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Molecular Mechanics and Semi-empirical Analysis of the Interaction Between Co^{2+} and the Amino Acids in Solution in Water

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The interaction between Co^{2+} and 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 modeling. For the metal ion and the two amino acid combinations, 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. Cobalt(II) is found to form predominantly 1 : 4 complex with L-histidine and 1 : 3 complex with 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: Amino acids, Histidine, Arginine, Transition metal ions, Complexes, UV-visible spectra.

INTRODUCTION

A number of metal ions perform diverse essential functions in living systems[1], although often unknown at the molecular level. Cobalt is found in vitamin B_{12} which is a cyano complex in which a methyl or methylene group replaces CN in the native enzyme[2]. Cobalamines provide rare examples of a naturally occurring metal-carbon σ-bond.

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 a solid state and in solution in water using a number of instrumental techniques[3–9]. 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.*[10] reported the metal ion selectivity data based on DFT calculations of interaction energies of amino acid side chains with selected transition metal ions.

As a part of our study to explore the interaction between metal ions and biological ligands, herein the results of a study carried out on the interaction between Co^{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* transition of the metal ions combined with molecular modelling are reported. In an earlier study, molecular modelling was also used to explore the interaction between Ni^{2+} and nucleobases, nucleosides and nucleotides[11].

As a transition metal ions such as Co^{2+} complexes, the ligand field causes splitting of its *d* orbitals resulting into observable *d-d* transitions associated with the absorption of UV, visible or near infrared photons. The number of bands and their position on the spectrum are dependent on the symmetry and the strength of the ligand field. For example, in the octahedral ligand field, the five *d* orbitals of a transition metal ion are split into two groups—three of one kind, equivalent to one another and labelled t_{2g}, and two of another kind, equivalent to each other, labelled e_g. The e_g orbitals are of higher energy than the t_{2g} orbitals. The difference in energy between the two groups of *d* orbitals may correspond to the energy carried by a UV-Visible photon. Thus, UV-Visible spectrophotometry offers a simple technique to study the interaction between transition metal ions and various ligands including amino acids.

EXPERIMENTAL

Analytical grade cobalt(II) chloride 6-water ($CoCl_2·6H_2O$) was purchased from Ajax Chemicals, NSW, Australia. Amino acids were purchased from Sigma-Aldrich Pvt. Ltd., NSW, Australia.

The solutions of $CoCl_2$ (0–4 mL, 33.3 mM) and 100.0 mM amino acid (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°C for 7 d at the end of which the UV-Visible spectrum from 190 to 900 nm of solution 1 (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 (given in Table-1) were then plotted against the added concentrations of the amino acid and Co^{2+} to determine the stoichiometry of the adducts formed.

HyperChem Calculations

The proposed structures of the Co-histidine and Co-arginine complexes were optimised and their electronic spectra generated based on molecular mechanics and semi-empirical calculations using HyperChem 5 Molecular Visualization and Simulation program[12]. Geometry optimizations based on molecular mechanics (using MM^+ force field) and semi-empirical calculations (using ZINDO/1)[13] 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[14] 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-1
INTERACTION BETWEEN 33.3 mmol L^{-1} Co^{2+} and 100.0 mmol L^{-1} AMINO ACIDS (His OR Arg): ABSORBANCE VALUES

Solution	A	B	C	D	E	F	G	H	I
mL M^{2+}	4.00	3.75	3.50	3.25	3.00	2.75	2.50	2.25	2.00
mL AA	0.00	0.25	0.50	0.75	1.00	1.25	1.50	1.75	2.00
$[Co^{2+}]$ mM	33.3	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
Molar ratio: $n(AA)/n(Co^{2+})$	0.000	0.200	0.429	0.692	1.000	1.364	1.800	2.333	3.000
Abs at 617 nm[1]	0.044	0.149	0.268	0.403	0.571	0.792	1.042	1.069	1.300
Abs at 358 nm[2]	0.033	0.045	0.058	0.069	0.810	0.0922	1.105	1.125	0.176

Solution	J	K	L	M	N	O	P	Q	R	S
mL M^{2+}	1.75	1.50	1.25	1.125	1.00	0.875	0.75	0.50	0.25	0.00
mL AA	2.25	2.50	2.75	2.875	3.00	3.125	3.25	3.50	3.75	4.00
$[Co^{2+}]$ 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
Molar ratio: $n(AA)/n(Co^{2+})$	3.857	5.000	6.600	7.667	9.000	10.69	13.00	21.00	45.00	—
Abs at 617 nm[1]	1.558	1.319	1.057	0.955	0.820	0.699	0.585	0.353	0.139	0.005
Abs at 358 nm[2]	0.226	0.198	0.167	0.152	0.137	0.122	0.104	0.072	0.038	0.006

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

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

Molecule	X (Å)	Y (Å)	Z (Å)	Maximum number of water molecules
$Co(His)_4(H_2O)_2$	23.16	23.16	23.16	411
$Co(Arg)_3(H_2O)_3$	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[15]. 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.

RESULTS AND DISCUSSION

Complexes between Co^{2+} and L-histidine

Fig. 1 gives the absorbance *vs.* concentration of plot applying to the continuously varying mixtures of 33.3 mM $CoCl_2$ and 100 mM L-histidine. The maximum in the graph indicates the formation of predominantly 1 : 4 complex between Co^{2+} and L-histidine.

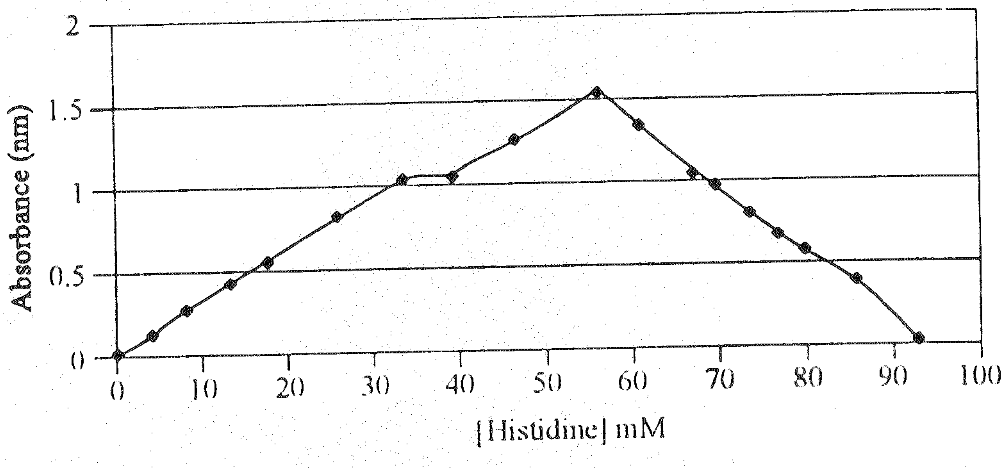

Fig. 1. Absorbance *vs.* concentration of plot applying to the continuously varying mixtures of 33.3 mM $CoCl_2$ and 100 mM L-histidine indicating the formation of predominantly 1 : 4 complex

For cobalt(II)-L-histidine complex, best agreement between observed and predicted electronic spectra was found when cobalt(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 $Co(His)_4(H_2O)_2$.

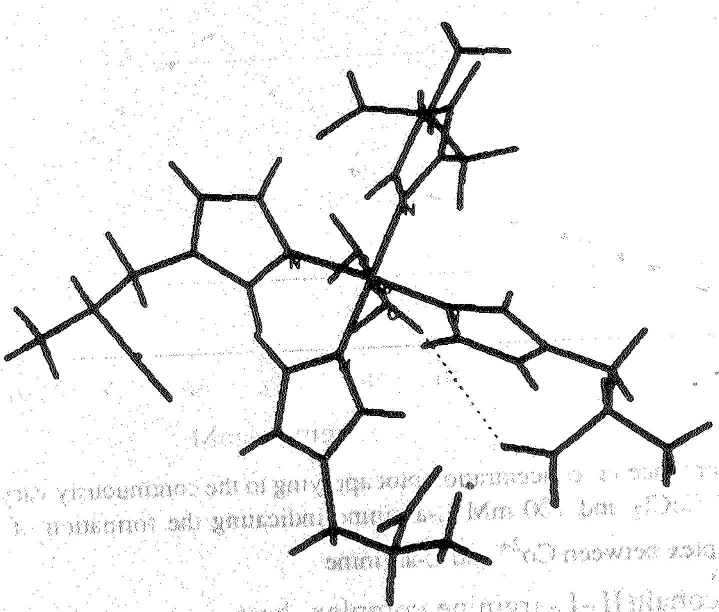

Fig. 2. Proposed structure of $Co(His)_4(H_2O)_2$ in which Co^{2+} is bonded to four histidine ligands through imidazole nitrogens and two water molecules

The structure gave a much better agreement between observed and predicted electronic spectra than other structures that would result if L-histidine was considered to be a polydentate ligand or if it was bonded to the metal ion through the carboxyl oxygen. In this structure, there is an intramolecular H-bond between a coordinated water molecule and a carboxyl oxygen. The predicted absorption maxima in the optimised structure of $Co(His)_4(H_2O)_2$ were found to be at 314 and 497 nm as compared to the observed values of 354 and 500 nm. It should be noted that cobalt(II) can also form tetrahedral complexes, more readily than other transition metal ions[16]. This is because the stability difference between octahedral and tetrahedral complexes is small for a d^7 ion so that both octahedral and tetrahedral complexes may exist with the same ligand and may often be in equilibrium. However, when Co^{2+} was considered to be bonded to four histidine ligands in a tetrahedral geometry, it was found that there was a much poorer agreement between observed and predicted absorption maxima. As the complex was prepared in air, it is possible that Co^{2+} could be oxidized to Co^{3+}. The interaction of cobalt(II) complexes in solution with oxygen has been the subject of intense study[17]. Cobalt(III) complexes undergo ligand exchange reactions more slowly than cobalt(II) complexes.

However, when the proposed structure of the Co-histidine complex was optimized with cobalt in the +3 oxidation state, it was found that the agreement between predicted and observed spectral lines was worsened as compared to that with Co in the +2 oxidation state.

Complexes between Co^{2+} and L-arginine

Fig. 3 gives the absorbance *vs.* concentration plot applying to the continuously varying mixtures of 33.3 mM $CoCl_2$ and 100 mM L-arginine indicating the formation of predominantly 1 : 3 complex between Co^{2+} and L-arginine.

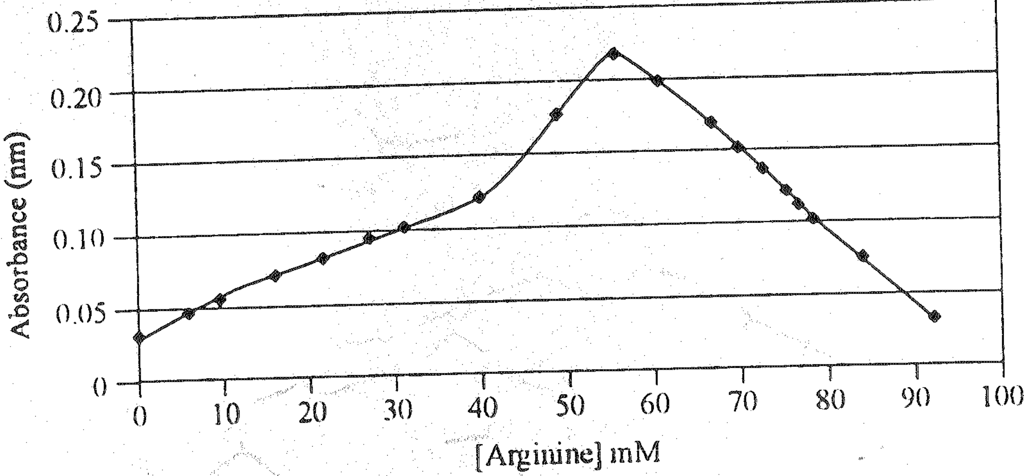

Fig. 3. Absorbance *vs.* concentration plot applying to the continuously varying mixtures of 33.3 mM $CoCl_2$ and 100 mM L-arginine indicating the formation of predominantly 1 : 3 complex between Co^{2+} and L-arginine

For the cobalt(II)-L-arginine complex, best agreement between observed and predicted electronic spectra was found when cobalt 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 $Co(Arg)_3(H_2O)_3$. In the proposed structure, there are two intramolecular hydrogen bonds—one between coordinated water and arginine side-chain nitrogen and the other between amino group and arginine side chain resulting in the formation of macrochelates.

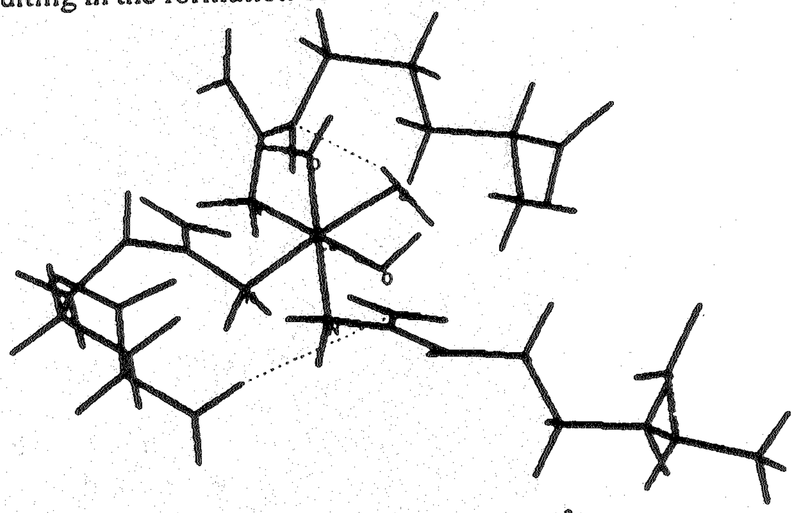

Fig. 4. Proposed structure of $Co(Arg)_3(H_2O)_3$ in which Co^{2+} is bonded to three arginine ligands through side-chain nitrogens and three water molecules

The predicted absorption maxima for the structure were found to be 358 and 468 nm as against the observed values of 344 and 533 nm. In this structure, there are two intramolecular H-bonds involving coordinated water molecules and arginine side chains, one of which produces a macrochelate.

In both $Co(His)_4(H_2O)_2$ and $Co(Arg)_3(H_2O)_3$, cobalt has a distorted octahedral coordination geometry with Co-N distances ranging from 1.87 to 1.88 Å, Co-O distances ranging from 1.84 to 1.85 Å. In the case of $Co(His)_4(H_2O)_2$, the four in-plane N—Co—N angles together add up to 364.5° where the angle OCo—O is 178.3°. In the case of $Co(Arg)_3(H_2O)_3$, the axial positions are occupied by an O and an N whereas the equatorial coordinations are with 2 N and 2 O centres.

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

Complex	Observed λ_{max} values (nm)	Structure/Total Energy/ΔH_f	Predicted spectral lines (nm)
$Co(His)_4$	233 (vs); 354 (vs); 500 (s)	$Co(His)_4(H_2O)_2$; –3678089.12; –3451711.58	762.8 (0.008); 635.0 (0.039); 530.2 (0.008); 514.5 (0.008); 496.8 (0.012); 492.6 (0.006); 397.5 (0.011); 313.8 (0.022); 279.4 (0.14); 257.7 (0.061)
$Co(Arg)_3$	344 (vs); 533 (s)	$Co(Arg)_3(H_2O)_3$; –242777.24; –38645.31	559.5 (0.001); 468.3 (0.017); 357.7 (0.037); 337.5 (0.001); 324.5 (0.003); 263.2 (0.001); 253.9 (0.084); 250.4 (0.040)

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

Conclusion

In solution in water, cobalt(II) formed 1 : 4 complex with L-histidine and 1 : 3 complex with L-arginine. Molecular modelling analysis suggested that in Co(II)-His complex, the metal ion was bonded to four imidazole nitrogens and two water molecules and in Co(II)-Arg complex, it was bonded to three amino nitrogens of arginine side-chains and three water molecules.

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