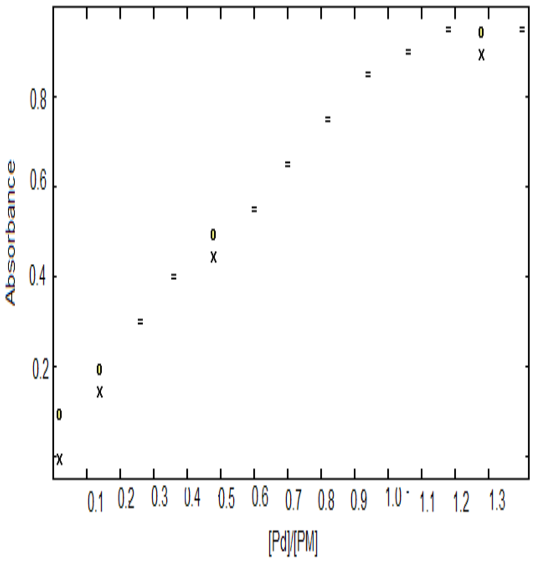

Fig. 6. Computer fits of the plots of absorbance vs. [Pd]/[PM] mole ratios at 25 ◦C: (x) experimental point, (o) calculated point, (=) experimental and calculated points are the same within the resolution of the plots.

of the complexation constants. The formation constants were measured as a function of temperature (288, 298,305 and 315 K).

In all cases, the plots of log Kf versus 1/T were linear and the ΔH◦ and ΔS◦ values were determined in the usual manner from the slope and intercept of the plots. The values of ΔH° obtained for Pd (II), Cu(II) and Ni(II) are −9.249, -5.160 and -6.894.3 KJ. mol^{-1}, respectively. The calculated thermodynamic parameters for all systems are listed in Table 1.

3.6 Quantification and application to dosage forms

Metal complexing ability of PM is a very important character of this group of compounds . This character was utilized to develop a method for determination of PM in bulk powder and pharmaceutical formulations. The proposed method based on complex formation between PM with palladium(II) chloride ,copper (II) nitrate and nickel(II) chloride the resulting complex is then quantified spectrophotometrically at λmax 472, 579 and 672 nm, respectively (Figs. 3-5). A linear relationship between the absorbance and the concentration of PM was obtained over the range 35 – 5 and 20-4 and 8-56 µg/ml (Table 2). The reproducibility of the procedure was determined by running five replicate samples. The high percentage recoveries and the values of standard deviation (Tables 2, 3) indicate the good accuracy and repeatability of the proposed method. The detection limit of the method was found to be 0.47, 0.177 and 5.56 µg/ml.

This study describes an accurate, sensitive, more convenient and less time consuming

Table 1: Average values of logK, ΔG° and ΔS° of metal ions with PM at different temperature.

Complex	*logK*	*ΔS°,J/mol.k*	*-ΔG°,J/mol*
15° C			
Pd(II) /PM	5.3944	71.036	29707.86
Cu(II)/PM	5.002738	95.64	27551.03
Ni(II)/PM	4.563	36.54	3630.62
25° C			
Pd(II) /PM	5.717	72.15	32577.75
Cu(II)/PM	5.002748	95.646	28507.66
Ni(II)/PM	4.672	35.93	3815.1
35° C			
Pd(II) /PM	5.731	79.56	33753.3
Cu(II)/PM	5.00279	95.647	28507.66
Ni(II)/PM	4.734	35.29	3976.82
45° C			
Pd(II) /PM	5.7877	81.002	35193.6
Cu(II)/PM	5.00295	95.65	30421.94
Ni(II)/PM	4.845	34.78	4167.13

Table 2. Optical characteristics and statistical data of the regression equations for the complexes of metal ions with PM.

Parameters	Cu(II)/PM	Pd(II) /PM	Ni(II) /PM
$\lambda_{\max}\ (nm)$	579	472	672
Molar absorbitivity(l mol^{-1} cm^{-1})	7.573×10^{-3}	2.37×10^{-3}	9.19×10^{-3}
Beer s law rang($\mu g ml^{-1}$)	4-20	5-35	8-56
Limit of detection($\mu g ml^{-1}$)	5.87×10^{-2}	0.156	5.56
Limit of quantitation($\mu g ml^{-1}$)	0.177	0.47	7.11
Slope(b)	0.0236	0.0074	0.7
Intercept(a)	0.0408	0.05	0.0271
Correlation coefficient(r)	0.998	0.9985	0.998

Table 3: Evaluation of the accuracy and precision of the proposed method for PM determination

Metal	Added ($\mu g\ ml^{-1}$)	Found ($\mu g\ ml^{-1}$)	SD	RSD(%)	Recovery(%)	$\bar{x}-\mu$	±ts/√s
Pd	5	4.89	0.00035	0.390	94.45	0.004	0.0009
	10	9.98	0.00033	0.189	99	0.014	0.0008
	15	14.85	0.00564	1.64	98.9	0.121	0.0063
	25	24.7	0.0005	0.238	97.1	0.03	0.0012
	35	34.8	0.00237	0.88	98	0.009	0.0036
Cu	4	3.992	0.00042	0.52	94.6	0.02	0.0009
	8	7.908	0.00215	1.32	99.8	0.012	0.0058
	12	11.97	0.00038	0.179	97.2	0.015	0.0008
	16	15.986	0.0032	0.978	99.9	0.013	0.0044
	20	19.99	0.0053	1.15	97.9	0.029	0.007

spectrophotometric method for rapid determination of PM in raw material and in pharmaceutical formulations. The advantages of the proposed method over already existing methods are rapidness, simplicity and inexpensiveness.

4. Conclusion

The metal complexes formed under the above mentioned conditions with PM and measured spectrophotometrically can offer a sensitive, simple, reproducible and accurate procedure for the determination of PM in bulk and tablets forms. The formed complexes were found to be soluble in acetate buffer solutions of pH 2.5-/5.5, without the need for organic solvent to extract the reaction products. From the calculation of stability constants of the complex, the later was found to be stable.

Continuous variation and the mole ratio method support this metal-to-ligand ratio. Moreover, it is difficult for a bulky ligand to make complexation easily due to steric hindrance, i.e., $\Delta G^o = \Delta H^o - T\Delta S^o$. The stability constants were slightly greater at 45 °C. The rise in temperature unfolds the ligand and makes it more comfortable to have a complex with metal ions.

The stability decreases with basicity of the metal ions i.e. Cu(II) forms more stable complex than other metal ions. This has a good agreement with Irving-Williams series. This result is in conformity with Jahn-Teller distortion necessary in d9 Cu(II) ion. The Ni(II) and Pd(II) complexes have an absorption band each at 472 and 672 nm that are assigned to 3A2g → 3T1g(P) and 3A2g → 3T1g(F) transition, respectively. As expected, Cu (II) complex showed a broad band at 579 nm attributed to 2Eg→ 2T2g. These bands are mostly shifted in the complexes or the new band appeared in Cu(II) complex, due to coordination.

The heterocyclic S atom as the coordination site for a soft ion and hetrocyclic N atom as the site for a relatively harder ion in the complexes can be justified based on Pearson,s HSAB interactions. In coordination, the soft acid, Pd(II) prefers a soft S end while the harder acids, Cu(II) and Ni(II), prefer to coordinate with harder N site of the ligand.

References

[1] S.Snyder, H. Amer. J. Psychiatry, 133 (1976) 197.

[2] O. Bratfos, J.O. Haug, Acta Psychiat Scand., 1 (1979) 60

[3] A.R. Katritzky , A.J. Boulton, (Eds.), Advances in hete-rocyclic Chemistry, Academic press, New York ,1968.

[4] C. Orvig , M.J. Abrams , Chem. Rev. 99 (1999) 2201.

[5] B.K.Keppler, (Ed.) p p. 159. Metal complexes in cancer chemotherapy, VCH, Weinheim, 1993.

[6] P.K. Maier, Eur. J. Clin. Pharmacol, 47(1994) 1.

[7] P.J .Sadler, Guo, Z.Pure and Appl.Chem. 70 (1998) 863.

[8] R. S. Srivastava,:. Inorg. Chim. Acta, 55 (1981) 71.

[9] N. B Behrens, G.M. Diaz , D.M.L Goodgame. Inorg. Chim. Acta, 125 (1986) 21.

[10] E. Canpolat, , M. Kaya , S . Gur , Turk. J. Chem. 28 (2004)235.

[11] P.A. Jansen, G. Peters International Encyclopedia of Pharmacology and Therapeutics, C.J.Cavallito (ed.) pp.37 Section S, Structure.Activity. Relationships.,Oxford, New York, 1973.

[12] M.J. Clare, Coord. Chem. Rev.12 (1974) 349.

[13] D.K. Yarmokhumetova : Chemistry of Phenothiazine, Frunze, Kirg SSSR, 1979.

[14] J. Smutz, C.W. Picard: Psychotropic Agents, Part 1: Antipsychotics and Antidepressants in Foffmeistes and G.Style (eds.), pp.3, Springer-Verlag, Berlin, 1980.

[15] E.J. Lloyd, P.R. Andrews, J. Med. Chem., 29 (1986) 453

[16] Y. Moriyama, T. Takano, S. Ohkuma , Biochim. Biophis. Acta, 102 (1986) 854.

[17] R. R.Gupta, Phenothiazines and 1,4-phenothiazines. Chemical and Biochemical Aspects, Elsevier, Amsterdam,1988.

[18] M. Drudea, M. Pitea, M. Butan : Fenotiazine si medicamente structural inrudite, Ed. Dacia, Cluj Napoca,1992.

[19] E. Helen Haward Lock, J.K Colin, Comprehensive Coordination Chemistry, 1990.

[20] J.J. Aron, et al. J. Inclusion Phenom., Mol. Recognit. Chem. 69 (1994) 18.

[21] B. Keshavan, J. Seetharamappa, Polyhedron, 6(3) (1987) 465

[22] B. Keshavan, J. Seetharamappa, J., Synth. React. Met.-Org. Chem., 16(7) (1986) 979

[23] B. Keshavan , R. Janardhan, Ind. J. Chem., 26A (1987) 975

[24] Keshavan, B., R. Janardhan, Ind. J. Chem., 25A (1987) 1054

[25] M.F. Bakr, J. Chin. Chem. Soc. 339 (2003) 50.

[26] Y.M. Wang, T.H. Cheng, G.C. Liu, J. Chin. Chem. Soc. 47 (2000) 1083.

[27] L. Carbonaro, M. Isola, P.L. Pegna, L. Senator, Inorg. Chem. 38(1999) 5519.

[28] M. Shamsipur, J. Ghasemi, J. Coord. Chem. 36 (1995)183.

[29] V.A. Nicely, J. L. Dye, J. Chem. Educ. 48 (1971) 443.

[30] W.E. Wentworth, J. Chem. Educ. 42(1962) 96.

[31] M.J.D. Powell, Comput. J. 7 (1964)