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Determination of Stability Constants of Mixed Ligand Complexes of Picolinic Acid and Other Bioactive Ligands with Zn(II) by Potentiometric Titration Method

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The stability constants of ternary complexes of Zn(II) with picolinic acid as primary ligand and some of bioactive ligands (*e.g.*, amino acids and peptides) as secondary ligand were determined pH-metrically at 25 °C and ionic strength 0.1 mol/L $NaNO_3$ in water solution. The possible formation of ternary complexes *via* simultaneous mechanisms has been confirmed by comparison with constructed theoretical curves. The stability of each ternary complexes was also investigated and compared with those of the corresponding binary complexes in terms of the Δ log K parameter. In addition, the concentration distribution of the complexes formed in solution was evaluated.

Keywords: Picolinic acid, Mixed ligand complexes, Δ log K, Stability constants, Potentiometric studies.

INTRODUCTION

Picolinic acid (P) is, chemically, pyridine-2-carboxalic acid. It is a six-member ring structure compound (Fig. 1) that has been detected in a many of the biological systems[1]. The picolinic acid is present in many natural products and acts as a bidentate ligand by (N, COO-) coordination for many metal ions[2]. Examples include, cobalt(III)[3], copper(II)[4], chromium(VI)[5], manganese(II)[6], vanadium(III)[7] and palladium(II)[8]. Metallic complexes of picolinic acid have received increasing attention in last few decades[2] because of their variety applications in the chemical and pharmaceutical industry[9]. For example, chromium picolinate increases and regulates the secretion of insulin[10,11]. Also, zinc picolinate has a healing effect against herpes simplex virus[12].

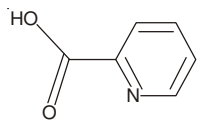

Fig.1. Structure of picolinic acid

Furthermore, the stability constants of zinc(II)-picolinic acid[13], zinc(II)-amino acid and zinc(II) peptides complexes[14] were previously studied. Until now, there are no reports on the speciation of ternary Zn(II)-picolinic acid complexes with amino acids and peptides by potentiometric titration. In the present work, equilibrium and the stability constants of mixed complexes composed of picolinic acid and bioactive ligands (amino acid and peptide) with Zn(II) were determined using potentiometric titration in water solution at 25 °C and an ionic strength (I) of 0.1 mol/L ($NaNO_3$).

EXPERIMENTAL

All chemicals in this work were of guaranteed grade and used without further purification. Picolinic acid was obtained from sigma. All the amino acids, related compounds and peptides used are glycine, alanine, valine, proline, β-phenylalanine, methionine, isoleucine, glutamic acid, threonine, serine, ornithine, cysteine, histidine, histamine-2HCl, pencill-amine, imidazole, mercaptoethanol methylamine, glycyl glycine, glycinamide and glutamine were provided by BDH-Biochemicals Ltd. The zinc content of solutions was determined by complexometric EDTA titrations[15]. Threonine, serine, ornithine, cysteine, histidine and pencillamine solutions were prepared in the protonated form by dissolution in two equivalents of nitric acid. All stock solutions of $NaNO_3$ and HNO_3 (Merck) were prepared in deionized water. $Zn(NO_3)_2{\cdot}6H_2O$ and $NaNO_3$ were provided by BDH-Biochemicals Ltd. The ionic strength of each solution was adjusted to 0.10 mol/L $NaNO_3$. Carbonate-free NaOH (titrant) was prepared and standardized against a potassium hydrogen phthalate solution.

All the pH-measurements were performed with a Metrohm 211 microprocessor (Hanna, Romania) in 0.1 M ionic strength at 298 K temperature. The microprocessor and electrode were calibrated with standard buffer solutions, prepared according to NBS specification[16].

Procedure and measurements: The dissociation constants of the primary ligand picolinic acid and other ligands were determined potentiometrically by titrating the ligand (40 mL) solution (1×10^{-2} mol/L). All titrations, HNO_3 solution was added in this work to ensure full protonation of ligands. The formation constant of the binary complex was determined using potentiometric data obtained from mixtures (40 mL) of zinc ion (5×10^{-3} mol/L) and the ligand in the concentration ratio of 1:1 and 1:2 (zinc:ligand) for picolinic acid, amino acids and peptides. Finally, the stability constants of the ternary complexes were determined by titrating 40 mL of a solution mixture contained equivalent amounts of zinc(II) ion, picolinic acid and the other ligand (1×10^{-2} mol/L), giving rise to molar ratios of 1:1:1 at I = 0.1 mol/L ($NaNO_3$) at 25 °C in water solution.

Data processing: The stability constants and stoichiometries of the complex species formed in water solutions were determined through the study of various possible composition models for the systems studied. In this study, all the calculations were performed for the dissociation and the complex formation constants using the computer program HYPERQUAD[17] and the speciation as a function of pH using the computer program HYSS[18].

RESULTS AND DISCUSSION

The dissociation constants of the ligands were determined in water solution and under the experimental conditions (25 °C, I = 0.1 mol/L $NaNO_3$), which were also used for determining the stability constants of the Zn(II) complexes and the results are given in Table-1.

Dissociation constants of picolinic acid: The calculated acid dissociation constants of the picolinic acid, expressed as pK_a values, were given in Table-1. In acid medium, the first protonation constant refers to the of the pyridine ($pKa_1 = 5.22$) and the second to the carboxylic acid ($pKa_2 = 1.52$). These results obtained are consistent with previous investigations undertaken for related systems[19].

Binary complexes: The titration curve of the Zn(II)-picolinic acid complex is markedly lower than the picolinic acid titration curve, indicating formation of Zn(II) complexes by displacement of protons (Fig. 2). In the binary systems of (Zn(II)-picolinic acid) the selected model with the best statistical fit was found to consist of Zn(picolinic acid) and Zn(picolinic acid)$_2$, where the picolinic acid binds the zinc ion by N-pyridine and O-carboxylato atoms. Beside, the selected model of zinc with bioligand was found to consist of Zn(L), Zn(L)$_2$ and Zn(L)$_3$ species.

Ternary complexes: In general, the overall formation constant can be written as follows (charges are omitted for simplicity):

$$l(zn) + p(P) + q(L) + r(H) \leftrightarrow (Zn)_l(P)_p(L)_q(H)_r$$

$$\beta_{lpqr} = \frac{[zn_lP_pL_qH_r]}{[Zn]^l[P]^p[L]^q[H]^r}$$

Ternary complexes involving Zn(II)-picolinic acid-amino acids: The possible formation of ternary complexes *via* simultaneous mechanisms has been confirmed by comparison with con structed theoretical curves. The titration data

TABLE-1
STABILITY CONSTANTS OF BINARY SYSTEMS Zn(II)-P, Zn(II)-L AND PROTON-ASSOCIATION CONSTANTS AT 25 °C AND I = 0.1 mol; L = $NaNO_3$

System	L	P	q	r[a]	log 10β[b]
Picolinic acid (P)	0	0	1	1	5.22 (0.008)
	0	0	1	2	6.74 (0.04)
	1	0	1	0	5.12 (0.02)
	1	0	2	0	9.42(0.03)
Glycine	0	0	1	1	9.64 (0.01)
	0	0	1	2	12.17 (0.02)
	1	0	1	0	4.91 (0.01)
	1	0	2	0	9.37 (0.02)
Alanine	0	0	1	1	9.80 (0.01)
	0	0	1	2	12.62 (0.03)
	1	0	1	0	4.75 (0.02)
	1	0	2	0	8.76 (0.02)
Valine	0	0	1	1	9.68 (0.00)
	0	0	1	2	12.18 (0.01)
	1	0	1	0	5.32 (0.02)
	1	0	2	0	9.19 (0.03)
Proline	0	0	1	1	10.65 (0.009)
	0	0	1	2	13.18 (0.01)
	1	0	1	0	5.24 (0.03)
	1	0	2	0	9.98 (0.05)
β-Phenyl alanine	0	0	1	1	9.20 (0.01)
	0	0	1	2	11.81(0.03)
	1	0	1	0	4.57 (0.02)
	1	0	2	0	8.25 (0.03)
Methionine	0	0	1	1	9.23 (0.02)
	0	0	1	2	12.04 (0.04)
	1	0	1	0	4.37 (0.03)
	1	0	2	0	8.75 (0.05)
Isoleucine	0	0	1	1	9.82 (0.01)
	0	0	1	2	12.46 (0.04)
	1	0	1	0	5.29 (0.02)
	1	0	2	0	8.97 (0.03)
Glutamic acid	0	0	1	1	9.46 (0.01)
	0	0	1	2	13.54 (0.01)
	1	0	1	0	5.70 (0.01)
	1	0	2	0	9.74 (0.02)
Threonine	0	0	1	1	9.06 (0.009)
	0	0	1	2	11.07 (0.03)
	1	0	1	0	4.62 (0.04)
	1	0	2	0	8.59 (0.05)
Serine	0	0	1	1	9.17 (0.01)
	0	0	1	2	11.54 (0.03)
	1	0	1	0	4.57 (0.01)
	1	0	2	0	8.51 (0.02)
Ornithine	0	0	1	1	10.47 (0.03)
	0	0	1	2	19.27 (0.04)
	0	0	1	3	20.98 (0.05)
	1	0	1	0	4.10 (0.04)
	1	0	2	0	7.30 (0.07)
Cysteine	0	0	1	1	9.68 (0.01)
	0	0	1	2	17.72 (0.02)
	0	0	1	3	19.35 (0.06)
	1	0	1	0	9.04 (0.03)
	1	0	2	0	17.54 (0.06)
Histidine	0	0	1	1	9.48 (0.01)
	0	0	1	2	15.76 (0.01)
	0	0	1	3	17.92 (0.04)
	1	0	1	0	6.13 (0.08)
	1	0	2	0	12.09 (0.09)
	1	0	1	1	11.17 (0.1)

System	L	P	q	r[a]	log 10β[b]
Histamine	0	0	1	1	9.88 (0.03)
	0	0	1	2	15.94 (0.05)
	1	0	1	0	5.31 (0.07)
	1	0	2	0	10.38 (0.09)
	1	0	1	1	12.46 (0.1)
Pencillamine	0	0	1	1	10.41 (0.02)
	0	0	1	2	18.29 (0.03)
	0	0	1	3	19.55 (0.09)
	1	0	1	0	9.42 (0.04)
	1	0	2	0	19.54 (0.06)
Imidazole	0	0	1	1	7.06 (0.01)
	1	0	1	0	2.67 (0.06)
	1	0	2	0	5.12 (0.03)
	1	0	3	0	7.52 (0.04)
Mercaptoethanol	0	0	1	1	9.52 (0.01)
	0	0	1	2	12.16 (0.02)
	1	0	1	0	7.61 (0.01)
Methylamine	0	0	1	1	10.07 (0.02)
	1	0	1	0	3.59 (0.04)
	1	0	2	0	6.82 (0.09)
Glycylglycine	0	0	1	1	8.26 (0.009)
	0	0	1	2	11.44 (0.02)
	1	0	1	0	3.38 (0.02)
Glycinamide	0	0	1	1	8.06 (0.01)
	1	0	1	0	3.30 (0.06)
Glutamine	0	0	1	1	8.99 (0.03)
	1	0	1	0	4.15 (0.06)

[a] l, p and q are the stoichiometric coefficient corresponding to Zn(II), P, (bioactive ligands) and H+, respectively, [b]Standard deviations are given in parentheses

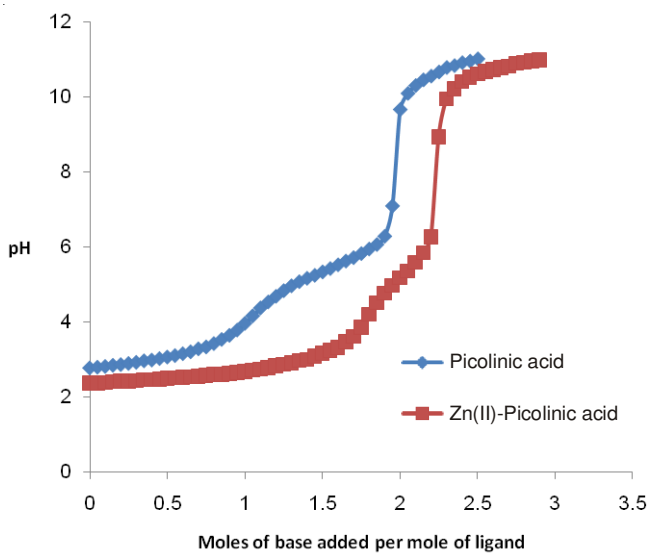

Fig. 2. Potentiometric titration curves of the Zn(II)-picolinic acid system

of the mixed ligand complexes with picolinic acid and amino acids fit satisfactorily with formation of the species: Zn(P), $Zn(P)_2$, Zn(L), $Zn(L)_2$, $Zn(L)_3$, Zn(L)H and Zn(P)(L). The mixed ligand complexes of amino acids are more stable than those for the corresponding monodentate methylamine and imidazole complexes, indicating that amino acids most likely coordinates with Zn(II)-P as a bidentate ligand through the amino and carboxylate groups, rather than as a monodentate ligand. In addition, the stability constant value of the methylamine complex is higher than that of the imidazole complex (Table-1). The observed extra stability of the methylamine complex may be due to the higher basicity of its amino group. The stability of ternary complexes containing α-alanine are found to be lower than those involving glycine, but this behaviour does not follow their basicity as expected. However, it is suggested that steric hindrance caused by the presence of a methyl group on the carbon bearing the amino group (α-alanine) and then the lower stability[20]. In addition to glycine, the phenyl alanine forms a more stable complex than alanine, although the amino group of the phenyl alanine is less basic than that of alanine. Probably due to some stacking interactions between the phenyl group of phenyl alanine and picolinic acid. This will contribute to the stabilization of the formed complex. Threonine and serine forms the Zn(P)(L) and Zn(P)(L)H-1 species. The latter complex is formed through induced ionization of the β-alcohol group as mentioned in the literature[21]. Our results show that the stability constants of mixed ligand complex of ornithine and histidine are larger than those of α-amino acids. It can be understood that ornithine most likely chelates *via* the two amino groups, whereas histidine interacts with zinc *via* the amino and imidazole nitrogen atoms (histamine-like). From Table-2, the stability constants of the pencillamine and cysteine complexes are larger of mercaptoethanol and much larger than those for α-amino acids, indicating the pencillamine and cysteineinteract with Zn(II) ion through the amino and deprotonated-SH groups. Fig. 3, shows the distribution diagram for the cysteine complex. The deprotonated

TABLE-2
STABILITY CONSTANTS OF THE TERNARY SPECIES IN THE Zn(II)-P-L SYSTEMS AT 25 °C AND I = 0.1 mol L $NaNO_3$

System	L	P	q	r[a]	$\log_{10}\beta$[b]	Δ log K
Glycine	1	1	1	0	12.30 (0.02)	2.27
Alanine	1	1	1	0	12.24 (0.02)	2.37
Valine	1	1	1	0	12.27 (0.02)	1.38
Proline	1	1	1	0	13.57 (0.02)	3.21
β phenyl alanine	1	1	1	0	12.28 (0.06)	2.59
Methionine	1	1	1	0	12.71 (0.02)	3.22
Isoleucine	1	1	1	0	13.17 (0.02)	2.76
Glutamic acid	1	1	1	0	13.30 (0.04)	2.48
Threonine	1	1	1	0	13.63 (0.01)	3.89
	1	1	1	-1	1.80 (0.05)	
Serine	1	1	1	0	13.51 (0.03)	3.82
Ornithine	1	1	1	0	17.01 (0.02)	7.79
Cysteine	1	1	1	0	20.62 (0.06)	6.46
Histidine	1	1	1	0	15.72 (0.03)	4.47
Histamine	1	1	1	0	14.55 (0.01)	4.12
Pencillamine	1	1	1	0	20.99 (0.02)	6.45
Imidazole	1	1	1	0	9.35 (0.02)	1.56
Mercaptoethanol	1	1	1	0	17.73 (0.03)	5.36
Methylamine	1	1	1	0	10.80 (0.03)	2.09
Glycylglycine	1	1	1	0	11.09 (0.05)	2.59
	1	1	1	-1	6.00 (0.02)	
	1	1	1	-2	-3.48 (0.04)	
Glycinamide	1	1	1	0	9.52 (0.06)	1.1
	1	1	1	-1	2.85 (0.03)	
	1	1	1	-2	-5.46 (0.05)	
Glutamine	1	1	1	0	12.33 (0.03)	3.06
	1	1	1	-1	5.48 (0.04)	
	1	1	1	-2	-4.61 (0.07)	

[a] l, p and q are the stoichiometric coefficient corresponding to Zn(II), P, (bioactive ligands) and H+, respectively.
[b] Standard deviations are given in parentheses.

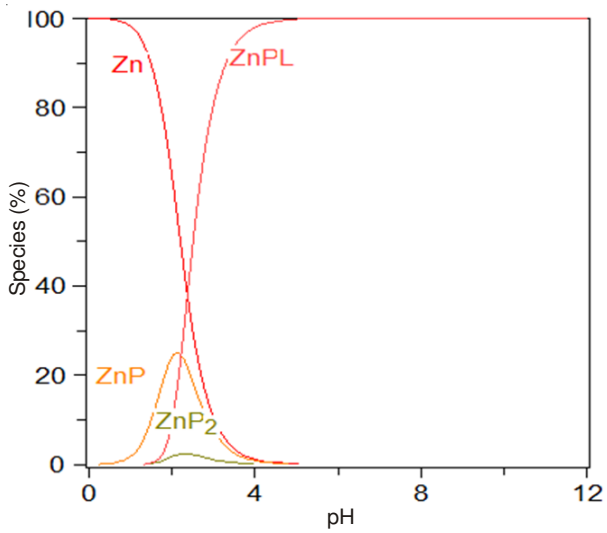

Fig. 3. Concentration distribution of various species with pH in the ternary Zn(II)-picolinic acid-cysteine system

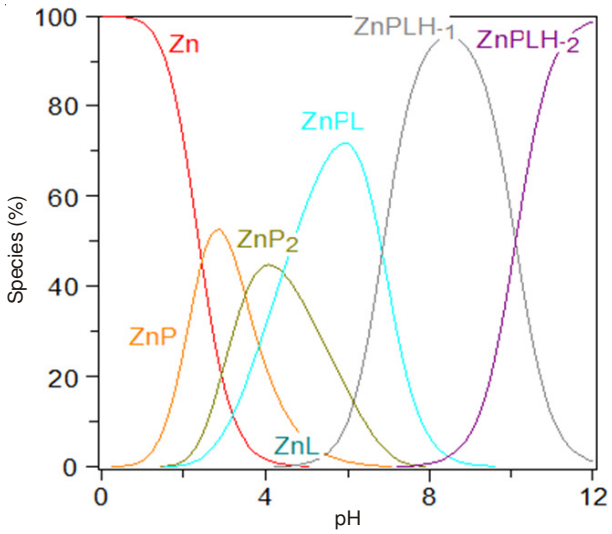

Fig. 4. Concentration distribution of various species with pH in the ternary Zn(II)-P-glutamine system

111-0 complex species predominates with a formation degree amounting to 99.46 % at pH = 4.77.

Ternary complexes involving Zn(II)-picolinic acid-peptides: All the ternary complex formation of amides proceeds also through a simultaneous mechanism and they form the complexes 111-0, 111-1 and 111-2. The amide may form the 111-0 complexes by coordination through the amine and carbonyl groups. On increasing the pH, the coordination sites should switch from carbonyl oxygen to amide nitrogen. Such changes in coordination modes are well documented[22]. The pK^H values are calculated by the following eqn. 1:

$$pK^H = \log 10\,\beta_{111-1} - \log 10\,\beta_{111-2} \quad (1)$$

The pK^H values of the amide group for glycylglycine, glycinamide and glutamine are 9.48, 8.31 and 10.09 respectively. Interestingly, to note that the pK^H for the glutamine complex is markedly higher than the pK^H of glycinamide. So this can be explained the formation of a seven membered chelate ring, which would be more strained and less favored. It is noteworthy that the peptide would coordinate to Zn-picolinic acid in entirely different fashions and under normal physiological conditions (pH 6-7). In Fig. 4, the mixed ligand species 1110 starts to form at pH-2 and with increasing of pH, its concentration increases reaching the maximum of 71.89 % at pH = 5.89. Increasing of pH is accompanied by a decrease in 1110 complex concentration and an increase of 111-1 complex concentration. Further increase of pH are accompanied by a decrease in the 111-1 complex concentration and an increase of the 111-2 complex concentration. Therefore, the species 111-0 and 111-1 predominates in the physiological pH range.

$\Delta \log_{10}$ K: The parameter Δ log K values are usually used to indicate the relative stability of the ternary complexes as compared to the binary ones as in the following eqns. 2 and 3:

$$Zn(P) + Zn(L) \rightleftharpoons Zn(P)(L) + Zn \quad (2)$$

$$\Delta \log_{10} K + \log_{10} \beta^{zn(P)}_{zn(P)L} - \left(\log_{10} \beta^{zn}_{zn(P)} + \log_{10} \beta^{zn}_{zn(L)}\right) \quad (3)$$

The Δ log K values in this paper are invariably positive, where positive values of amino acids and peptides are considered as evidence of enhanced stability as a result of intermolecular ligand-ligand interactions, hydrogen bonding, the π-back donation effect and/or hydrophobic effects.

Conclusion

The present investigation describespotentiometric study the formation constants of binary and ternary picolinic acid (P) complexes involving Zn(II) and some bioactive ligands in water solutions at 25 °C and ionic strength 0.1 mol/ L $NaNO_3$ by HYPERQUAD program. Beside, the relative stabilities of each ternary complexes are compared with those of the corresponding binary complexes. Additionally, the concentration distribution curves of the various complex species existing in solution were evaluated.

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REFERENCES

1. R.S. Grant, S.E. Coggan and G.A. Smythe, *Int. J. Tryptophan Res.*, **2**, 71 (2009).
2. H. Rosas, L.E. Sarmiento, M. Rodríguez and V. Lubes, *J. Solution Chem.*, **39**, 1021 (2010).
3. A. Syamal and P.K. Mandal, *Transition Metal Chem.*, **3**, 292 (1978).
4. S.M. Lee, S.K. Ryu, C.H. Jung, H.J. Won and W.Z. Oh, *Carbon*, **40**, 329 (2002).
5. B. Saha, M. Das, R.K. Mohanty and A.K. Das, *J. Chinese Chem. Soc.*, **51**, 399 (2004).
6. D. Pijper, P. Saisaha, J.W. de Boer, R. Hoen, C. Smit, A. Meetsma, R. Hage, R.P. van Summeren, P.L. Alsters, B.L. Feringa and W.R. Browne, *Dalton Trans.*, **39**, 10375 (2010).
7. G. Lubes, M. Rodríguez and V. Lubes, *J. Solution Chem.*, **39**, 1134 (2010).
8. H. Imam, B. Kumar and M. Shafayat, *Orient. J. Chem.*, **27**, 287 (2011).
9. W. Mangesh, W. Kailas and S. Shriram, *Res. J. Chem. Environ.*, **17**, 53 (2013).
10. T.L. Varadinova, P.R. Bontehev, C.K. Nachev and S.A. Shiskov, *J. Chemother.*, **5**, 3 (1993).

11. N.E. Chakov, R.A. Collins and J.B. Vincent, *Polyhedron*, **18**, 2891 (1999).
12. R. March, W. Clegg, R.A. Coxall, L. Cucurull-Sánchez, L. Lezama, T. Rojo and P. González-Duarte, *Inorg. Chim. Acta*, **353**, 129 (2003).
13. Z. Vargová, J. Kotek, J. Rudovský, J. Plutnar, R. Gyepes, P. Hermann, K. Györyová and I. Lukes, *Eur. J. Inorg. Chem*., **2007**, 3974 (2007).
14. M. Aljahdali and A.A. El-Sherif, *J. Solution Chem*., **41**, 1759 (2012).
15. F.J. Welcher, The Analytical Uses of Ethylenediaminetetraacetic Acid. Van Nostrand, Princeton, USA, edn 4, p. 143 (1965).
16. A. Jacques, (Complex Ion in Aqueous Solutions), Longmans, London (1914).
17. P. Gans, A. Sabatini and A. Vacca, *Talanta*, **43**, 1739 (1996).
18. L. Alderighi, P. Gans, A. Ienco, D. Peters, A. Sabatini and A. Vacca, *Coord. Chem. Rev*., **184**, 311 (1999).
19. K. Suzuki and K. Yamasaki, *Naturwissenschaft*, **44**, 396 (1957).
20. J.I. Liangnian and L.E. Xueyi, *Chin. Sci. Bull*., **47**, 1 (2002).
21. K. Suzuki and K. Yamasaki, *Naturwissenschaft*, **44**, 396 (1957).
22. M.C. Lim, *J. Chem. Soc., Dalton Trans*., 15 (1977).