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Research Article

Synthesis, Characterization, and Antimicrobial Activities of Coordination Compounds of Aspartic Acid

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Coordination compounds of aspartic acid were synthesized in basic and acidic media, with metal ligand M : L stoichiometric ratio 1 : 2. The complexes were characterized using infrared, electronic and magnetic susceptibility measurements, and mass spectrometry. Antimicrobial activity of the compounds was determined against three Gram-positive and three Gram-negative bacteria and one fungus. The results obtained indicated that the availability of donor atoms used for coordination was a function of the pH of the solution in which the reaction was carried out. This resulted in varying geometrical structures for the complexes. The compounds exhibited a broad spectrum of activity and in some cases better activity than the standard.

1. Introduction

Much attention is being paid to coordination compounds as potential antimicrobial agents in recent times. This is due to the improved activity of drugs administered as complexes [1–6]. It has been suggested that ligands with nitrogen and oxygen donor systems might inhibit enzyme production. This is because the enzymes which require these groups for their activity appear to be especially more susceptible to deactivation by the metal ion upon chelation [2]. Such compounds include coordination compounds of amino acids, such as aspartic acid. Aspartic acid (Figure 1) is a naturally occurring amino acid and a component of the active centre of some enzymes. It possesses three potential donor sites (one amine group and two carboxyl ones) [7, 8]. Aspartic acid has been reported as bidentate, as tridentate, and as a bridging ligand [9–15]. Its coordination behaviour may therefore be studied by comparing the complexes it forms with a series of metal ions of the same valency at relevant pH ranges [12, 14, 15]. Various structural possibilities for the corresponding metal complexes are thus expected [16–20]. Coordination compounds of amino acids, such as histidine [21], arginine, glutamic acid [14, 16], and aspartic acid [13, 22], have been studied. These coordination compounds were reported to demonstrate activity varying from marginal to significantly good antimicrobial properties. However, little attention has been focused on coordination compounds of aspartic acid as a tridentate ligand. As a result of resistance to the drugs currently in use and the emergence of new diseases, there is a continuous need for the synthesis and identification of new compounds as potential antimicrobial agents. Therefore we considered it necessary to study the effects of the possible varying structures of coordination compounds of aspartic acid on their antimicrobial activity, as this would yield information useful for designing antimicrobial agents. We therefore report the syntheses of coordination compounds of aspartic acid in acidic and basic media and their characterization and antimicrobial activities.

2. Experimental

2.1. Materials and Methods. All reagents and solvents used were of analytical grade. The infrared spectra were recorded on a Genesis II FTIR spectrophotometer in the range 450–4200 cm^{-1}. The electronic absorption spectra of

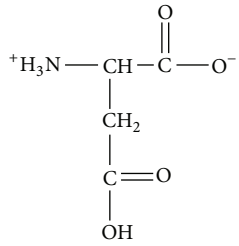

Figure 1

the complexes in the range 200–1000 nm were obtained with a Genesis 10 UV-Vis spectrophotometer, solid reflectance. Melting points or decomposition temperatures (m.p./d.t.) were measured using open capillary tubes on a Gallenkamp (variable heater) melting point apparatus. The *in vitro* antimicrobial properties of the complexes were determined using a modification of the literature procedure [23]. Magnetic susceptibility was obtained using a Gouy balance at room temperature. Mass spectrometry for one of the complexes was carried out using Fisons VG Quattro spectrophotometer.

2.2. Syntheses of Complexes. The complexes were prepared according to a modification of literature procedure [13, 24, 25]. The general equations for the reactions are as follows:

ML_2 complexes:

$$MCl_2 + 2H_2L \rightarrow MHL_2 + 2HCl$$

$Na_2[ML_2]$ complexes:

$$MCl_2 + 2H_2L + 2NaOH \rightarrow Na_2[ML_2] + 2HCl + 2H_2O$$

where M = Co(II), Cu(II), Mn(II), Ni(II), Cd(II); L = (+)-aspartic acid.

2.2.1. ML_2 Complexes. A solution of (+)-aspartic acid (0.02 M, 2.67 g) was added to 0.01 M of appropriate metal(II) chloride salt (1.62, 2.17, 2.43, 2.51, and 2.69 g) for copper, cadmium, nickel, cobalt, and manganese, respectively, and dissolved in 20 mL of distilled water, with stirring; pH range for the reactions was 2.01–2.21. The mixtures were heated with stirring for 2 h, using a water bath. The resultant solutions were further concentrated until a scum was formed and then cooled. Crystals obtained were filtered and washed with methanol and then dried in a vacuum oven at 60°C.

2.2.2. $Na_2[ML_2]$ Complexes. Appropriate metal(II) chloride salt solutions (0.02 M; 3.31, 4.47, 4.88, 5.05, and 5.34 g) for copper, cadmium, nickel, cobalt, and manganese, respectively, were dissolved in minimal amount of distilled water with warming until a clear solution was obtained. (+)-Aspartic acid (0.04 M, 5.42 g) was dissolved in distilled water and warmed over a steam bath. 0.04 M NaOH was then added with stirring, such that the pH range of the reaction was about 8–10. The metal(II) solution was then added and the mixture was refluxed for 2 h. The product obtained was allowed to cool overnight with the formation of crystals. The crystals obtained were filtered, washed with methanol, and dried in an oven at 60°C.

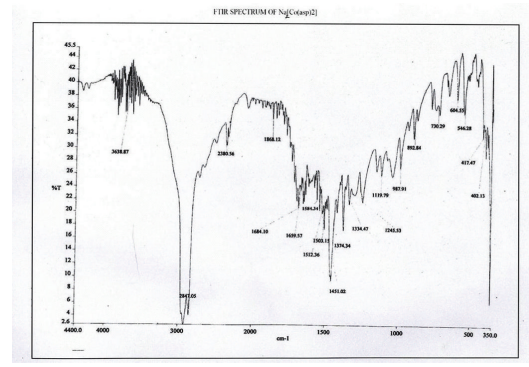

Figure 2: Infrared spectrum for $Na_2[Co(asp)_2]$.

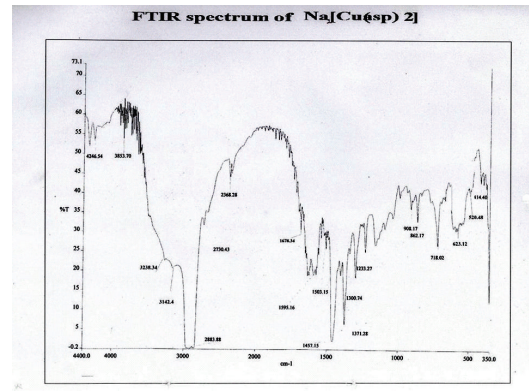

Figure 3: Infrared spectrum for $Na_2[Cu(asp)_2]$.

2.3. Antimicrobial Activity Using Disc Diffusion Assay. The *in vitro* antimicrobial screening effects of the ligand and complexes were evaluated using the disc diffusion method as previously reported [26]. The strains used were *Escherichia coli* NCTC 8196, *Pseudomonas aeruginosa* ATCC 19429, *Staphylococcus aureus* NCTC 6571, *Proteus vulgaris* NCIB, *Bacillus subtilis* NCIB 3610, and one Methicillin resistant *S. aureus* clinical isolate for bacteria and *C. albicans* NCYC 6 for fungi. All the tests were performed in triplicate.

3. Results and Discussion

3.1. Physicochemical Analysis. All the complexes were insoluble in major organic solvents; however they were soluble in hot water. The melting points or decomposition temperatures for the complexes are shown in Table 1. Most of the complexes decomposed before melting.

3.2. Infrared Spectra. The infrared spectrum of the free ligand exhibited a broad band at 3380 cm^{-1} which was assigned to the NH_2 stretching frequency. Intense bands at 1650 and 1583 cm^{-1} were observed and are attributed to COO^-_{asy} and COO^-_{sy} stretching frequencies, respectively [27, 28]. The COO^- asymmetric and symmetric stretching frequencies on coordination were shifted to higher and lower wave numbers, for $Na_2[ML_2]$ complexes, indicating that the oxygen atom of the carboxylate group of the ligand was used for coordination, Figures 2 and 3 [12, 28]. For the ML_2 complexes the COO^-

Table 1: Some physicochemical properties of the compounds.

Compound	Empirical formulae	Colour	m.p./d.t. (°C)	Yield (%)
$Co(d\text{-asp})_2$	$Co(C_4H_8O_4N)$	Lilac	217	74.20
$Cu(d\text{-asp})_2$	$Cu(C_4H_8O_4N)$	Blue	205	57.21
$Mn(d\text{-asp})_2$	$Mn(C_4H_8O_4N)$	White	304(*d*)	81.84
$Ni(d\text{-asp})_2$	$Ni(C_4H_8O_4N)$	Green	197(*d*)	66.00
$Cd(d\text{-asp})_2$	$Cd(C_4H_8O_4N)$	White	204(*d*)	62.40
$Na_2[Co(d\text{-asp})_2]$	$Na[Co(C_4H_8O_4N)]$	Purple	>320	62.60
$Na_2[Cu(d\text{-asp})_2]$	$Na[Cu(C_4H_8O_4N)]$	Blue	215(*d*)	84.20
$Na_2[Mn(d\text{-asp})_2]$	$Na[Mn(C_4H_8O_4N)]$	White	301–303(*d*)	68.50
$Na_2[Ni(d\text{-asp})_2]$	$Na[Ni(C_4H_8O_4N)]$	Green	294(*d*)	62.70
$Na_2[Cd(d\text{-asp})_2]$	$Na[Cd(C_4H_8O_4N)]$	White	287(*d*)	69.60

(*d*): decomposition temperature.

Table 2: Electronic spectra bands, for the compounds.

Compound	Band I	Band II	Band III	*d-d*	Magnetic moment (BM)
Aspartic acid	196	212	8231		—
$Cu(asp)_2$	241	259	391	628, 667	2.47
$Cd(asp)_2$	238	259	271	—	0.00
$Ni(asp)_2$	232	265	—	517	3.28
$Co(asp)_2$	—	259	—	499, 517, 520, 535	5.40
$Mn(asp)_2$	226	277	—	544, 568shld, 682, 829	5.82
$Na_2[Cu(asp)_2]$	226	238	259	667	2.20
$Na_2[Cd(asp)_2]$	226	241	256	833, 881	0.00
$Na_2[Ni(asp)_2]$	—	235	259	637, 652	1.15
$Na_2[Co(asp)_2]$	223	241	256	526, 541, 565	4.33
$Na_2[Mn(asp)_2]$	223	235	265	526, 541, 673	

asymmetric stretching frequencies were shifted to higher frequencies compared with that of the ligand in the order Co > Mn > Ni with the exception of the copper complex in which an hypsochromic shift was observed. No shift was observed for the cadmium complex. It is suggested that this arrangement may be as a result of the size of the metal ions [28–30]. In some of the $Na_2[ML_2]$ complexes (Table 2) two bands were observed on coordination for the COO^- asymmetric and symmetric stretching frequencies. These indicate the possible mode of coordination of aspartic acid to the central metal ion via both oxygen atoms of the α- and β-carboxylate ion. Consequently, in these complexes, aspartic acid may be said to be tridentate, an observation that is in agreement with that obtained by previous workers [10]. Hypsochromic shifts were observed for the $-NH_2$ frequencies on coordination, for the ML_2 and $Na_2[ML_2]$ complexes. This indicates bond elongation on coordination. It therefore suggests probable square planar and distorted octahedral geometry for the complexes, respectively. New bands in the spectra of the complexes at 500–598 cm^{-1} were assigned to (M–N) stretching frequency. The participation of the lone pairs of electrons on the N of the amino group in the ligand in coordination is supported by these band frequencies [31]. Bands in the region of 604–724 cm^{-1} indicate the formation of M–O bond and further support the coordination of the ligand to the central metal ions via the oxygen atom of the carboxylate group [29].

3.3. Electronic Spectra and Magnetic Moment. The electronic spectra of the ligands showed three absorption bands at 196, 212, and 232 nm assigned as the $n \rightarrow \sigma^*$, $n \rightarrow \pi^*$, and $\pi^* \rightarrow \pi^*$ transitions of the major chromophores, NH_2 and COO^-, present in the ligand molecules. On coordination, however, shifts were observed in these bands in addition to *d-d* transitions bands (Table 3). These in conjunction with the magnetic moment of the complexes were used to propose probable geometry of the complexes obtained.

3.3.1. $Na_2[ML_2]$ Complexes. The spectrum for the copper(II) complex displayed a well resolved band at 667 nm, Figure 4, assigned as $^2B_{1g} \rightarrow {}^2E_g$ transition, which suggests an octahedral geometry [32]. This proposed geometry was corroborated by its magnetic moment of 2.47 BM, indicative of a tetragonally distorted octahedral geometry [33]. A weak band at 833 nm assigned as charge transfer band was observed in the spectrum for the cadmium(II) complex. This was supported by its magnetic moment of zero, indicative of a diamagnetic Cd(II) complex with filled 4d orbital [32, 33]. The Ni(II) complex exhibited a shoulder at 637 nm and a strong band at 652 nm, which were assigned to $^3A_{2g}(F) \rightarrow {}^5T_{1g}$ and $^3A_{2g}(F) \rightarrow {}^1E_g$ transitions. The magnetic moment of 3.28 BM however is suggestive of an octahedral geometry [34, 35]. The cobalt(II) complex gave a shoulder at 526 nm,

Table 3: Relevant IR bands for the compounds.

Band	$\overline{\nu}_s(NH_2)$	$\overline{\nu}_{asy}(COO^-)$	$\overline{\nu}_{sy}(COO^-)$ (cm^{-1})	$\overline{\nu}$(M–N)	$\overline{\nu}$(M–O)
Aspartic acid	3380w	1650s	1583s	—	—
$Cu(asp)_2$	3433m	1641w	1509w	552s	656m
$Cd(asp)_2$	3333w	1650s	1539s	549s	724s
$Ni(asp)_2$	3357w	1674s	1559s	548w	721w
$Co(asp)_2$	3143br	1684s	1561s	566w	665m
$Mn(asp)_2$	3309w	1678m	1547w	550s	598m
$Na_2[Cu(asp)_2]$	3238, 3142br	1678s, 1595m	1503s, 1371s	520m	623br
$Na_2[Cd(asp)_2]$	3025br	1687s	1532br	598s	619s
$Na_2[Ni(asp)_2]$	3190w,br	1667sh	1547s	500m	672s
$Na_2[Co(asp)_2]$	—	1684s, 1584w	1512s, 1375s	546s	604s
$Na_2[Mn(asp)_2]$	3357br	1686s	1542m	550s	658s

asp: aspartic acid; w: weak; m: medium; s: strong.

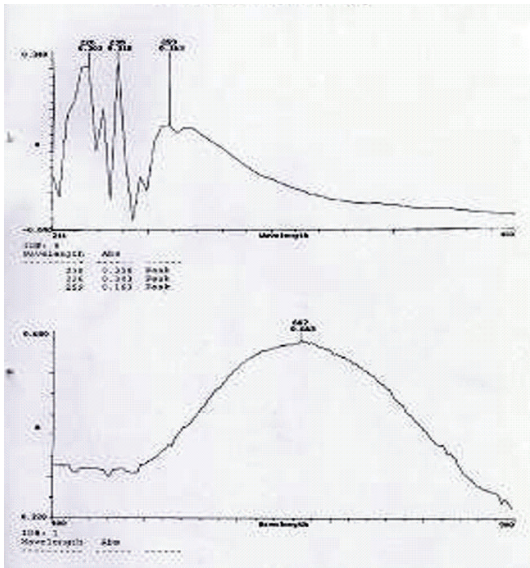

Figure 4: UV-Vis spectrum for $Na_2[Cu(asp)_2]$.

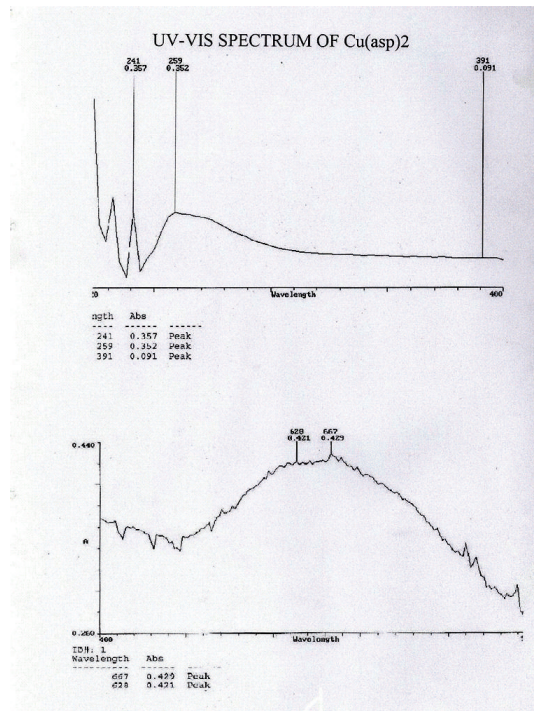

Figure 5: UV-Vis spectrum for $Cu(asp)_2$.

a strong band at 541 nm, and a weak band at 565 nm typical of a six coordinate, octahedral geometry for cobalt(II) and were attributed to $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$, $^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$, and $^4T_{1g}(F) \rightarrow {}^4T_{1g}(F)$ transitions. This geometry was corroborated by a magnetic moment of 5.40 BM [34–36]. The Mn(II) complex exhibited weak absorption bands at 526, 541, and 673 nm which are consistent with a six-coordinate, octahedral geometry and were assigned to $^6A_{1g} \rightarrow {}^4T_{2g}(G)$, $^6A_{1g} \rightarrow {}^4T_{1g}(G)$, and $^6A_{1g} \rightarrow {}^4E_g(G)$ transitions; its magnetic moment of 5.82 BM complements this [2].

3.3.2. ML_2 Complexes. The spectrum for the copper(II) complex displayed two bands at 628 and 667 nm, Figure 5, assigned to $^2B_{1g} \rightarrow {}^2E_g$ and $^2E_g \rightarrow {}^2A_{1g}$ transitions. The complex exhibited a magnetic moment of 2.2 BM indicative of a mononuclear copper(II) complex with 4-coordinate square planar geometry [37–39]. The cadmium complex exhibited no *d-d* transition band. A magnetic moment of zero corroborates this; however based on valence bond theory a tetrahedral geometry is proposed, and this is in agreement with previous reports [32, 39]. The nickel complex exhibited a well-defined band at 517 nm assigned as $^3A_{2g} \rightarrow {}^1E_g$. A magnetic moment of 1.15 BM was observed for this complex. This is interpreted as a low spin–high spin equilibrium mixture of tetrahedral-square planar complex [40]. The Co(II) complex exhibited two absorption bands at 499 and 520 nm, assigned as $^4A_{2g} \rightarrow {}^4T_{2g}(F)$ and $^4A_{2g} \rightarrow {}^4T_{1g}(F)$, respectively, typical for a tetrahedral geometry. This is corroborated by a magnetic

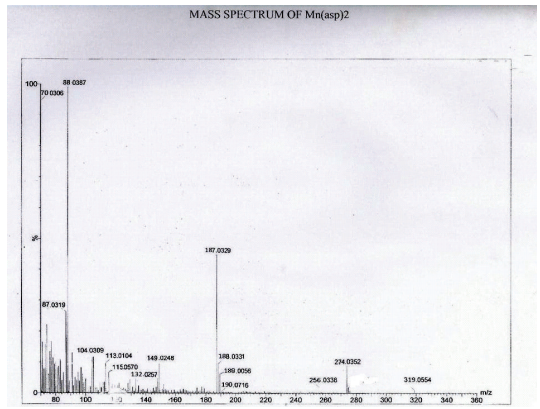

Figure 6: Mass spectrum of $Mn(asp)_2$.

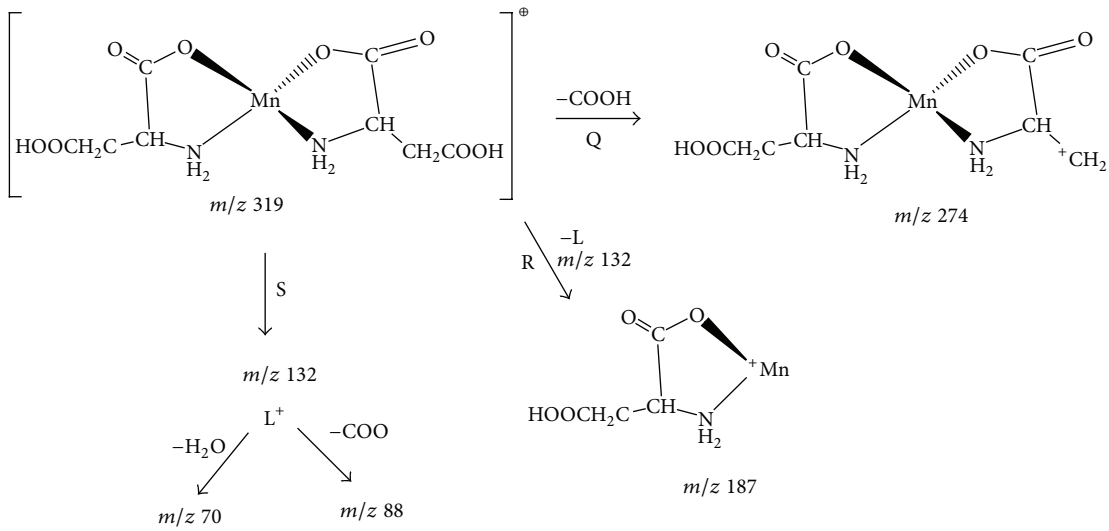

Figure 7: Proposed fragmentation pattern of $Mn(asp)_2$.

moment of 4.33 BM [38]. Bands at 544, 568, and 682 for the Mn(II) complex were assigned to $^6A_{1g} \rightarrow {}^4T_{1g}$, $^6A_{1g} \rightarrow {}^4E_g$, and $^6A_{1g} \rightarrow {}^4E_g$ transitions and a charge transfer band at 829 nm [41].

3.4. Mass Spectrometry. The electronic impact mass spectrum of the complex $Mn(asp)_2$ (Figure 6) was obtained and a probable fragmentation pattern was proposed (Figure 7). The spectrum showed a weak peak at *m/z* 319 (4%), which coincides with the calculated molecular ion. The fragmentation of the molecular ion was proposed to occur via three pathways, Q, R, and S. Pathway Q corresponds to the loss of β-COOH to give a peak at *m/z* 274 (9%). Pathway R corresponds to the extrusion of a ligand as a radical to give a peak at *m/z* 187 (42%). While for pathway S the molecular ion fragments with the ligand as a positive ion with *m/z* 132 (4%). This ion further fragmented with the loss of COO to yield a peak at *m/z* 88, the base peak. It also fragmented giving a peak at *m/z* 70 (92%) with the loss of a water molecule.

Thus, from the foregoing, it was proposed that the coordination mode of aspartic acid is a function of the pH at which the reaction was carried out, as this may invariably determine the donor atoms of the ligand available for coordination [42, 43]. From previous reports, it has been reported that the participation of a particular functional group in metal binding depends partly on its acid dissociation constant [42]. In this case, aspartic acid has α-carboxylic acid moiety with pK_a of 2.09 and a β-carboxylic acid moiety with pK_a of 3.86. This implies that for the donor atoms to be readily available for complex formation the pH of the reaction must fall within these ranges. This was evident in the complexes formed; this is because at pH ranges greater than 4.0, both the oxygen donor atoms from the α- and β-carboxylic group were available for binding [9–11]. It therefore acts as a tridentate ligand [9–11, 42].

It is further suggested that energy consideration as a result of the stability of the chelate ring also enhanced the coordination mode of the ligand. This is because although the NH_3^+ ion has a pK_a value of 9.82 (Figure 8), even at low pH,

Table 4: Antimicrobial activities of the compounds.

Microorganisms	*E. coli*	*P. aeruginosa*	*P. vulgaris*	*S. aureus*	*B. subtilis*	MRSA	*C. albicans*
Aspartic acid	6.0 ± 0.2	6.0 ± 0.7	6.0 ± 0.0	6.0 ± 0.1	6.0 ± 0.1	6.0 ± 0.5	8.0 ± 1.0
$Cu(asp)_2$	6.0 ± 0.0	12.0 ± 0.3	6.0 ± 0.2	12.0 ± 0.7	12.0 ± 0.0	16.0 ± 0.5	6.0 ± 0.3
$Cd(asp)_2$	8.0 ± 0.2	8.0 ± 0.0	6.0 ± 0.6	11.0 ± 0.1	8.0 ± 0.3	11.0 ± 0.0	17.0 ± 0
$Ni(asp)_2$	6.0 ± 0.5	6.0 ± 0.1	6.0 ± 0.7	6.0 ± 1.0	6.0 ± 0.9	6.0 ± 0.2	6.0 ± 0.2
$Co(asp)_2$	6.0 ± 0.6	6.0 ± 0.1	6.0 ± 0.1	6.0 ± 0.0	6.0 ± 0.0	6.0 ± 0.8	6.0 ± 0.6
$Mn(asp)_2$	8.0 ± 0.5	8.0 ± 0.8	8.0 ± 0.3	14.0 ± 0.2	20.0 ± 0.5	10.0 ± 0.3	6.0 ± 0.4
$Na_2[Cu(asp)_2]$	9.0 ± 1.0	6.0 ± 0.3	10.0 ± 0.7	36.0 ± 0.8	16.0 ± 0.3	23.0 ± 0.8	16.0 ± 0.9
$Na_2[Cd(asp)_2]$	6.0 ± 0.0	11.0 ± 0.4	6.0 ± 1.0	10.0 ± 0.5	6.0 ± 0.6	6.0 ± 0.3	37.0 ± 0.1
$Na_2[Ni(asp)_2]$	8.0 ± 0.7	6.0 ± 0.8	6.0 ± 0.4	11.0 ± 0.9	13.0 ± 0.4	18.0 ± 0.3	15.0 ± 0.9
$Na_2[Co(asp)_2]$	14.0 ± 0.3	6.0 ± 0.5	6.0 ± 1.1	6.0 ± 0.2	10.0 ± 0.2	18.0 ± 0.1	17.0 ± 0.0
$Na_2[Mn(asp)_2]$	6.0 ± 0.7	6.0 ± 0.9	13.0 ± 0.0	6.0 ± 0.2	6.0 ± 0.7	13.0 ± 0.3	6.0 ± 0.1
C	20.0 ± 0.4	6.0 ± 0.0	15.0 ± 0.6	20.0 ± 0.2	6.0 ± 0.9	6.0 ± 0.7	19.0 ± 0.1

C: Acriflavine.
+: Gram-positive bacteria.
−: Gram-negative bacteria.

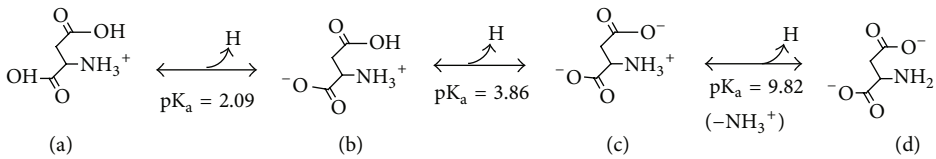

Figure 8: Coordination behaviour of aspartic acid: a function of the pH of the reaction. (a) In strong acid (below pH 1); net charge = +1. (b) Around pH 3; net charge = 0. (c) Around pH 6–8; net charge = −1. (d) In strong alkali (above pH 11) net charge = −2.

the nitrogen atom may be used for coordination. Previous studies have shown this to be due to the strong electron-donor (basic) character of the N atom of the NH_2 group and stability of the chelate ring [42–44]. This in addition is supported by the flexibility of the amino acid ligand. It was also observed that the geometry of the complexes was not determined only by the ligand, but the metal ions as well [13, 16–20]. This is because the complexes assume geometries better suited for the metal ions, resulting in the variations observed for some of the complexes.

3.5. Antimicrobial. The results obtained indicated that the compounds exhibited a broad spectrum of activity against the tested bacteria and fungi strains and in some cases better activity compared to the standard. Some of the complexes exhibited better activity compared to the ligand, consequently lending support to the chelation theory [2, 26, 45–50]. In line with previous reports the compounds exhibited better activity generally against Gram-positive bacteria. This has been attributed to the increased hydrophobic character of these molecules in crossing the cell membrane of the microorganism. As a consequence, the utilization ratio of the compounds is enhanced [1–6, 26, 45].

Generally the ML_2 complexes exhibited better activity compared to the $Na_2[ML_2]$ complexes with the exception of the copper and manganese complexes. The better activity of the ML_2 complexes compared to the $Na_2[ML_2]$ complexes in some cases may be ascribed to the enhanced lipophilicity of the former as a result of its nonionic nature as against the positively charged latter [2, 26, 45–50]. The $Na_2[Cd(asp)_2]$ complex gave good activity against *C. albicans*, while $Cd(asp)_2$ exhibited marginal activity against the fungi (Table 4). This indicates the activity of the metal ion as an antifungal agent. It also points to the fact that enhanced lipophilicity as a result of the tridentate nature of the ligand may increase the activity of the complex [2, 26, 45–50]. It is suggested that the size and number of chelate rings may play a role in the enhanced activity of these compounds in this case. The $Cu(asp)_2$ complex exhibited the best activity, contrary to that obtained in previous report for similar coordination compounds [24, 26, 51]. The $Na_2[Cu(asp)_2]$ exhibited good activity against *S. aureus*, indicating the effect of the metal ion as an antimicrobial agent [51]. The activity of some of the complexes against *B. subtilis*, MRSA, *Ps. Aeruginosa*, and *C. Albicans* (Table 4) was significantly higher than the standard drug ($p < 0.05$). This indicates their potentials as antimicrobial agents against these microbes.

4. Conclusion

In this study coordination compounds of aspartic acid were synthesized in both acidic and basic media. It was concluded that the geometry assumed by the synthesized compounds was a function of available donor atoms of the ligand and this is dependent on the relevant pH in which the reaction was carried out. The complexes exhibited a broad

spectrum of activity. In some cases complexes synthesized in basic medium exhibited better activity compared to their counterpart complexes obtained in acidic medium. This was attributed to their enhanced lipophilicity as a result of the increased number of chelate rings.

Competing Interests

The authors declare that they have no competing interests.

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