Asian Journal of Chemistry Vol. 18, No. 1 (2006), 45–49

Molecular Mechanics and Semi-empirical Analyses of the Interaction between Nickel(II) and L-histidine and L-arginine in Solution in Water

FAZLUL HUQ* and MARIE C.R. PETER
School of Biomedical Sciences, Faculty of Health Sciences, C42, The University of Sydney
PO Box 170, Lidcombe, NSW 1825, Australia
Fax: (61)(2)93519520; Tel: (61)(2)93519522
E-mail: f.huq@fhs.usyd.edu.au

The interaction between nickel(II) and the amino acids (*viz.*, L-histidine and L-arginine) in solution in water has been investigated by UV-visible spectrophotometry using the technique of continuous variation and molecular modelling. The absorbance values at λ_{max} were plotted against concentrations of reactants. The maxima in the absorbance *vs.* concentration graphs gave the ratios at which the metal ion and amino acids combined. Nickel(II) is found to form predominantly 1 : 3 complex with both L-histidine and L-arginine. As expected, the *d-d* absorption bands due to nickel(II) have been found to show a shift to shorter wavelengths when complexed with L-histidine and L-arginine. The proposed structures of the complexes have been optimized and their electronic spectra generated based on molecular mechanics and semi-empirical calculations. Comparison of the observed and predicted electronic spectra suggested the most likely structures present in solution.

Key Words: Molecular mechanics, Semi-empirical, Histidine, Nickel(II), Arginine, UV-visible spectra.

INTRODUCTION

A number of metal ions perform diverse essential functions in living systems[1], although often unknown at the molecular level. The interactions of metal ions with biomolecules belong to one of the most studied fields in bioinorganic chemistry. Amino acids provide excellent donor centres for transition metal ions. Metal ion-amino acid interaction has been studied widely both in the solid state and in solution in water using a number of instrumental techniques[2–8]. But the works done on modelling the interaction between transition metal ions and amino acids in solution in water appear to be limited. Recently, Rulisek *et al.*[9] report on metal ion selectivity based on DFT calculations of interaction energies of amino acid side chains with selected transition metal ions.

In this paper, the results of a study carried out on the interaction between Ni^{2+} and the amino acids (AA) (L-histidine (His) and L-arginine (Arg)) using as a probe the effect of binding on the visible *d-d* transisiton of the metal ions (and in some cases the effect on the ultraviolet absorption spectrum of the amino acids) combined with molecular modelling is reported. In an earlier study, we used molecular modelling to explore the interaction between Ni^{2+} and nucleobases, nucleosides and nucleotides[10].

EXPERIMENTAL

Analytical grade nickel chloride ($NiCl_2 \cdot 6H_2O$) was purchased from Ajax Chemicals, NSW, Australia. Amino acids were purchased from Sigma-Aldrich Pty Ltd, NSW, Australia.

0–4 mL of solutions of $NiCl_2$ (33.3 mM) and amino acid (100.0 mM) (His or Arg), both made in milli Q (mQ) water, were mixed in varying proportions and the total volume made up to 4 mL (Table-1). The solutions were placed in sealed plastic tubes and left at 22.0°C for 24 h. The UV-Visible spectrum from 190–900 nm of solution I (Table-1) was recorded using a Cary 1A UV-Visible spectrophotometer, to determine the wavelength (λ_{max}) at which the absorbance was a maximum. A scan rate of 200 nm per min and band width of 2 nm were used. The absorbance at λ_{max} was then measured for each solution A to S. Milli Q water was used as the blank. The absorbance values (Table-1) were then plotted against the added concentrations of the amino acid and Ni^{2+} to determine the stoichiometry of the adducts formed.

TABLE-1

INTERACTION BETWEEN Ni^{2+} (33.3 mmol L^{-1}) AND AMINO ACIDS (100.0 mmol L^{-1}) (His or Arg): ABSORBANCE VALUES

Solution	A	B	C	D	E	F	G	H	I
M^{2+} (mL)	4.00	3.75	3.50	3.25	3.00	2.75	2.50	2.25	2.00
AA (mL)	0.00	0.25	0.50	0.75	1.00	1.25	1.50	1.75	2.00
$[Ni^{2+}]$ (mM)	33.30	31.3	29.2	27.1	25.0	22.9	20.8	18.7	16.7
[AA] (mM)	0	6.3	12.5	18.8	25.0	31.3	37.5	43.8	50.0
$n(AA)/n(Ni^{2+})$	0.000	0.200	0.429	0.692	1.000	1.364	1.800	2.333	3.000
Abs at 533 nm[1]	0.124	0.147	0.190	0.391	0.455	0.639	1.242	1.763	1.784
Abs at 364 nm[2]	0.049	0.065	0.083	0.106	0.121	0.144	0.169	0.204	0.234

Solution	J	K	L	M	N	O	P	Q	R	S
M^{2+} (mL)	1.75	1.50	1.25	1.125	1.00	0.875	0.75	0.50	0.25	0.00
AA (mL)	2.25	2.50	2.75	2.875	3.00	3.125	3.25	3.50	3.75	4.00
$[Ni^{2+}]$ (mM)	14.6	12.5	10.4	9.4	8.3	7.3	6.2	4.2	2.1	0
[AA] (mM)	56.3	62.5	68.8	71.9	75.0	78.1	81.3	87.5	93.8	100
$n(AA)/n(Ni^{2+})$	3.857	5.000	6.600	7.667	9.000	31.93	13.00	21.00	45.00	—
Abs at 533 nm[1]	1.558	1.319	1.057	0.955	0.820	0.699	0.585	0.353	0.139	0.005
Abs at 364 nm[2]	0.226	0.198	0.167	0.152	0.137	0.122	0.104	0.072	0.038	0.006

[1] Ni^{2+} and His; [2] Ni^{2+} and Arg

HyperChem Calculations

The proposed structures of the metal-amino acid complexes were optimized and their electronic spectra generated based on molecular mechanics and semi-empirical calculations using HyperChem 5 Molecular Visualization and Simulation program[11]. Geometry optimizations based on molecular mechanics (using MM^+ force field) and semi-empirical calculations (using ZINDO/1)[12] were used to find the coordinates of molecular structures that represent a potential energy minimum. For geometry optimization using both molecular mechanics and semi-empirical calculations, Polak-Ribiere routine with RMS gradient of 0.02 as the termination condition was used. To simulate the conditions in solution, the molecules were placed in a periodic box of TIP3P water molecules[13] followed by further cycles of geometry optimization. The actual dimensions of the box used and the maximum number of water molecules present are given in Table-2.

TABLE-2
DIMENSIONS OF PERIODIC BOX IN ANGSTROMS AND MAXIMUM NUMBER OF WATER MOLECULES

Molecule	X (Ångströms)	Y (Ångströms)	Z (Ångströms)	Maximum number of water molecules
$Ni(His)_3(H_2O)_3$	23.16	23.16	23.16	411
$Ni(Arg)_3(H_2O)_3$	29.47	29.47	29.47	845

The minimum distance between solvent molecules and solute atoms was set at 2.3 Å. Molecular dynamics calculations were used to obtain a lower energy minimum by enabling molecules to cross potential barriers[14]. The parameters used in simulated annealing were: heat time = 1 ps, run time = 0.5 ps, cool time = 0 ps, step size = 0.0005 ps, bath relaxation time = 0.1 ps, starting temperature = 100 K, simulation temperature = 300 K, temperature step = 30 K and data collection period = 4 time steps.

For the optimized structures, electronic spectra were generated using the routine ZINDO/S following a singly excited configuration interaction (CI) calculation with semi-empirical method. HyperChem performs a self consistent field (SCF) calculation to obtain the reference electronic configuration associated with the ground state. Next, it generates a series of singly excited configurations, computes Hamiltonian matrix elements between them and then diagonalizes the matrix to get the spectrum of the electronic states. The number of occupied and unoccupied orbitals set in the single point CI calculations was both set equal to ten.

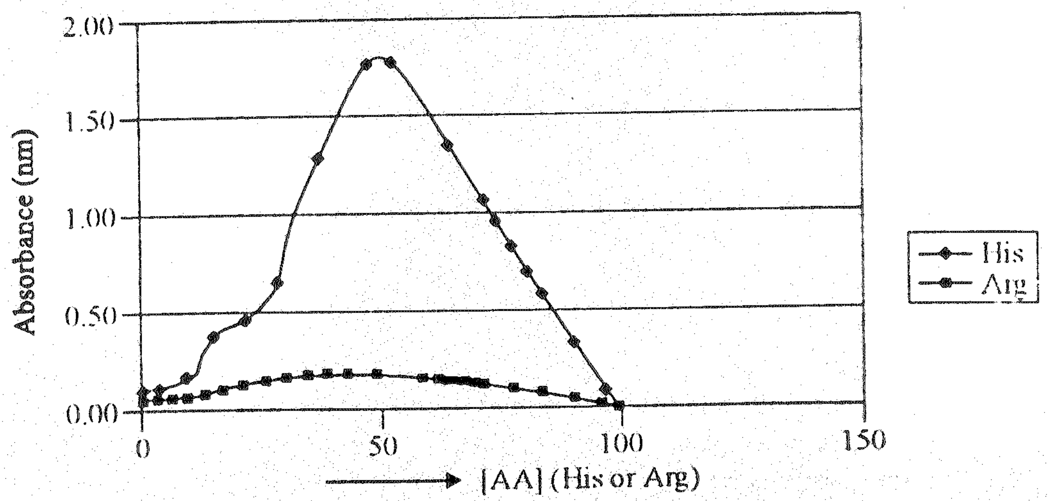

Fig. 1. Plot of absorbance against concentration of amino acid (His or Arg)

RESULTS AND DISCUSSION

Nikel(II) formed 1 : 3 complex with both L-histidine and L-arginine. There are three observed bands in the spectrum of $Ni(H_2O)_6^{2+}$ at 400 nm, 714 nm and 1111 nm in accordance with three spin-allowed transitions for d^8 ions. These bands have been assigned respectively as being due to $^3A_{2g} \rightarrow {}^3T_{2g}$, $^3A_{2g} \rightarrow {}^5T_{1g}$ and $^3A_{2g} \rightarrow {}^3T_{1g}$ transitions. The splitting of the middle band in the spectrum of $Ni(H_2O)_6^{2+}$ is due to spin-orbit coupling that mixes the $^3T_{1g}(F)$ and ^1E_g states, which are very close in energy at Δ_0 value given by $6H_2O$. In nickel(II)-histidine complex, the band corresponding to the maximum at 400 nm in $Ni(H_2O)_6^{2+}$ is found to be shifted to 358 nm and that at 725 nm is shifted to 530 nm. In the Ni(II)-L-arginine complex, there were two maxima at 364 and 610 nm. For the Ni(II)-L-histidine complex, best agreement between observed and predicted electronic spectra was found when Ni(II) was considered to be coordinated to four histidine ligands (through pyridine nitrogens of imidazole side chains) and two water molecules so that the complex had the stoichiometry $Ni(His)_3(H_2O)_3$. The predicted absorption maxima for the structure were found to be at 223, 385 and 547 nm as against the observed values of 239, 358 and 550 nm.

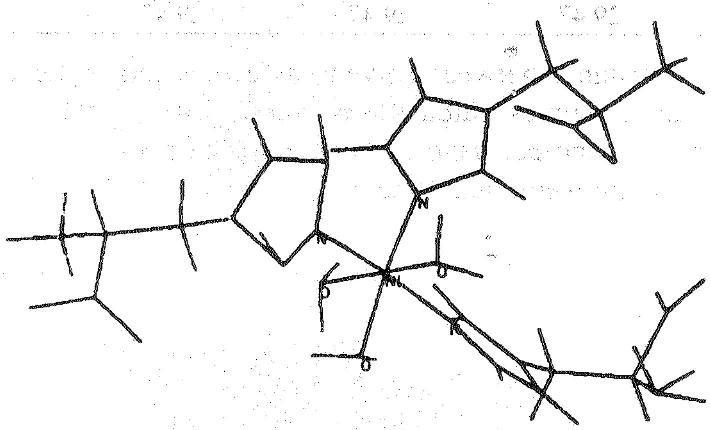

Fig. 2. Proposed structure of $Ni(His)_3(H_2O)_3$ in which Ni^{2+} is bonded to three histidine ligands through imidazole nitrogens and three water molecules

TABLE-3
OBSERVED AND COMPUTED UV-VISIBLE SPECTRAL LINES*

Complex	Observed λ_{max} values (nm)	Structure/Total Energy/ΔH_f	Predicted spectral lines (nm)
$Ni(His)_3$	239 (vs); 358 (m); 550 (w)	$Ni(His)_3(H_2O)_3$; –2379476.79; –2379476.43	574.5 (0.0111); 546.6 (0.0811); 398.2 (0.0362); 384.6 (0.114); 360.3 (0.0460); 243.6 (0.0116); 222.7 (0.0145)
$Ni(Arg)_3$	230; 364; 610	$Ni(Arg)_3(H_2O)_3$; –2681364.87; –2473847.91	517.4 (0.004); 395.7 (0.065); 363.4 (0.001); 311.0 (0.061); 280.2 (0.004); 261.3 (0.022); 248.4 (0.021); 241.1 (0.012); 229.8 (0.065)

*Energy values in kcal mol^{-1}; s: strong, vs: very strong, m: medium, w: weak.

For the nickel(II)-L-arginine complex, the best agreement between observed and predicted electronic spectra was found when nickel was considered to be bonded to three amino nitrogens of L-arginine side-chains and three water molecules so that the complex had the stoichiometry $Ni(Arg)_3(H_2O)_3$.

The computed absorption maxima for the optimized structure were found to be at 230, 396 and 517 nm as against the observed values of 230, 364 and 610 nm. In this structure, there were four intramolecular hydrogen bonds involving nitrogen and oxygen centres.

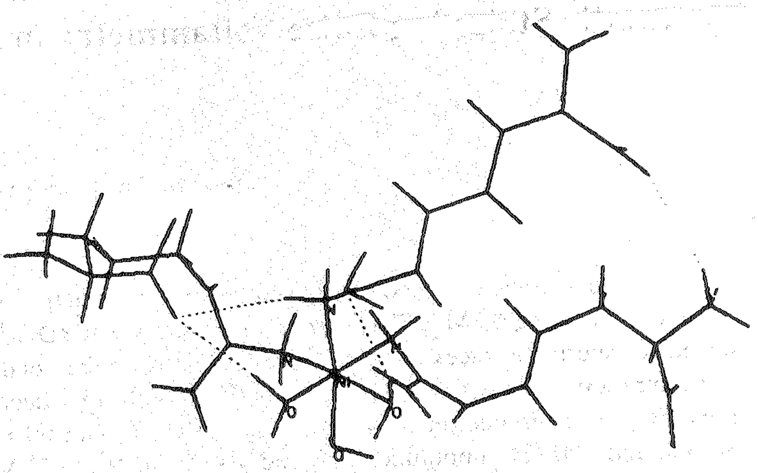

Fig. 3. Proposed structure of $Ni(Arg)_3(H_2O)_3$ in which Ni^{2+} is bonded to three arginine ligands through side-chain nitrogens and three water molecules

Conclusion

In solution, nickel(II) was found to form 1 : 3 complexes with both L-histidine and L-arginine. Molecular modelling analysis suggested that in Ni(II)-His complex, Ni^{2+} was bonded to three imidazole nitrogens and three water molecules and in Ni(II)-Arg complex, it was bonded to three amino nitrogens of arginine side-chains and three water molecules.

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(*Received*: 9 August 2004; *Accepted*: 22 August 2005) AJC-4361