Asian Journal of Chemistry; Vol. 27, No. 10 (2015), 3821-3825

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2015.18998

Synthesis and Characterization of Mannich Aminomethylation Products of Metal(alaninato) Complexes Using 1-Nitropropane as Carbon Acid

S. SUPRIYA[1,*] and A. RAGHAVAN[2]

[1]Department of Chemistry, Sathyabama University, Rajiv Gandhi Road, Chennai-600 119, India
[2]Department of Polymer Science, University of Madras, Guindy Campus, Chennai-600 025, India

*Corresponding author: Fax: +91 44 24502344; Tel: +91 44 24503150; E-mail: supriyasubrahmani@gmail.com

Received: 8 January 2015; *Accepted*: 16 February 2015; *Published online*: 22 June 2015; AJC-17355

Mannich aminomethylation products have been synthesized by one-pot template condensation reaction of *bis*(alaninato)metal(II) complexes, $M(aa)_2$, with formaldehyde and 1-nitropropane. The DL-isomer and the L-isomer of the metal(alaninato) complexes of Cu(II), Ni(II) and Zn(II) were used separately for the synthesis of Mannich aminomethylation products in order to study the differential reactivities of the stereoisomers of the complexes. Differential reactivities were observed for the isomers in the form of different products isolated at the end of the reaction. Role of pH in Mannich aminomethylation reaction was studied by carrying out the reactions under acidic (pH = 4-5) and basic (pH = 9) conditions. The synthesized complexes were characterized by elemental analysis, ESI mass analysis, UV, IR, NMR and ESR.

Keywords: Metal(alaninato) complexes, Mannich aminomethylation, 1-Nitropropane.

INTRODUCTION

α-Amino acids perform various biological functions and their side chain groups are important for the structural integrity and catalytic activity in proteins[1]. Metal template synthesis of complexes involving α-amino acids have attracted much interest[2] and have become established as high-yielding and selective routes for the synthesis of new ligands and their metal complexes. Synthesis of Mannich aminomethylation products starting from metal amino acid complexes have gained much attention due to their applications as potent stimulators for the release of hormones[3], as catalysts[4], as thermoelectric switches and in polymerization reactions[5].

Introduction of various functional groups in metal amino acid complexes *via* Mannich aminomethyaltion reactions have proved to be successful due to different electronic and molecular behaviour of the products obtained. Also, the Mannich aminomethylation products are found to be more efficient than their parent compounds[6].

Mannich reactions involving various carbon acids have been reported in literature[7]. Here, we report the synthesis of Mannich aminomethyaltion products formed using 1-nitropropane as the carbon acid with the metal (alaninato) complexes of Cu, Ni and Zn.

EXPERIMENTAL

DL-alanine (DL-ala), L-alanine (L-ala) were supplied by SRL laboratories, 1-nitropropane were obtained from Lancaster chemicals, 37 % aqueous formaldehyde solution was purchased from Merck. $Cu(aa)_2$, $Ni(aa)_2$ and $Zn(aa)_2$ (aa = DL-alanine, L-alanine) were prepared by the general synthesis methods as reported in literature.

Electronic spectra of the complexes and the kinetic measurements were carried out on a Zhimadzu UV-160A spectrophotometer. For the electronic spectra, solutions of about 1×10^{-3} M concentration of the complexes were used and the pH was adjusted by the addition of microlitres of HCl solution. The infrared spectra were recorded on a Thermo Mattson Satellite FT-IR spectrophotometer from 4000-450 cm^{-1} as KBr discs. Elemental analyses were carried out with an Elementar Vario EL III Carlo Erba 1108 analyzer available at CDRI, Lucknow, India. ESI mass spectra were recorded on a Micromass Ouattro II analyzer available at CDRI, Lucknow, India. ESR measurements were conducted using BRUKER X-Band EMX-EPR spectrometer available at CLRI, Chennai. About 3 mM solutions of the complexes in DMSO were used for the measurements at 77 K. ^{1}H and ^{13}C NMR spectra were recorded at ambient temperature with a Jeol GSX 400 MHz and 100 MHz NMR spectrometer respectively in DMSO-d_6 with TMS as the internal reference.

Experimental procedure

[3,7-Dihydroxymethyl-2,8-dimethyl-5-nitro-5-ethyl-3,7-diazanonanedioato]copper(II), (CLNPA): To a solution of $Cu(L\text{-}ala)_2$ (1 g, 4.1 mmol) in 100 mL of water:methanol mixture (3:1), formaldehyde (4.5 mL, 0.06 mol) and 1-nitropropane (1.5 mL, 16.7 mmol) were added dropwise with constant stirring. After complete addition of formaldehyde and 1-nitropropane, the reaction mixture was stirred continuously at room temperature for 24 h. The solution was then concentrated (about 30 mL) using rotary evaporator and filtered. Blue coloured product formed after several days on standing at room temperature was filtered from solution, washed with ethanol, ether and then dried over $CaCl_2$. Yield: 0.96 g, 56 %.

Elemental analysis calculated for $C_{13}H_{23}N_3O_8Cu$: C, 37.81; H, 5.57, N, 10.18; Cu, 15.42; Found: C, 39.91; H, 6.19, N, 11.71; Cu, 16.46 %; $\lambda_{max}(H_2O)$/nm 285 (ε/dm^{3}mol^{-1}cm^{-1} 1065.6) and 614 (135.1). IR (KBr, ν_{max}, cm^{-1}): 3465, 3213, 3127, 2944, 1655, 1549, 1443, 1370, 1349, 1292, 1252, 1207, 1117, 1044, 1019, 913, 860, 832, 779, 718, 640, 554, 420. Mass (ESI) *m/z* = 412 (M$^+$).

Under alkaline condition, at pH = 9.0, no stable product could be isolated under the above mentioned conditions and also under various experimental conditions. No stable product could be isolated with the DL-form of the Cu(II) alaninato complex.

[5-Ethyl-2,8-dimethyl-5-nitro-3,7-diazanonanedioato]-nickel(II) monohydrate, (NDNPA): The complex was prepared by the same procedure as that described for the synthesis of CLNPA, using Ni(DL-ala)$_2$·3H$_2$O as the starting material. Yield: 0.77 g, 56 %.

Elemental analysis calculated for $C_{11}H_{19}N_3O_6Ni\cdot H_2O$: C, 36.09; H, 5.74; N, 11.48. Found: C, 36.57; H, 5.92; N, 11.56 %. λ_{max}(DMSO)/nm 285 (ε/dm^3 mol^{-1} cm^{-1} 69.8) and 636 (1.9). IR (KBr, ν_{max}, cm^{-1}): 3437, 3290, 2988, 2944, 1570, 1545, 1464, 1398, 1366, 1345, 1321, 1268, 1146, 1105, 1060, 1003, 966, 905, 828, 766, 701, 567, 412. Mass (ESI) *m/z* = 366 (M$^+$).

Reaction of Ni(L-ala)$_2$·3H$_2$O with HCHO and 1-nitropropane also resulted in the formation of the same product with 56 % yield. No product was obtained for the reaction carried out under alkaline condition above pH = 9.0.

[2,8-Dimethyl-3,7-di(2-hydroxymethyl-2-nitrobutyl)-5-ethyl-5-nitro-3,7-diazanonanedioato]zinc(II), (ZDNPA): The complex was prepared by the same procedure as that described for the analogous CLNPA, using Zn(DL-ala)$_2$·H$_2$O as the starting material. Yield: 1.48 g, 58 %.

Elemental analysis calculated for $C_{21}H_{37}N_5O_{12}Zn$: C, 40.87; H, 6.00; N, 11.35; Zn, 10.64. Found: C, 43.39; H, 5.87; N, 10.73; Zn, 10.00 %. $\lambda_{max}(H_2O)$/nm 285 (ε/dm^3 mol^{-1} cm^{-1} 210.3). IR (KBr, ν_{max}, cm^{-1}): 3437, 2984, 2944, 1623, 1537, 1443, 1398, 1370, 1337, 1288, 1256, 1207, 1170, 1084, 1052, 1011, 954, 934, 889, 844, 807, 791, 718, 677, 587, 538, 518, 420. ^{1}H NMR (DMSO-*d*$_6$): δ 4.54 (d, 2H, -OH-), 4.30 (q, 1H, -N-CH-COO-), 4.20 (q, 1H, -N-CH- COO-), 3.67 (d, 2H, -CH$_2$-O-), 3.52 (d, 2H, -CH$_2$-O-), 3.26 (d, 4H, -N-CH$_2$-C-), 2.92 (d, 4H, - N-CH$_2$-C-), 1.73 (q, 6H, -C-CH$_2$-C), 1.14 (d, 6H, -C-CH$_3$-), 0.75 (t, 9H, -CH$_3$). ^{13}C NMR (DMSO-*d*$_6$): δ 177.21, 88.30, 84.26, 69.94, 58.21, 50.71, 27.67, 15.76, 7.15.

Yield of the product is maximum at pH 5.0. No product could be isolated for the reaction carried out under alkaline condition above pH = 8.0.

[N,N'-1,3-(2-oxapropanediyl)*bis*(N,N'-(2-hydroxymethyl-2-nitrobutyl)alaninato)]zinc(II), (ZLNPA): The complex was prepared by the same procedure as that described for the analogous ZDNPA, using Zn(L-ala)$_2$.H$_2$O as the starting material. Yield: 1.35 g, 60 %.

Elemental analysis calculated for $C_{18}H_{32}N_4O_{11}Zn$: C, 39.59; H, 5.86; N, 10.26. Found: C, 39.35; H, 4.69; N, 10.64 %. $\lambda_{max}(H_2O)$/nm 285 (ε/dm^3 mol^{-1} cm^{-1} 90.4). IR (KBr, ν_{max}, cm^{-1}): 3453, 3274, 3233, 2988, 2939, 2886, 1610, 1545, 1464, 1431, 1382, 1345, 1309, 1280, 1186, 1125, 1052, 1023, 983, 930, 897, 860, 840, 783, 681, 591, 506. Mass (ESI) *m/z* = 545 (M$^+$).

Yield of the product is maximum at pH 5.0. No product could be isolated for the reaction carried out under alkaline condition above pH = 8.0.

RESULTS AND DISCUSSION

All amino acid complexes undergo Mannich aminomethylation reaction with 1-nitropropane at pH = 4.5 to give variously substituted products with different metal ions. No stable product could be isolated for the reaction of M(ala)$_2$ complexes under alkaline condition above pH = 9.0. Reaction of M(ala)$_2$ complexes with HCHO and 1-nitropropane resulted in the formation of a single major product under the conditions mentioned in the experimental section. At pH = 4.5, reaction of [Ni(DL-ala)$_2$] and [Zn(DL-ala)$_2$] with formaldehyde and 1-nitropropane gave NDNPA and ZDNPA respectively as their products. The complexes [Cu(L-ala)$_2$], [Ni(L- ala)$_2$] and [Zn(L-ala)$_2$] resulted in the formation of CLNPA, NLNPA and ZLNPA respectively as their products. No stable product could be isolated with the DL-form of the Cu(II) alaninato complex. The product complexes are found to be stable in dil. HCl for several hours and showed no appreciable shift in the *d-d* transition band in their electronic spectra upon decreasing the pH from 7 to 2. Hence all the synthesized products should necessarily have a bridged structure which makes them stable in acid solution as observed for the other bridged complexes reported in literature[8].

Electronic spectra: The products obtained from the reaction of Cu(II) and Ni(II) complexes with formaldehyde and 1-nitropropane showed an intense ligand-ligand charge transfer band in the region 285-291 nm and a *d-d* transition band in the region 614-676 nm. The Zn(II) complexes, showed only one intense band in the charge transfer region around 291 nm due to the ligand-ligand charge transition. Appearance of a single *d-d* transition band in the region around 630 nm indicates four-coordinated planar geometry around the copper and nickel atoms. No ligand-metal transition bands were observed in the electronic spectrum of the complexes. The electronic spectrum of the complex CLNPA is shown in Fig. 1.

Infrared spectra: The IR spectra of all the metal complexes shows strong absorption peak around 1550 cm^{-1} and 1350 cm^{-1} corresponding to -NO$_2$ stretching vibrations. Peaks corresponding to –NH vibrations are absent in the IR spectra of the products except for the complex NDNPA. The IR spectra of the complexes shows strong absorption peak around 3400 cm^{-1} corresponding to the –OH stretching frequency. Absence of a triplet in the region 1200-1080 cm^{-1}, shows that the products does not have oxazolidine ring. All the complexes show typical carboxylate asymmetric and symmetric stretching frequencies around 1630-1580 cm^{-1} and 1430-1390 cm^{-1} respectively. It is

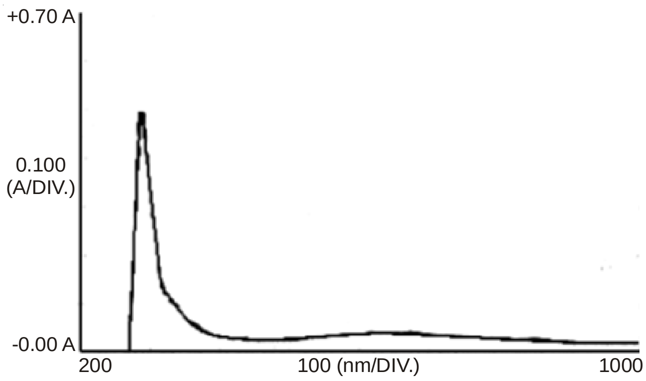


Fig. 1. Electronic spectrum of the complex CLNPA

thus clear that the products formed are different from their parent compounds. The IR spectra of the complexes are shown in Figs. 2-4.

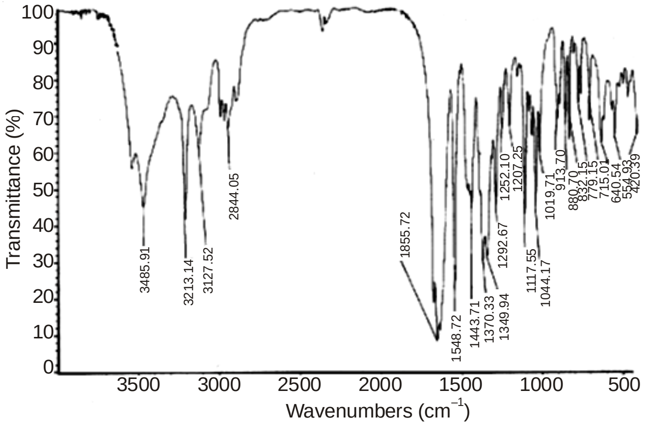


Fig. 2. FTIR spectrum of the complex CLNPA

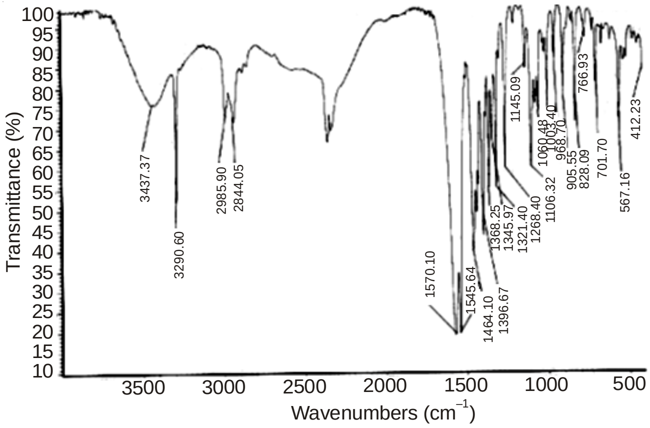


Fig. 3. FTIR spectrum of the complex NDNPA

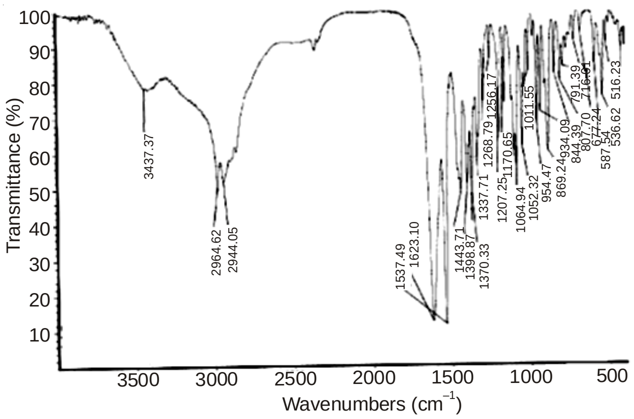


Fig. 4. FTIR spectrum of the complex ZDNPA

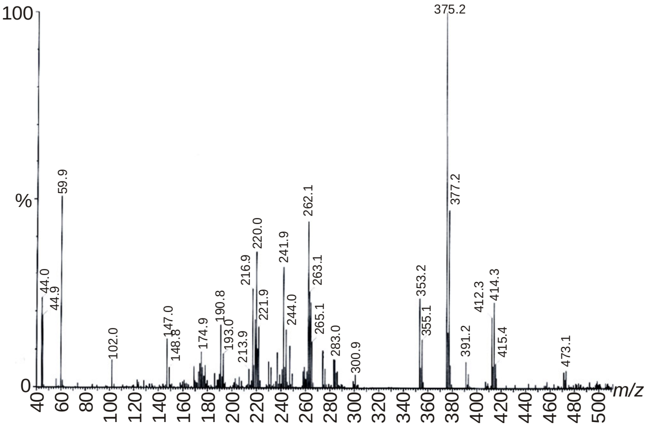


Fig. 5. ESI mass spectrum of the complex CLNPA

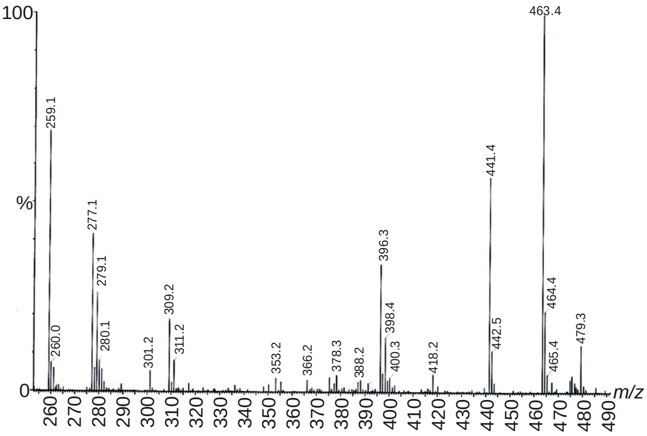
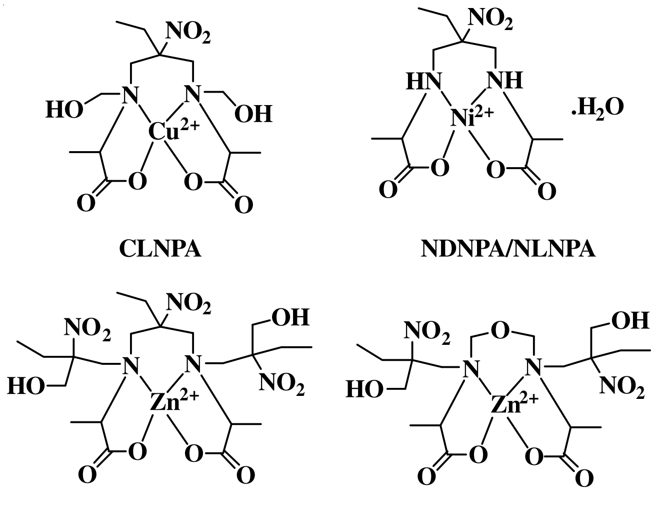


Fig. 6. ESI mass spectrum of the complex NDNPA

Mass spectra: The proposed structures of all the metal complexes are further supported by microanalysis and mass spectra. The ESI-mass spectra of the complexes CLNPA and NDNPA are shown in Figs. 5 and 6. The spectra show the cleavage of low molecular weight fragments from the parent molecule. The ESI-mass spectra of the complexes CLNPA and NDNPA show corresponding molecular ion peak at *m/z* values 412 and 366 respectively. Comparison of the mass spectra of the complexes reveals different fragmentation pattern for the complexes CLNPA and NDNPA. The spectra of these compounds show base peak at *m/z* value 375 and at 463 for CLNPA and NDNPA respectively, which shows that the products synthesized using 1-nitropropane as the carbon acid follow different fragmentation pattern thereby producing different type of stable intermediates.

Based on these observations, the proposed structures of the products synthesized using 1-nitropropane as the carbon acid are shown in **Scheme-I**.

Reactions of amino acid complexes with formaldehyde and the 1-nitropropane are found to give Mannich aminomethylation products exhibiting a bridged structure which is proved from the stability of the complexes at low pH values in the electronic spectrum. In the product complexes, the ring capping at the amine nitrogen atoms are either from the 1-nitro-



CLNPA **NDNPA/NLNPA**

ZDNPA **ZLNPA**

Scheme-I

propane or by the formaldehyde molecules *via* hydroxymethylation reaction resulting in the formation of an ether bridged structure, observed in the case of ZLNPA, similar to that obtained for the reaction of amino acid complexes with formaldehyde reported earlier[9]. The α-carbon protons of 1-nitropropane are also found to be sufficiently acidic and are found to undergo hydroxymethylation reaction by the formaldehyde molecules when not involved in the ring capping process *via* Mannich aminomethylation reaction. This might be due to the low pK_a value (9.3) of 1-nitropropane and also, the presence of nitro group, a strong electron withdrawing group, makes the protons attached to the α-carbon atom more acidic. Thus in majority of the complexes, all four amino protons are found to be hydroxymethylated.

In the absence of a base, the L-isomer of the Cu(II) alaninato complex, gave the Mannich aminomethylation product CLNPA in which 1-nitropropane is involved in the ring capping of the amino groups of the chelated amino acid complex and two hydroxymethyl groups remain unreacted. With the DL form of the Cu(II) complex, no Mannich aminomethylation product was obtained under different experimental conditions. Hence differential reactivities were noticed with the stereoisomers of the alaninato complexes of Cu(II) under acidic condition. The product NLNPA synthesized using $[Ni(L\text{-}ala)_2]$ complex as the starting material was assigned a structure similar to that of the product NDNPA, based on the IR and elemental analysis data. Different products were obtained from the reaction of the stereoisomers of the alaninato complexes of Zn(II). In the product obtained from the DL isomer, the ring capping of the amino acid is from the 1-nitropropane, whereas, in the L-isomer, the amino groups are bridged by an ether type linkage by the attack of the formaldehyde molecules.

Thus, DL and L isomers of the Cu(II) and Zn(II) alaninato complexes show differential reactivities with the 1-nitropropane and therefore yield different products as a result of Mannich aminomethylation reaction.

NMR spectra: The ^{1}H NMR spectrum of the complex ZDNPA is shown in Fig. 7. In the ^{1}H NMR spectrum of the complex, the peak corresponding to –OH group is present at δ 4.542 ppm. The –CH- protons of the amino acid couples with the adjacent methyl group and hence exhibit a quartet at δ 4.283 ppm. The two hydroxymethyl groups are present in chemically different environment, therefore the protons of the two $-CH_2$ groups absorb at two different δ values *viz.*, 3.639 and 3.493. Peaks corresponding to the $-CH_2$ groups of the formaldehyde molecules which are directly attached to the amino nitrogen atoms of the amino acid can be differentiated into two types. One type is involved in the ring capping and the other type forming a part of the linear chain. The corresponding signals are obtained at δ 3.267 and 2.889 ppm. The methylene protons of the 1-nitropropane molecule show corresponding peaks at δ 1.699 ppm. The methyl protons of the alanine units are present as a doublet at δ 1.128 ppm and the $-CH_3$ group from 1-nitropropane show corresponding triplet peak at δ 0.740 ppm.

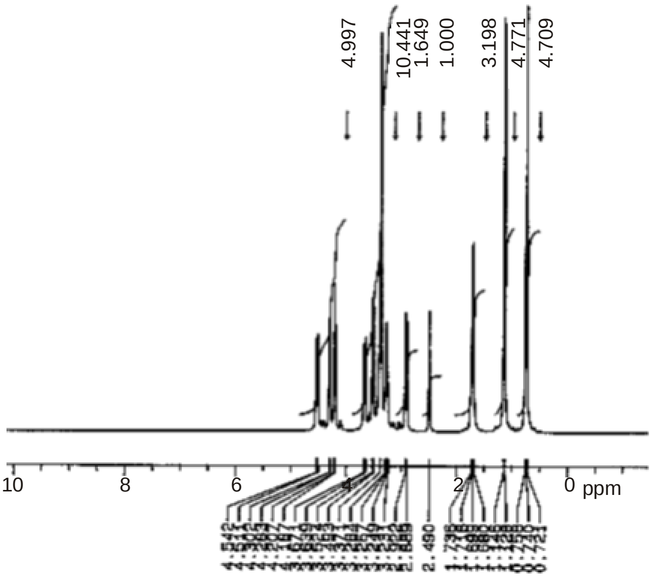


Fig. 7. 400 MHz ^{1}H NMR spectrum of the complex ZDNPA in DMSO-d_6

The ^{13}C NMR spectrum of the complex shows nine peaks corresponding to nine chemically and magnetically different carbon atoms. The carbon atom of the acetato group is observed at δ 177.219 ppm. The two carbon atoms attached directly to the $-NO_2$ group show peaks at δ 88.301 and 84.263 ppm. The carbon atom of the hydroxymethyl group shows corresponding peak at δ 69.949 ppm. The $-CH_2$ group of the formaldehyde molecules forming part of the ring and those involved in linear chain formation show peaks at δ 58.216 and 50.717 ppm. The carbon atom of the –CH- group of the alanine units show corresponding signal at δ 27.676 ppm. The carbon atoms of the methylene and methyl groups of 1-nitropropane show signals at δ 15.760 and 7.153 ppm respectively. Thus ^{1}H NMR and ^{13}C NMR shows the presence of chemically and magnetically different protons and carbon atoms in the proposed structure of the complexes. The ^{13}C NMR spectrum of the complex ZDNPA is shown in Fig. 8.

The ^{1}H NMR and ^{13}C NMR for the complex ZLNPA couldn't be obtained due to its poor solubility in DMSO-d_6.

ESR spectrum: ESR spectrum of the complex CLNPA in frozen DMSO solution showed a characteristic profile of an axial environment around the copper(II) center. The spectral parameters for the complex CLNPA are given in Table-1. The

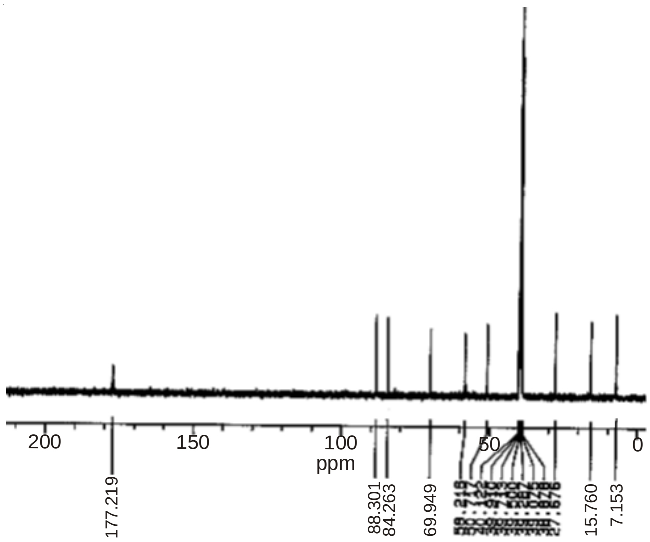


Fig. 8. 100 MHz ^{13}C NMR spectrum of the complex ZDNPA in DMSO-d_6

TABLE-1
ESR PARAMETERS FOR THE COPPER COMPLEX PREPARED IN FROZEN DMSO SOLUTION AT 77 K

Compound	$g_{\parallel}$	$g^{\perp}$	$A_{\parallel}$ (cm^{-1})	$g_{\parallel}/A_{\parallel}$ (cm)
CLNPA	2.23	2.04	205.7×10^{-4}	108.4

trend $g_{\parallel} > g^{\perp} >$ ge (2.0023) observed for the complex shows that the unpaired electron is in the orbital of the copper(II) ion[10]. The empirical ratio $g_{\parallel}/A_{\parallel}$ can be used to evaluate the tetrahedral distortions in copper(II) complexes[11]. Based on this, the complex is found to have distorted tetrahedral symmetry around the copper(II) ion in the product complexes. Fig. 9 shows the ESR spectrum of the complex CLNPA. The ESR spectrum of the complex CLNPA shows that the product exists predominantly in its monomeric state though the presence of minor amount of dimeric units in solution cannot be ruled out completely which is also clear from the ESR spectrum. Therefore the complex exists as an equilibrium mixture of monomeric and dimeric species in solution, that is, both singlet and triplet state of the complex are present in solution.

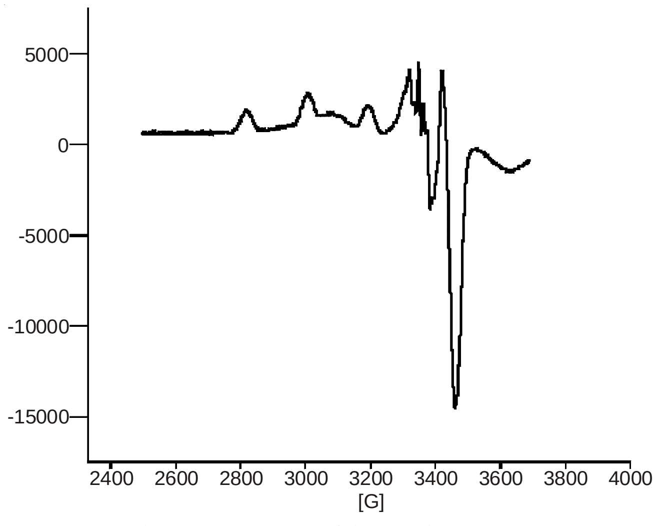


Fig. 9. ESR spectrum of the complex CLNPA

Conclusion

Mannich aminomethylation products involving metal-(alaninato) complexes of Cu, Ni and Zn, formaldehyde and 1-nitropropane have been synthesized and characterized by various spectroscopic methods. The DL-isomers and the L-isomers of the metal complexes reacted to form products only below pH = 5. Higher pH values were found to be unsuitable for Mannich aminomethylation reaction. No stable product could be isolated from the DL-isomer of Cu(II) complex. With the Ni(II) complex, both the DL-isomer and the L-isomer were found to give the same product. Hence, it is clear that the 1-nitropropane is sufficiently acidic to involve in Mannich aminomethylation reaction with all the three metal(alaninato) complexes of Cu, Ni and Zn.

ACKNOWLEDGEMENTS

The authors thank University of Madras for providing the necessary facilities to carry out this work.

REFERENCES

1. Y. Shimazaki, M. Takani and O. Yamauchi, *J. Chem. Soc., Dalton Trans.*, 7854 (2009).
2. (a) R.D. Hancock and A.E. Martell, *Chem. Rev.*, **89**, 1875 (1989); (b) P.V. Bernhardt and G.A. Lawrance, *Coord. Chem. Rev.*, **104**, 297 (1990).
3. A. Barnea and G. Cho, *Endocrinology*, **115**, 936 (1984).
4. V.B. Valodkar, G.L. Tembe, R.N. Ram and H.S. Rama, *Catal. Lett.*, **90**, 91 (2003).
5. (a) A. Puzari and J.B. Baruah, *React. Funct. Polym.*, **47**, 147 (2001); (b) P.K. Sahoo, M. Dey and S.K. Swain, *J. Appl. Polym. Sci.*, **74**, 2785 (1999).
6. S. Supriya, A. Raghavan, V.R. Vijayaraghavan, K. Chinnakali, H.-K. Fun and J. Subramanian, *Polyhedron*, **26**, 3217 (2007).
7. (a) S. Supriya, A. Raghavan, V.R. Vijayaraghavan and J. Subramanian, *Polyhedron*, **26**, 3388 (2007); (b) P. Comba, T.W. Hambley, G.A. Lawrence, L.L. Martin, P. Renold and K. Varnagy, *J. Chem. Soc., Dalton Trans.*, 277 (1991); (c) C.H. Ng, C.M. Lim, T.M. Chang, S.G. Teoh, S.W. Yap and S.W. Ng, *Polyhedron*, **25**, 1287 (2006).
8. N. Arulsamy, B. Srinivas and P.S. Zacharias, *Transition Met. Chem.*, **15**, 309 (1990).
9. C.R.K. Rao, N. Arulsamy, P.S. Zacharias and D.J. Hodgson, *J. Chem. Soc., Dalton Trans.*, 3581 (1993).
10. F.E. Mabbs and D. Collison, EPR of Transition Metal Compounds, Elsevier, Amsterdam, p. 379 (1992).
11. U. Sakaguchi and A.W. Addison, *J. Chem. Soc., Dalton Trans.*, 600 (1979).