Palladium(II) Complexes Containing Dipicolinic Acid (DPA), Iminodiacetic Acid (IDA), and Various Biologically Important Ligands

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Ternary 1:1:1 complexes of Pd(II) with dipicolinic acid (DPA) or iminodiacetic acid (IDA) as primary ligands and some selected mono- and dicarboxylic amino acids (glycine, α-alanine, leucine, valine, phenylalanine, tryptophan, methionine, histadiene aspartic acid, and glutamic acid), aromatic carboxylic acids (salicylic and phthalic), and aliphatic carboxylic acids (succinic, oxalic, malic, maleic, malonic, and tartaric) as secondary ligands have been investigated by using the potentiometric technique at $T = 30$ °C and $I = 0.1$ mol·dm^{-3}. The ternary complexes are formed in a stepwise mechanism. Confirmation of the ternary complexes in solution has been carried out using conductometric measurements.

Introduction

Interest in the study of the reaction of Pd(II) ions with various donor atom ligands of biological importance began with the discovery of Rosenberg et al. that certain platinum complexes exhibit carcinostatic activity.[1] Among the first to be used for clinical trials against tumors were analogues to cisplatin, a Pt chemotherapy drug, and complexes of Pd(II), *cis*-Pd(en)Cl_2, and *cis*-Pd(DACH)$_2Cl_2$ because Pd(II) has a very similar chemistry to Pt(II), forming square planar complexes.[2] Both Pd(II) and Pt(II) are soft Lewis acids and form stronger bonds with nitrogen or sulfur donors (soft bases) than oxygen donors (hard base). The difficulty in studying the platinium complexes directly is their kinetic inertness. Because of the similarities in the general chemistry of Pt(II) and Pd(II), as well as the increased rates of reaction of Pd(II) ions (on average approximately 10^3 times faster than platinum), palladium analogues are studied instead of, or as well as, the platinum compounds. It was also suggested that the faster aquation of palladium(II) than of platinum(II) in vitro makes the former a better model for studies of the reactions of the latter in vivo[3,4] with biological molecules, since these reactions always start with the aquation of the platinum(II) complexes. The Pd(II) ions are capable of interacting with DNA.[5−7] Das and Livingstone[8] have suggested that S,N-chelate complexes of Pd(II) were expected to exhibit antitumor and antimicrobial activities, despite the nonactivity and high toxicity of its complexes with monodentate ligands.

Dipicolinic acid (pyridine 2,6-dicarboxylic acid, DPA) is present in nature as an oxidative degradation product of vitamins, coenzymes, and alkaloids. DPA shows various biological functions including activation/inactivation of some metalloenzymes[9,10] and inhibition of electron transport systems[11] and acts as a potent inhibitor of low density lipoprotein oxidation.[12] DPA is a desirable metal ion ligand because of its low toxicity and amphophilic nature. DPA is furthermore related to pyridine-2,3-dicarboxylic acid (quinolinic acid), which is also an intermediate in the tryptophan degradation pathway and a precursor of nicotinamide adenine dinucleotide (NAD).

In the present work, we report a study on the solution equilibria involved in the formation of ternary Pd(II) complexes involving DPA and iminodiacetic acid (IDA), an important biological complexing agent, as primary ligands and some amino acids (glycine, α-alanine, leucine, valine, phenylalanine, tryptophan, methionine, histadiene aspartic acid, and glutamic acid), aromatic carboxylic acids (salicylic and phthalic), and aliphatic carboxylic acids (succinic, oxalic, malic, maleic, malonic, and tartaric) as secondary ligands by using a potentiometric technique at $T = 30$ °C and $I = 0.1$ mol·dm^{-3}.

Experimental Section

Materials and Solutions. $PdCl_2$, DPA, and IDA were from Fluka. Amino acids (glycine, α-alanine, leucine, valine, phenylalanine, tryptophan, methionine, histidine, aspartic acid, and glutamic acid), aromatic carboxylic acids (salicylic and phathalic), and aliphatic carboxylic acids (succinic, oxalic, malic, maleic, malonic, and tartaric) were analytical-grade (Aldrich or Merck) products. Stock solutions of Pd salt were prepared in deionized water. A carbonate-free sodium hydroxide (titrant, prepared in 0.1 mol·dm^{-3} $NaNO_3$ solution) was standardized potentiometrically with KH phthalate (Merck AG). A nitric acid solution (0.04 mol·dm^{-3}) was prepared and used after standardization. Sodium hydroxide, nitric acid, and sodium nitrate were from Aldrich.

Apparatus and Procedure. The titrations were performed at (30 ± 0.1) °C in a double-walled cell fitted with a thermostat. A Schott CG 825 pH meter using a glass electrode was used to monitor the pH changes. The titrant (CO_2-free standard NaOH) was added to the titration cell, and the pH changes were monitored through the pH meter. The pH meter was calibrated with standard buffer solutions (pH 4.0 and 10.0) before the pH measurements. The ionic strength was kept constant (0.10

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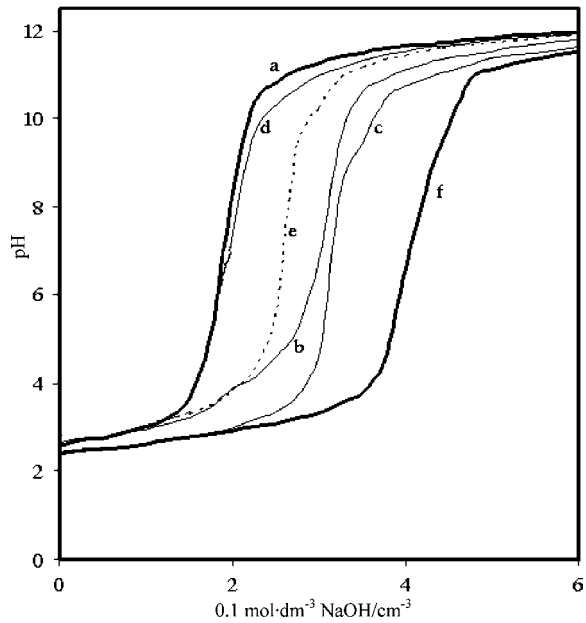

Figure 1. Potentiometric titration curves for the Pd(II) + DPA + valine system at 30 °C and $I = 0.1$ mol·dm^{-3} $NaNO_3$: 0.004 mol·dm^{-3} HNO_3 + 0.1 mol·dm^{-3} $NaNO_3$ (a), solution a + 0.001 mol·dm^{-3} DPA (b), solution b + 0.001 mol·dm^{-3} Pd(II) ion (c), solution a + 0.001 mol·dm^{-3} valine (d), solution d + 0.001 mol·dm^{-3} Pd(II) ion (e), and solution a + 0.001 mol·dm^{-3} Pd(II) ion + 0.001 mol·dm^{-3} DPA + 0.001 mol·dm^{-3} valine (f).

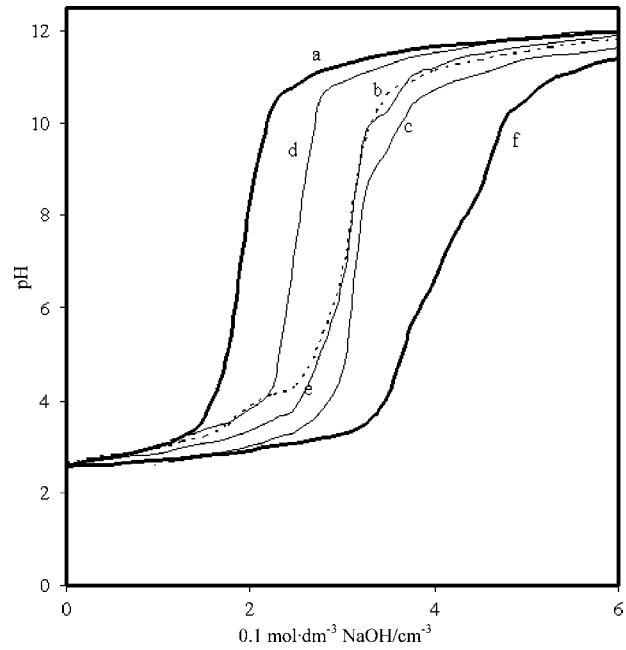

Figure 2. Potentiometric titration curves for the Pd(II) + DPA + salicylic acid system at 30 °C and $I = 0.1$ mol·dm^{-3} $NaNO_3$: 0.004 mol·dm^{-3} HNO_3 + 0.1 mol·dm^{-3} $NaNO_3$ (a), solution a + 0.001 mol·dm^{-3} DPA (b), solution b + 0.001 mol·dm^{-3} Pd(II) ion (c), solution a + 0.001 mol·dm^{-3} salicylic acid (d), solution d + 0.001 mol·dm^{-3} Pd(II) ion (e), and solution a + 0.001 mol·dm^{-3} Pd(II) ion + 0.001 mol·dm^{-3} DPA + 0.001 mol·dm^{-3} salicylic acid (f).

mol·dm^{-3}) using a $NaNO_3$ solution, and a total volume of 50 cm^{-3} was used for each titration.

For the study of ternary (1:1:1) complexes, the different solutions titrated were as follows: 0.004 mol·dm^{-3} HNO_3 + 0.1 mol·dm^{-3} $NaNO_3$ (a), solution a + 0.001 mol·dm^{-3} DPA or IDA (b), solution b + 0.001 mol·dm^{-3} Pd(II) ion (c), solution a + 0.001 mol·dm^{-3} amino acid or carboxylic acid (d), solution d + 0.001 mol·dm^{-3} Pd(II) ion (e), and solution a + 0.001 mol·dm^{-3} Pd(II) ion + 0.001 mol·dm^{-3} DPA or IDA + 0.001 mol·dm^{-3} amino acid or carboxylic acid. The ternary metal complex solutions under investigation do not show any precipitation up to the pH value corresponding to complete complex formation, which reveals that these ternary complexes have no tendency to form hydroxo complex species. In analyzing the titration data for the determination of the proton dissociation constants of the free ligands and the stability constants of binary and ternary metal−ligand complexes in solution, Bjerrum and Calvine and Wilson's pH titration technique,[13,14] as adopted by Irving and Rossotti[15,16] for binary systems and by Chidambaram and Bhattacharya[17] for ternary systems, has been used at (30 ± 0.1) °C. It is worth mentioning that many papers related to the protonation constants of the ligands under investigation and their stability constants with the Pd(II) ion, have been extensively measured and discussed.[18−22] It is beyond the scope of this article to calculate the stability constant of the binary systems.

Conductometric titrations were followed with a HANNA HI 9835, a microprocessor conductivity/TDS meter. The following mixture was titrated conductometrically against a 0.10 mol·dm^{-3} NaOH solution: 0.01 mol·dm^{-3} Pd(II) (10 cm^3) + 0.01 mol·dm^{-3} DPA or IDA (10 cm^3) + 0.01 mol·dm^{-3} amino acid or carboxylic acid (10 cm^3).

Results and Discussion

Representative pH metric equilibrium titration curves for the free and Pd(II) complexed ligands are depicted in Figures 1, 2, 3, and 4. When a solution contains two different ligands and a metal ion, they may exist in equilibria in which either (i) both the ligands may combine with the metal ion simultaneously or (ii) the two ligands may be combined one by one at different pH. As is evident from the titration curves in the present study, the addition of two ligands is stepwise. It was deduced that DPA or IDA interacts first with the Pd(II) ion, followed by the interaction with the amino acid or carboxylic acid; that is, the ternary complex formation could be considered in stepwise complexation equilibria, or the formation of a ternary complex can be represented by the stepwise equilibria

$$M + A \rightleftharpoons MA \quad (1)$$

$$MA + L \rightleftharpoons MAL \quad (2)$$

$$K_{MAL}^{MA} = [MAL]/[MA][L] \quad (3)$$

where M = Pd(II), A represents the primary ligand (DPA or IDA), and L represents the secondary ligand (amino acid or carboxylic acid). For instance, examining Figure 1, one may observe that the curves obtained for the different 1:1:1 ternary complex solutions (curve f) overlap with the titration curve of the 1:1 binary Pd(DPA) (curve c) at low pH values and a divergence of the ternary complex titration curve from that of the binary Pd(DPA) is observed at higher pH. This shows the coordination of the valine to the Pd(DPA)-binary complex in a stepwise manner as represented by the following equations:

$$Pd(II) + (DPA) \rightleftharpoons Pd(DPA) \quad (4)$$

$$Pd(DPA) + \text{valine} \rightleftharpoons Pd(DPA)(\text{valine}) \quad (5)$$

Part of the information required for determining the stability constants of ternary complexes is the protonation constants of

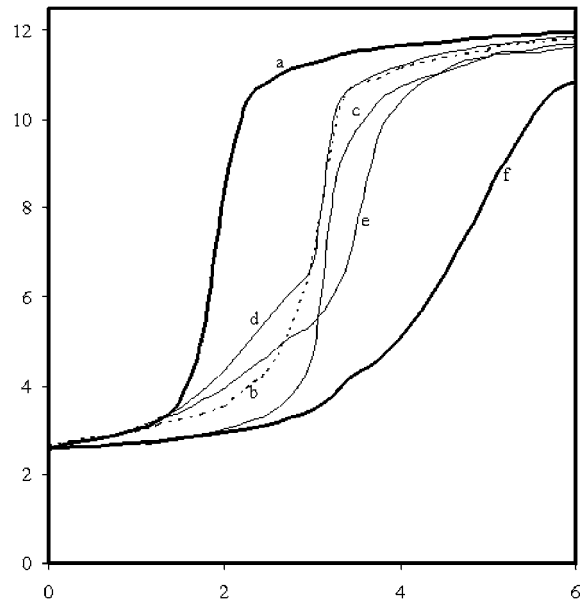

Figure 3. Potentiometric titration curves for the Pd(II) + DPA + succinic acid system at 30 °C and $I = 0.1$ mol·dm^{-3} $NaNO_3$: 0.004 mol·dm^{-3} HNO_3 + 0.1 mol·dm^{-3} $NaNO_3$ (a), solution a + 0.001 mol·dm^{-3} DPA (b), solution b + 0.001 mol·dm^{-3} Pd(II) ion (c), solution a + 0.001 mol·dm^{-3} succinic acid (d), solution d + 0.001 mol·dm^{-3} Pd(II) ion (e), and solution a + 0.001 mol·dm^{-3} Pd(II) ion + 0.001 mol·dm^{-3} DPA + 0.001 mol·dm^{-3} succinic acid (f).

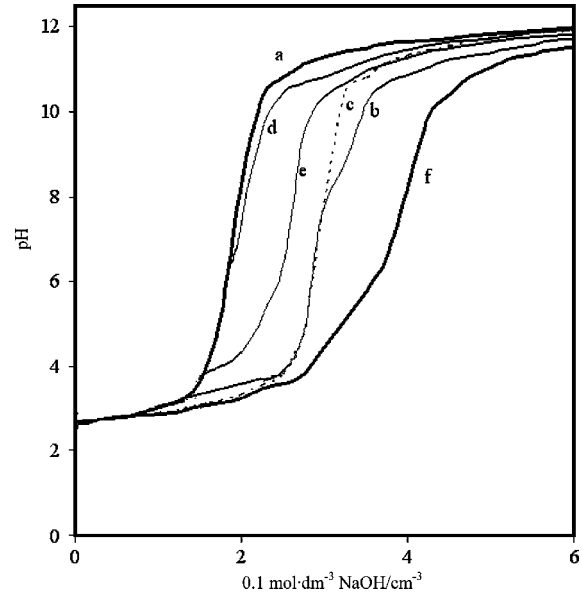

Figure 4. Potentiometric titration curves for the Pd(II) + IDA + α-alanine system at 30 °C and $I = 0.1$ mol·dm^{-3} $NaNO_3$: 0.004 mol·dm^{-3} HNO_3 + 0.1 mol·dm^{-3} $NaNO_3$ (a), solution a + 0.001 mol·dm^{-3} IDA (b), solution b + 0.001 mol·dm^{-3} Pd(II) ion (c), solution a + 0.001 mol·dm^{-3} α-alanine (d), solution d + 0.001 mol·dm^{-3} Pd(II) ion (e), and solution a + 0.001 mol·dm^{-3} Pd(II) ion + 0.001 mol·dm^{-3} IDA + 0.001 mol·dm^{-3} α-alanine (f).

the ligands under study. Therefore, prior to determining the stability constants of mixed complexes, the protonation constants of the ligands under study are determined.

From the titration curves of the solutions a, b, and d, the average number of protons associated with the ligands, $\bar{n}_H$, was calculated using eq 6, where y is the number of dissociable protons. V_a, V_b, and V_d are the volumes of NaOH consumed to reach the same pH values in curves a, b, and d, respectively. E^o and N^o are the concentrations of HNO_3 and NaOH, respectively. T_L^o is the initial total molar concentration of the primary ligands and secondary ligands studied in the titrated solution = $1.0 \cdot 10^{-3}$ mol·dm^{-3}, and V^o is the original volume (50 cm^3).

$$\bar{n}_H = = y - \frac{(V_b \text{ or } V_d - V_a)(E^o + N^o)}{(V_o + V_a)T_L^o} \qquad (6)$$

The calculated protonation constants are reported in Table 1. However, the obtained protonation constants are in fairly good agreement with literature values obtained under similar experimental conditions.[23−25] The first ionizations, pK_{a1}, for DPA, IDA, and the amino acids investigated are very low (≤ 2.30) and dissociate in strongly acidic solutions. Therefore, these values could not be measured and were not used in the calculations.

On the other hand, the horizontal distance between curves c and f (Figure 1) was determined and used for the calculation of

Table 1. Acidity Constant of Ligands in Aqueous Solution at 30 °C and $I = 0.1$ mol·dm^{-3} ($NaNO_3$)

ligand	pK_{a1}	pK_{a2}	pK_{a3}
DPA		4.65 ± 0.05	
IDA		2.59	9.44
glycine		9.72 ± 0.04	
alanine		9.81 ± 0.06	
valine		9.67 ± 0.03	
phenylalanine		9.23 ± 0.05	
tryptophan		9.55 ± 0.07	
methionine		9.34 ± 0.06	
lucine		9.18 ± 0.06	
aspartic acid		9.87 ± 0.05	3.90 ± 0.03
glutamic acid		9.76 ± 0.04	4.21 ± 0.05
histidine		9.28 ± 0.07	6.32 ± 0.07
phthalic acid	2.82 ± 0.04	5.47 ± 0.05	
salicylic acid	2.78 ± 0.06	13.40[a]	
succinic acid	4.12 ± 0.03	5.72 ± 0.05	
malonic acid	2.84 ± 0.06	5.68 ± 0.05	
malic acid	3.32 ± 0.04	5.28 ± 0.07	
oxalic acid		4.35 ± 0.05	
tartaric acid	3.10 ± 0.03	4.42 ± 0.06	

[a] Ref 25.

Table 2. Formation Constant of the Ternary Complexes of Pd(II) Involving DPA and IDA as a Primary Ligands and Amino Acid or Aliphatic and Aromatic Acid as a Secondary Ligand at 30 °C and $I = 0.1$ mol·dm^{-3}($NaNO_3$)

ligand	log $K^{Pd(DPA)}_{Pd(DPA)(L)}$	log $K^{Pd(IDA)}_{Pd(IDA)(L)}$
glycine	5.35 ± 0.06	5.24 ± 0.04
alanine	5.30 ± 0.05	5.17 ± 0.07
valine	5.93 ± 0.06	6.31 ± 0.05
phenylalanine	5.49 ± 0.07	5.20 ± 0.05
tryptophan	6.02 ± 0.05	5.96 ± 0.06
methionine	6.16 ± 0.04	5.72 ± 0.05
leucine	6.09 ± 0.05	5.92 ± 0.06
aspartic acid	6.20 ± 0.07	5.64 ± 0.05
glutamic acid	6.18 ± 0.04	6.23 ± 0.06
histidine	6.33 ± 0.06	6.31 ± 0.05
phthalic acid	6.83 ± 0.04	6.62 ± 0.06
salicylic acid	6.89 ± 0.03	6.54 ± 0.04
succinic acid	6.70 ± 0.05	6.42 ± 0.04
malonic acid	6.23 ± 0.04	6.03 ± 0.06
malic acid	5.41 ± 0.06	5.10 ± 0.05
oxalic acid	5.92 ± 0.05	5.80 ± 0.03
tartaric acid	5.18 ± 0.07	5.09 ± 0.05

the average number of moles of the secondary ligand, $\bar{n}_{mix}$, from the following equation:

$$\bar{n}_{mix} = = \frac{(V_f - V_c)[(E^o + N^o) + T_L^o(y - \bar{n}_H)}{(V_o + V_c)[T^o_{M(primary\ ligand)}]\bar{n}_H} \quad (7)$$

where V_f and V_c are the volumes of NaOH consumed to reach the same pH value in the curves f and c, respectively; $[T^o_{M(primary\ ligand)}]$ is the concentration of the binary complex which is equivalent to the initial Pd(II) ion concentration (T^o_M); $\bar{n}_H$ is the average number of protons associated with the secondary ligand; T^o_L is the initial concentration of the secondary ligand; and y is the number of dissociable protons per molecule of the secondary ligand. V_o, E^o, and N^o have the same meaning as mentioned before.

Since $E^o + N^o \gg T^o_L$

$$\bar{n}_{mix} = = \frac{(V_f - V_c)[E^o + N^o]}{(V_o + V_c)[T^o_{M(primaryligand)}]\bar{n}_H} \quad (8)$$

From the values of $\bar{n}_{mix}$ so obtained, the free secondary ligand exponent, pL'_{mix} was calculated using the equation

$$pL'_{mix} = \log\left\{\frac{1 + 10^{pK_{a2}}(1/10^{pH})}{T^o_L - \bar{n}_{mix}T^o_M} \cdot \frac{(V_o + V_f)}{V_o}\right\} \quad (9)$$

Here, pK_{a2} is the second dissociation constant of the secondary ligands. All other terms have the same meaning as defined above. The formation curves corresponding to the different ternary complexes under investigation were constructed by plotting $\bar{n}_{mix}$ versus pL'_{mix}. At $\bar{n}_{mix}$ equals 0.5, the pL'_{mix} value is the corresponding stability constant of the ternary complex formed in the solution (1:1:1). The stability constants for ternary complexes have been calculated at 30 °C and $I = 0.1$ mol·dm^{-3} and are tabulated in Table 2.

In general, the observed order of stability of ternary systems with respect to the primary ligand is DPA > IDA, which might be a result of the π acidic character in DPA, because of the possibility of $M \rightarrow N\,\pi$ bond formation. A similar behavior has been previously observed in M-dipyridyl-L systems.[26]

In Figure 5, a representative conductometric titration curve for the ternary complex of Pd(II) with IDA and α-alanine is displayed. The titration curve shows an initial decrease and an inflection at $a = 2$ (a = moles of base added per mole of ligand). This probably corresponds to the neutralization of H^+ ions originating from the formation of the Pd(II) + IDA binary complex. In the $3 \geq a \geq 2$ range, the conductance increases slightly because of the formation of a ternary complex associated with the release of a H^+ ion from α-alanine. Beyond $a = 3$, the conductance increases appreciably because of the presence of an excess of NaOH.

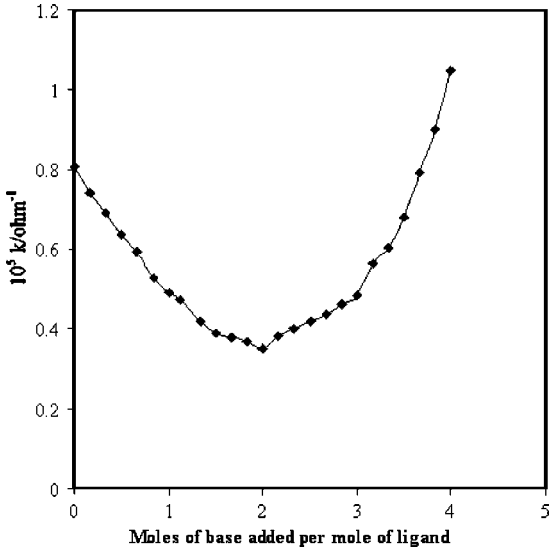

Figure 5. Conductometric titration curve for Pd(II)−IDA−α-alanine systems at 30 ± 0.1 °C and $I = 0.1$ mol·dm^{-3} $NaNO_3$; $1\cdot10^{-2}$ mol·dm^{-3} Pd(II) + $1\cdot10^{-2}$ mol·dm^{-3} IDA + $1\cdot10^{-2}$ mol·dm^{-3} α-alanine.

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