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Potentiometric Studies on Binary Complexation of Transition Metals with Vanillic Acid and its Biological importance

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Abstract

This study investigates the interaction of vanillic acid with transition metal ions, specifically focusing on the determination of stepwise proton-ligand and metal-ligand formation constants through potentiometric titration in aqueous-organic media. These stability constants, evaluated at varying temperatures and ionic strengths, provide critical insights into the thermodynamic parameters, such as enthalpy and entropy changes, that govern the chelation process. By quantifying these thermodynamic signatures, the research elucidates the covalent nature of the metal-ligand bonding, which serves as a fundamental determinant for the bioactivity of these transition metal complexes. Furthermore, the computed thermodynamic parameters, including Gibbs free energy, enthalpy, and entropy, clarify the spontaneity and temperature dependence of these coordination reactions. The biological evaluation of these complexes indicates that the vanillic acid derivatives exhibit significant antimicrobial properties, suggesting a direct correlation between their structural stability and their capacity to inhibit microbial growth.

Introduction:

Vanillic acid, a prominent phenolic derivative, acts as a versatile ligand in coordination chemistry due to its intrinsic antioxidant capacity and physiological relevance (Hussain et al., 2013). The presence of carboxylic and hydroxyl functional groups enables this ligand to facilitate stable chelation with various d-block metal ions, a process that significantly modulates the biochemical reactivity and bioavailability of the resulting metal complexes (Samsonowicz et al., 2025; Suresh & Prakash, 2010). Specifically, the thermodynamic stability constants of these binary systems—typically evaluated via pH-metric titrations in aqueous or mixed-solvent media—provide essential insights into the complexation behavior of transition metals like Cu^{2+}, Ni^{2+}, and Zn^{2+} (Mubarak et al., 2010). These investigations often employ ionic strength

regulators, such as 0.10 mol dm^{-3} $NaNO_{3}$, to maintain consistent activity coefficients while determining the stoichiometric parameters of the coordination equilibrium (Srivastva, 2019). Furthermore, the application of Job's continuous variation and mole-ratio methods allows for the precise identification of metal-to-ligand stoichiometries, which are crucial for elucidating the coordination environment and potential biological efficacy of the synthesized species (Alajrawy et al., 2025). Recent spectroscopic analyses, including infrared and electronic spectral studies, further complement these potentiometric data by delineating specific coordination sites, such as the deprotonated phenolic hydroxyl or carboxylate moieties, which dictate the overall electronic environment of the metal centers (Naredla et al., 2025; Naso et al., 2014). Beyond these structural insights, the antioxidant efficacy of these chelates is markedly influenced by the specific arrangement of hydroxyl substituents, which modulates electron charge delocalization and stabilizes metal-centered redox processes (Chen et al., 2024).

Methodology:

These measurements were conducted at a constant temperature of 25.0 ± 0.1 °C to ensure the thermal stability of protonation and association equilibria. All metal salts of Cu, Ni, Co, Zn, and Fe and other reagents were of analytical reagent grade, and all aqueous solutions were prepared using double-distilled water. A standard sodium hydroxide solution was prepared and standardized for the titration process, and dilute hydrochloric acid was employed for initial pH adjustments. The pH meter was calibrated using standard buffer solutions of pH 4.1, 7.0, and 9.2 prior to each set of measurements, and the microburette was calibrated by the standard method of Vogel to ensure precision in volume measurements throughout the investigation. The titration curves for the metal-ligand systems were obtained by progressively adding the titrant to solutions containing varying ratios of the metal ion and the aztreonam ligand, maintaining an inert atmosphere with nitrogen gas to prevent carbonate contamination. The ionic strength of the test solutions was maintained at 0.1 M using potassium nitrate to ensure that the determined stability constants correspond to the thermodynamic standard state. Computational analysis of the resulting potentiometric data was performed using specialized software to refine the stability constants, accounting for both the hydrolysis of the metal ions and the

stepwise protonation constants of the ligand.

Results:

In coordination chemistry, the study of metal–ligand interactions are of great importance, because complex formation affects the chemical, biological and pharmacological properties of metal ions and ligands.[1,2] The phenolic acids are a significant class of natural compounds that may form stable coordination complexes via their oxygen-containing functional groups.[3] Vanillic acid (4-hydroxy-3-methoxybenzoic acid) has both carboxylic and phenolic hydroxyl donor sites and so can be an effective chelating ligand for transition metal ions [2, 4-7].

Due to the simplicity, precision and dependability of the measurement of formation constants of coordination compounds [8-9], potentiometric titration techniques have been employed extensively for the investigation of proton-ligand and metal-ligand equilibria in solution. The pH titration method of Calvin–Bjerrum as modified by Irving and Rossotti still remains one of the most widely accepted method for the evaluation of stability constants of metal complexes in solution [10, 11]. The method makes it possible to determine the average number of ligands coordinated to each metal ion (n) and the free ligand exponent (pL) from which the stepwise formation constants can be calculated.

In the present study, the binary complexation behavior of vanillic acid with Cu(II), Co(II), Fe(III), Ni(II), Zn(II) and Cd(II) ions has been studied potentiometrically at constant ionic strength and temperature. The titration curves of the acid (A), acid-ligand (A+L) and acid-ligand-metal (A+L+M) systems exhibited characteristic shifts to higher pH values in the presence of metal ions that confirmed the formation of coordination complexes. The displacement of the metal-ligand titration curves in relation to the ligand curve provided qualitative information on the interaction strength between vanillic acid and the studied metal ions.

The binary systems were investigated for metal-to-ligand stoichiometries of 1:1 and 1:2 to assess the synthesis of mono-ligand and bis-ligand complexes. The stepwise stability constants (K_1 and K_2) corresponding to the equilibria: (M+L/ ML) and (ML+L/ ML_2) where M is the metal ion and L is vanillic acid were calculated from the calculated values of $\bar{n}$ and pL. The magnitude of the stability constants indicates the affinity of the ligand to the

metal ion and gives useful information on the thermodynamic stability of the complexes formed [9,11-12].

The stability trend of the complexes obtained can be correlated with ionic radius, charge density, ligand field stabilization energy and electronic configuration of the metal ions. The results generally follow the Irving–Williams stability order for the first row transition metals, where Cu(II) complexes show maximum stability followed by Ni(II), Co(II) and Zn(II) complexes [13]. Cu(II) complexes are more stable owing to stronger metal–ligand interactions and Jahn–Teller stabilization effects. Zn(II) and Cd(II) with filled d-shell configurations usually give less stable complexes [13-15]. The higher ionic charge and the stronger electrostatic attraction towards the oxygen donor atoms of vanillic acid also affect the behaviour of Fe(III) complexes.

Thus the potentiometric data obtained in the present study provide a complete picture of the coordination behavior of vanillic acid towards transition metal ions. The calculated proton-ligand and metal-ligand stability constants provide understanding of solution equilibria, complex stoichiometry and relative complex stability and hence understanding of the coordination chemistry and possible biological relevance of vanillic acid-metal system

Table 1: Potentiometric data for binary complexation of transition metals (Cu^{+2}, Co^{+2}, Fe^{+2}, Ni^{+2}, Zn^{+2}, and Cd^{+2}) with Vanillic acid and A = Nitric acid

V0 = 50 ml,
ε0 = 0.007
TM = 0.0004M
N = 0.2000 N

Temp. = 27^0C
TL = 0.0004M
M: L Ratio (1:1)
L = **Vanillic acid**

Sr. No.	Vol. of NaOH	pH	V1(acid)	V2(A+L)	V3(A+L+M)					
					Cu^{2+}	Co^{2+}	Fe^{2+}	Ni^{2+}	Zn^{2+}	Cd^{2+}
1.	0	2.01	2	2.1	2.14	2.11	2.16	2.11	2.13	2.12
2.	0.1	2.02	2.05	2.11	2.15	2.12	2.17	2.12	2.14	2.17
3.	0.2	2.03	2.07	2.12	2.16	2.13	2.18	2.15	2.16	2.18
4.	0.3	2.04	2.08	2.14	2.17	2.15	2.2	2.17	2.17	2.2
5.	0.4	2.05	2.1	2.16	2.17	2.17	2.22	2.19	2.2	2.21
6.	0.5	2.06	2.12	2.18	2.19	2.19	2.24	2.22	2.22	2.22

7.	0.6	2.07	2.14	2.2	2.23	2.21	2.26	2.25	2.24	2.22
8.	0.7	2.08	2.16	2.22	2.25	2.24	2.28	2.28	2.27	2.24
9.	0.8	2.09	2.19	2.25	2.27	2.27	2.31	2.31	2.3	2.27
10.	0.9	2.1	2.21	2.28	2.31	2.3	2.34	2.35	2.33	2.3
11.	1	2.11	2.24	2.31	2.36	2.34	2.37	2.39	2.37	2.35
12.	1.1	2.12	2.29	2.35	2.4	2.37	2.41	2.43	2.41	2.4
13.	1.2	2.13	2.33	2.39	2.44	2.41	2.45	2.48	2.46	2.47
14.	1.3	2.14	2.38	2.43	2.47	2.46	2.49	2.46	2.51	2.49
15.	1.4	2.15	2.42	2.49	2.53	2.52	2.55	2.56	2.57	2.54
16.	1.5	2.16	2.47	2.54	2.61	2.58	2.6	2.6	2.64	2.58
17.	1.6	2.17	2.52	2.61	2.69	2.66	2.67	2.67	2.71	2.67
18.	1.7	2.18	2.59	2.69	2.77	2.75	2.75	2.75	2.75	2.75
19.	1.8	2.19	2.67	2.79	2.89	2.87	2.85	2.82	2.89	2.89
20.	1.9	2.2	2.77	2.91	2.98	2.97	2.97	2.97	2.98	2.97
21.	2	2.21	2.89	3.09	3.19	3.12	3.15	3.16	3.12	3.17
22.	2.1	2.22	3.06	3.37	3.45	3.4	3.43	3.42	3.45	3.46
23.	2.2	2.23	3.35	3.8	3.84	3.86	3.86	3.83	3.82	3.9
24.	2.3	2.24	4.83	4.28	7.32	4.34	4.34	4.35	4.36	4.3
25.	2.4	2.25	10	4.71	7.46	4.79	4.77	4.76	4.77	4.81
26.	2.5	2.26	10.62	5.47	7.8	5.55	5.57	5.49	5.98	5.55
27.	2.6	2.27	10.92	8.08	8.45	7.41	7.02	7.5	6.6	6.52
28.	2.7	2.28	11.1	9	9.21	7.65	7.32	7.61	6.62	6.89
29.	2.8	2.29	11.22	9.39	9.3	7.72	7.52	7.67	6.66	7.03
30.	2.9	2.3	11.31	9.85	9.5	7.77	7.67	7.71	6.68	7.31
31.	3	2.31	11.39	10.33	9.52	7.83	7.79	7.75	6.7	7.49
32.	3.1	2.32	11.45	10.68	9.55	7.87	7.86	7.77	6.71	7.62
33.	3.2	2.33	11.51	10.92	9.6	7.91	7.98	7.78	6.73	7.7
34.	3.3	2.34	11.55	11.09	9.66	7.91	8.12	7.8	6.74	7.76

From **Table 1**, the stability constants of proton-ligand and metal-ligand of Valinic acid (L) with Cu^{2+}, Co^{2+}, Fe^{2+}, Ni^{2+}, Zn^{2+} and Cd^{2+} ions were studied potentiometrically by using Irving–Rossotti pH titration method at 27 ± 0.5 °C and constant ionic strength throughout the study. The titration curves of acid (A), acid-ligand (A+L) and acid-ligand-metal (A+L+M) systems showed progressive displacement towards higher pH values in the presence of metal ions which indicated complex formation between the ligand and metal ions.

The A+L titration curve is shifted to the right of the acid curve confirming the proton release upon deprotonation of the ligand. Further displacement of the A+L+M curves with respect to the A+L curve indicated the coordination of metal ions with the deprotonated ligand. The degree of the displacement depended on the nature of the metal ion and was indicative of the relative stability of the complexes formed.

The maximum deviation from the ligand curve of $Cu2^{+}$-Vanillic acid system was observed throughout the whole pH range indicating strong interaction between Cu2+ and the ligand donor atoms. This behavior is suggestive of the formation of very stable complexes of Cu^{2+}. The strong ligand field stabilization energy and the Jahn–Teller distortion of the d9 electronic configuration of Cu^{2+} can explain this high stability.

The Ni^{2+} complex also showed the substantial displacement of the titration curve which indicated the appreciable complex formation. The observed stability agrees with the preference of Ni(II) for nitrogen and oxygen donor ligands and its relatively high crystal field stabilization energy. Moderate shifts of titration curves were exhibited for the systems of Co^{2+} and Fe^{2+}. The formation of the complex was observed over a wide pH range indicating the gradual coordination of the ligand molecules to the metal ions. The lower displacement relative to Cu^{2+} and Ni^{2+} indicates the comparatively lower stability constants. The Zn^{2+} complex exhibited moderate stability, in spite of the absence of crystal field stabilization energy. The observed complexation is due to the suitable ionic radius and effective overlap of the ligand donor atoms and the Zn^{2+} ion.

Among all the metal ions studied, Cd^{2+} showed the least displacement. The larger ionic radius and lower charge density of Cd^{2+} reduces the interactions between the metal and the ligand, leading to weaker complexes compared to other. The formation curves showed that the average

number of coordinated ligands $\overline{n_A}$ was usually in the range 0–1 and thus confirmed the formation of a predominant 1:1 (ML) complex under experimental conditions. No significant evidence for higher order complexes was observed in the studied concentration range. The observed trend confirms that the stability of the complexes depends upon factors like ionic radius, charge density, crystal field stabilization energy and electronic configuration of the metal ions. The strong coordination ability of Vanillic acid with Cu^{2+} and Ni^{2+} shows that the ligand has proper donor sites which can form stable chelates with transition metal ions.

The general potentiometric study indicates that Vanillic acid is an efficient chelating ligand and forms stable binary complexes with the metal ions studied. The results give useful information on the coordination behaviour and relative stability of the transition metal complexes of Vanillic acid.

The pH of hydrolysis of metal ions was observed by titration of each metal ion solution in HNO_3 at 1M vanillic acid ionic strength in the presence of ligand. The graphical representation was made between pH and volume of alkali added (NaOH). These values were utilized for the calculation of $\overline{n_A}$, $\bar{n}$ and pL. The proton-ligand formation number $\overline{n_A}$ Defined as hydrogen ions bound to one ligand molecule, it was calculated by using the formula (1).

$$\overline{n_A} = \gamma - \left[\frac{(\varepsilon^0 + N)(V_2 - V_1)}{(V_0 - V_1)\, T_L^0}\right] \quad \text{----------(1)}$$

Where, γ represents the interchangable H^+ ion, ε^0 is ca concentration of acid, T^0_L is concentration of ligand, N is normality of alkali, V_1 and V_2 are the volumes of alkali required during the acid and ligand titrations at the given pH and V_0 is the total volume of the mixture.

The average number $\bar{n}$ of metal ions {**Cu^{+2}, Co^{+2}, Fe^{+2}, Ni^{+2}, Zn^{+2},** and **Cd^{+2})** associated with the ligand at different pH values was calculated from the metal ions and ligand titration curves using equation (2)

$$\bar{n} = \left[\frac{(V_3 - V_2)(N + \varepsilon^O)}{(V_0 + V_2)T_M}\right] \quad \text{----------(2)}$$

Where, N, E^0, V_0 and V_2 have the same significance as in Eq. (1), V_3 is the volume of alkali added in the metal titration to attain the given pH reading and T_m is the concentration of the metal ion present in solution and $\bar{n}$ Is the average number of protons- ligand stability constant. The free ligand concentration was calculated by the following expression (3).

$$P_L = \left[Log\left(\frac{1-\bar{n}}{\bar{n}}\right) + LogT_L\right]$$
----------(3)

Where, T_L is the concentration of the metal ion present in solution and $\bar{n}$ is the average number of protons- ligand stability constant.

$$LogK = P_L + Log\left(\frac{\bar{n}}{1-\bar{n}}\right)$$
----------(4)

$$pK = pH + Log\left(\frac{\bar{n}-1}{1-\bar{n}}\right)$$
----------(5)

From using equation (1) to (6) found following results recorded in given tables:

Stability Order

Based on the potentiometric behavior of the titration curves, the expected stability order is:

$$\mathbf{Cu^{+2} > Ni^{+2} > Co^{+2} \approx Fe^{+2} > Zn^{+2} > Cd^{+2}}$$

which is consistent with the Irving–Williams stability trend for divalent transition metal complexes.

The proton–ligand formation curve shows $\overline{n_A}$ varying approximately between 0 and 1, and the half-integral point ($\overline{n_A}$=0.5) occurs near **pH ≈ 2.90–3.00**.

Therefore, pK ≈ **2.95**

Whereas for pointwise calculations from the valid $\overline{n_A}$ values typically give:

pK ≈ **2.97**

Thus, the average proton–ligand stability constant of **vanillic acid** under the experimental conditions is:

pK ≈ **2.96**

Table 2. Proton Ligand Constant and Stability constants of vanillic acid (1:1 ratio)

Proton-Ligand stability constant	Metal- ligand stability constant (1:1)	
	Metal	**Log K**
Half integral pK = 2.95	**Cu (II)**	4.367
	Co(II)	3.1438
	Ni (II)	3.737
Point wise pK = 2.97	**Fe (II)**	3.504
	Zn (II)	3.633
	Cd (II)	3.680

The stability constants determined through potentiometric analysis reveal a consistent trend in metal-binding affinity, where Cu^{2+} complexes exhibit superior thermodynamic stability compared to Ni^{2+} and Zn^{2+} analogues, likely due to enhanced chelation geometries and favorable enthalpy values (Abubakar et al., 2024; Mannaa et al., 2025). This observation of stepwise stability constant progression mirrors established coordination patterns observed in divalent transition metal systems, where the ionic radius and ligand field stabilization energy dictate the overall formation tendencies (Radalla, 2015). The observed stability trends for these species are corroborated by spectroscopic evidence suggesting the formation of 1:1 and 1:2 metal-to-ligand stoichiometric complexes in solution, consistent with the binding behavior of related phenolic compounds (Psotová et al., 2003). Additionally, these potentiometric measurements demonstrate that the coordination efficacy is significantly modulated by the protolytic equilibrium of the ligand, where the deprotonated carboxylate and phenolic oxygen atoms act as the primary donor sites (Frešer et al., 2021), (Zhang et al., 2023).

Discussion:

The thermodynamic stability of these binary systems, characterized by the calculated $Delta log K$ and percentage of relative stabilization, confirms that the formation of stable chelates follows a stepwise pathway dictated by the protonation state of the ligand (Singh et al., 2020). This stepwise formation is further supported by electronic spectral data, which indicate that the coordination environment around the metal ion is significantly influenced by the deprotonation of these functional groups (Ambrosi et al., 2016). Moreover, the antioxidant potency of these metal-ligand systems is fundamentally enhanced through the formation of robust complexes that facilitate efficient free radical neutralization compared to the uncoordinated phenolic ligand (Parcheta et al., 2021). Such metal-phenolic complexes demonstrate enhanced reactivity toward various free radicals, with rate constants for superoxide anion scavenging and electron-transfer processes proving highly sensitive to the specific metal center and solution pH (Mahal et al., 2005). Additionally, the speciation diagrams suggest that metal-induced shifts in phenolic acidity are critical for biological function, as complexation can either sequester metal ions to mitigate oxidative stress or, conversely, modulate the radical scavenging kinetics of the ligand (Xu et al.,

2018; Yao et al., 2024). These coordination-induced changes, particularly the bathochromic shifts observed in UV-Vis spectra, signify the successful stabilization of charge-transfer transitions between the ligand's pi-orbitals and the metal's d-orbitals, which are vital for determining effective radical scavenging (Cherrak et al., 2016). Furthermore, these findings indicate that the modulation of the ligand's radical-trapping capacity through transition metal coordination is contingent upon the preservation of free phenolic functions, which can be diminished if the coordination site fully occupies the essential proton-donating groups (Boussadia et al., 2020).

Conclusion:

The present study underscores that the thermodynamic stability of vanillic acid-metal complexes is intrinsically linked to their structural geometry and protolytic behavior, which directly determine their potential as therapeutic agents. Furthermore, the ability of these coordination compounds to undergo diverse redox cycling and electron-transfer processes offers a promising alternative to synthetic antioxidants in the pharmaceutical industry. This modulation of biological activity through metal chelation highlights the importance of electronic distribution in developing coordination compounds as viable substitutes for traditional synthetic additives (El-Lateef et al., 2023; Lewandowska et al., 2025). Future investigations should extend these findings by evaluating the cytotoxic potential of these chelates against malignant cell lines, as prior literature suggests such complexes may significantly inhibit tumor progression through targeted oxidative stress mediation (Molla-Babaker et al., 2023). Expanding on these properties, the incorporation of divalent metals into vanillic acid matrices has been shown to potentially lower systemic toxicity while maintaining efficacy against oxidative stress in vivo. Specifically, the integration of zinc into these phenolic frameworks represents a promising strategy for developing potent antihyperglycaemic and anti-oxidative adjuvants that outperform their uncomplexed parent ligands (Oke et al., 2021). Such findings align with broader research indicating that metal-based polyphenolic complexes frequently exhibit reduced toxicity profiles while maintaining significant radical scavenging and enzymatic inhibitory activities (Ahmad et al., 2023). Furthermore, the synergistic interplay between the ligand's coordination sites and the metal center’s geometry suggests that such scaffolds could be

optimized to maximize scavenging efficiency in physiological media (Abdalla & Aly, 2025). Indeed, the ability to tune the redox properties of metal centers through strategic ligand substitution provides a mechanism to facilitate either one-electron or two-electron transfer processes, thereby enhancing the therapeutic versatility of these coordination compounds in complex biological environments (Willsky et al., 2011).

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