Complexes of Aminophosphonates. I. Transition Metal Complexes of Aminophosphonic Acid Analogues of α-Alanine, β-Alanine, Phenylalanine and Tyrosine

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Abstract

The stoichiometries and stability constants of the proton, cobalt(II), nickel(II), copper(II) and zinc(II) complexes of 1-aminoethanephosphonic acid (α-Ala-P), 2-aminoethanephosphonic acid (β-Ala-P), 1-amino-2-phenylethanephosphonic acid (Phe-P) and 1-amino-2-(4-hydroxyphenyl)ethanephosphonic acid (Tyr-P) have been determined pH-metrically at 25 °C and at an ionic strength of 0.2 mol dm^{-3} (KCl).

From these data and the spectral parameters of the complexes it has been established that these simple aminophosphonic acids coordinate similarly to aminocarboxylic acids, forming chelate complexes MA and MA_2. However an MAH species with only phosphonate group coordination also exist at low pH. The differences between the complex-forming properties of aminophosphonates and aminocarboxylates have been explained by the differences in basicity, charge and size of the $-PO_3^{2-}$ and $-COO^-$ groups.

Introduction

Aminophosphonic acids are analogues of aminocarboxylic acids in which a –COOH group is replaced by a $-PO_3H_2$ group. These ligands are of considerable interest because of their occurrence in many living organisms and their biological activity. The natural and synthetic aminophosphonic acids and their derivatives (phosphonopeptides, phosphonolipids, phosphonoglycolipids, etc.) include neuroactive compounds, antibiotics and herbicides [1]. Their biological activity is mainly displayed through their inhibition of various enzymes (metalloenzymes) having amino acid substrates. The differences in size, shape and basicity of the carboxylate and phosphonate groups may play important roles in the differences in the enzyme–substrate interactions. Hence, the investigation of their interactions with various metal ions may contribute to a better understanding of their powerful metalloenzyme inhibitory effect and biological activity.

Although the metal complexes of aminophosphonic acids have been studied fairly extensively in the solid state [2–5], solution studies are quite limited [6–8]. The most important finding is that aminocarboxylic acids behave in a similar way to aminophosphonic acids in forming stable MA_n type chelate complexes at high pH, but MAH species involving only phosphonate coordination also exist at low pH.

The aim of the present work is to establish the stoichiometries, stability constants and bonding modes of the species formed in the equilibrium systems containing cobalt(II), nickel(II), copper(II) and zinc(II) and the following simple aminophosphonic acids: α-Ala-P, β-Ala-P, Phe-P and Tyr-P, which are the phosphonic acid analogues of α-alanine, β-alanine, phenylalanine and tyrosine, respectively. Furthermore, by comparing these data with those for the aminocarboxylic acid analogues we hope to establish the differences in the complex-forming properties of simple aminophosphonates and aminocarboxylates.

Experimental

Aminophosphonic acids were obtained by the method described in refs. 9 and 10. The exact concentrations of their solutions were determined pH-metrically by the method of Gran [11]. The concentrations of the metal chloride stock solutions were measured gravimetrically via precipitation of the oxinates.

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The stability constants of the proton and metal complexes of the ligands were determined by pH-metric titration of 5 or 10 cm^3 samples. The concentration of the ligand in the samples was 4×10^{-3} mol dm^{-3}, the metal ion:ligand ratio was 1:1, 1:2, 1:4 or 1:6, and in each case the ionic strength was adjusted to 0.2 mol dm^{-3} with KCl. The titrations were performed over the pH range 3–11 with KOH solution of known concentration (*ca.* 0.2 mol dm^{-3}).

The pH was measured with a Radiometer pHM 64 instrument with G2040 B glass and K4040 Calomel electrodes using a TTA 80 titration unit. The electrode system was calibrated by the method of Irving *et al.* [12], so that the pH-meter readings could be converted into hydrogen-ion concentrations. In all cases the temperature was 25.0 ± 0.1 °C.

For determination of the proton complex formation, microconstants of Tyr-P, pH-spectrophotometric titrations were performed as described previously [13]. To establish the bonding modes in the species formed, visible spectra were recorded for the cobalt(II), nickel(II) and copper(II) complexes of α-Ala-P and β-Ala-P with a Beckman Acta MIV double-beam recording spectrophotometer. EPR spectra were obtained on a Jeol JMN-3X spectrometer at 9.15 GHz and 120 K.

The stability constants $\beta_{pqr} = [M_pA_pH_r]/[M]^p[A]^q[H]^r$ were calculated with the aid of the PSEQUAD computer program [14].

Results and Discussion

The pH-metrically determined dissociation constants of the ligands are given in Table I. In the pH range studied (pH 3–11) α-Ala-P, β-Ala-P, and Phe-P contain two dissociable protons, while Tyr-P contains three. In the former ligands these protons are involved in the dissociation of the $-PO_3H^-$ and $-NH_3^+$ groups, respectively. (The pK characteristic of the dissociation of $-PO_3H_2$ is ~1.0 [6, 7], and thus it is fully deprotonated in the pH range studied.)

TABLE I. Dissociation Constants of some Aminophosphonic Acids at 25 °C and I = 0.2 mol dm^{-3} (KCl)

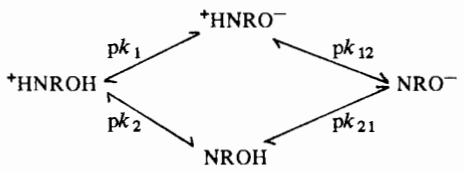
Ligands	pK_1	pK_2	pK_3
α-Ala-P	5.55 ± 0.01	10.11 ± 0.01	
β-Ala-P	6.21 ± 0.01	10.92 ± 0.01	
Phe-P	5.43 ± 0.01	9.62 ± 0.01	
Tyr-P	5.50 ± 0.01	9.45 ± 0.01	10.42 ± 0.01

As with tyrosine, the dissociation processes of the phenolic hydroxy group and the ammonium group of Tyr-P overlap one another, and thus the values of pK_2 and pK_3 cannot be ascribed unambiguously to one or the other process. The dissociation microconstants characteristic of the acidity of the individual groups were determined by selectively monitoring the dissociation of the phenolic hydroxy group via the UV band of the phenolate [13]. The values obtained, together with those for tyrosine [13], are listed in Table II.

It can be seen from Table II that for tyrosine the $-NH_3^+$ group is more acidic than the phenolic hydroxy group (pk_1 > pk_2), while for the phosphonic analogue the acidity sequence is just the opposite (pk_1 < pk_2). This can be attributed to the stronger electron-releasing effect of the $-PO_3^{2-}$ group than that of $-COO^-$, and therefore the acidity of $-NH_3^+$ decreases more significantly for Tyr-P than for Tyr. This change in the acidity of the $-NH_3^+$ group appears for the other aminophosphonic acids too; the pK_2 values are ~0.5 log units larger than those of the corresponding aminocarboxylic acid analogues.

The stability constants obtained for the metal(II) complexes of the ligands are given in Tables III and IV. Tyr-P contains a phenolic hydroxy group separated from the chelate-forming aminophosphonate side-chain and thus, as with tyrosine, the direct participation of this group in the coordination is strongly hindered sterically. Its acidity is low, and consequently the ligand HA^{2-} containing a pro-

TABLE II. Dissociation Microconstants of Tyrosine and its Phosphonic Analogous at 25 °C and I = 0.2 mol dm^{-3} (KCl):



Ligands	pk_1	pk_2	pk_{21}	pk_{12}	k_1/k_2
Tyr-P	9.65 ± 0.01	9.88 ± 0.01	9.99 ± 0.01	10.22 ± 0.01	1.70
Tyr[a]	9.54	9.20	9.92	9.58	0.46

[a]See ref. 13.

TABLE III. Stability Constants of the Metal Complexes of some Aminophosphonic Acids at 25 °C and I = 0.2 mol dm^{-3} (KCl)

		$\log \beta_{MAH}$	$\log \beta_{MA}$	$\log \beta_{MA_2}$	$\log \beta_{MA_3}$
α-Ala-P	Co(II)		4.55 ± 0.02	7.70 ± 0.05	
	Ni(II)	11.98 ± 0.05	5.42 ± 0.02	9.31 ± 0.03	12.20 ± 0.7
	Cu(II)	12.29 ± 0.09	8.29 ± 0.01	14.94 ± 0.02	
	Zn(II)	11.79 ± 0.09	5.99 ± 0.04		
β-Ala-P	Co(II)	13.14 ± 0.03	5.16 ± 0.02	8.82 ± 0.09	
	Ni(II)	12.37 ± 0.08	5.34 ± 0.01	9.04 ± 0.09	
	Cu(II)	13.62 ± 0.09	8.53 ± 0.02	14.96 ± 0.07	
	Zn(II)	12.93 ± 0.05	6.09 ± 0.02	10.94 ± 0.04	
Phe-P	Co(II)		4.70 ± 0.03	8.02 ± 0.05	
	Ni(II)	11.17 ± 0.08	5.46 ± 0.01	9.36 ± 0.03	11.83 ± 0.14
	Cu(II)	12.30 ± 0.06	8.30 ± 0.01	15.18 ± 0.02	

TABLE IV. Stability and Derived Equilibrium Constants of the Metal Complexes of Tyr-P at 25 °C and I = 0.2 mol dm^{-3} (KCl)

	$\log \beta_{MAH_2}$	$\log \beta_{MAH}$	$\log \beta_{M(AH)_2}$	$\log \beta_{MA_2H}$	$\log \beta_{MA_2}$	$\log \beta_{M(AH)_3}$
Co(II)		14.44 ± 0.09	27.83 ± 0.09	18.3 ± 0.1	8.09 ± 0.09	
Ni(II)		15.54 ± 0.01	29.59 ± 0.03	20.10 ± 0.03	10.10 ± 0.03	42.2 ± 0.2
Cu(II)	22.93 ± 0.06	18.67 ± 0.01	35.98 ± 0.03	26.48 ± 0.06	16.40 ± 0.09	

Process	Co(II)	Ni(II)	Cu(II)
$M + HAH \rightleftharpoons M(HA)H$			12.94
$M + HA \rightleftharpoons M(HA)$	4.45	5.55	8.68
$M(HA) + HA \rightleftharpoons M(HA)_2$	3.37	4.06	7.32
$M(HA)_2 \rightleftharpoons MHA_2 + H^+$	9.53	9.49	9.50
$MHA_2 \rightleftharpoons MA_2 + H^+$	10.21	10.00	10.08
$M(HA)_2 + HA \rightleftharpoons M(HA)_3$		12.2	

tonated phenolic hydroxy group may be regarded as the complex-forming species in the parent complexes of type $M(HA)_n$. The equilibrium constants were therefore calculated for complex formation corresponding to the processes $M + nHA \rightleftharpoons M(HA)_n$ and for deprotonation of the species $M(HA)_n$. These derived data were obtained in accordance with the actual conditions with the use of microconstant pk_2 for the dissociation of the ammonium group; they are given in Table IV.

In the zinc(II)–Phe-P and zinc(II)–Tyr-P systems, precipitation was observed at pH 4.5–5.0, even in the case of the highest ligand excess, and thus the equilibrium study of these systems was impossible. The different behaviour of the aromatic phosphonic acids from that of the aliphatic Ala-P can probably be explained by the presence of the hydrophobic aromatic ring, which decreases the solubility of the zinc(II)–phosphonate complexes in water.

It can be seen from Tables III and IV that complexes of compositions MAH, MA and MA_2 (and for nickel(II), MA_3 too) are formed in the systems studied. In contrast to the results of Wozniak and Nowogrocki [7], we could not prove unambiguously the existence of protonated 1:2 complexes in any system. Such species were found in the computation, in some cases, but the large uncertainty in their stability constants, their very low (<5%) concentrations, and the agreement of the fit (within the experimental error) between the experimental and the calculated titration curves with or without the assumption of these protonated complexes, mean that the formation of these species can be regarded as negligible. Complexes 1:3 are formed in measurable concentrations only with nickel(II).

At lower pH, MAH species are formed in the systems studied; in these complexes, only the phosphonate group is coordinated to the metal ion and the amino group is protonated. This species is not formed with the aminocarboxylate analogues because of the lower basicity of the carboxylate group. The equilibrium constants $\log \beta_{MAH} - pK_{NH_3^+}$ calculated on the assumption of metal(II)–PO_3^{2-} coordination for the MAH complexes are listed in Table V, together with the stability data on the metal(II)–HPO_4^{2-} and metal(II)–AMP complexes [15].

TABLE V. Stabilities of Metal Complexes of HPO_4^{2-}, AMP and MAH of some Aminophosphonic Acids at 25 °C and I = 0.2 mol dm^{-3} (KCl)

	$\log K_{MHPO_4}$ [a]	$\log K_{MAMP}$ [a]	$\log K_{MAH}-pK_{NH_3^+}$			
			α-Ala-P	β-Ala-P	Phe-P	Tyr-P
Co(II)	2.18	2.19		2.22		
Ni(II)	2.08	2.62	1.87	1.45	1.55	
Cu(II)	3.2	3.04	2.18	2.70	2.68	3.08
Zn(II)	2.4	2.23	1.68	2.01		
pK	6.70	6.14	5.55	6.21	5.43	5.50

[a]See ref. 15, I = 0.1 ($NaClO_4$).

TABLE VI. Spectral Data for the Copper(II) and Nickel(II) Aminophosphonate MA_2 Complexes

System	Ratio	pH	λ_{max} (nm)	ϵ ($dm^3\ mol^{-1}\ cm^{-1}$)
Cu(II)–α-Ala-P-OH^-	1:2:4	8.1	645	50
Cu(II)–α-Ala-OH^-	1:2:2	8.0	615	56
Cu(II)–β-Ala-P-OH^-	1:2:4	8.9	632	54
Cu(II)–β-Ala-OH^-	1:2:2	8.4	638	56
Ni(II)–α-Ala-P-OH^-	1:2:4	9.4	640	6
			380	13
Ni(II)–α-Ala-OH^-	1:2:2	8.7	616	5
			368	12
Ni(II)–β-Ala-P-OH^-	1:4:6	9.3	650	10
			382	22
Ni(II)–β-Ala-OH^-	1:4:3	9.1	635	8
			378	19

It is clear from the data that, taking into account the differing acidity of the donor groups, the tabulated data for the MAH complexes generally agree well with the stability constants obtained for the metal(II)–HPO_4^{2-} and metal(II)–AMP complexes, which confirms the assumed bonding mode in the MAH complexes.

At high pH, the aminophosphonic acids coordinate in a similar way to the aminocarboxylic acids, forming chelate species MA and MA_2, in which the ligands are bound to the metal ions via the amino and the $-PO_3^{2-}$ groups. The d–d transition energy found for the MA_2 species in the nickel(II) and copper(II) systems with α-Ala-P and β-Ala-P (see Table VI) corresponds well to the coordination of two nitrogens. For purposes of comparison, Table VI contains the spectral parameters of the corresponding complexes of α-Ala and β-Ala too. The EPR parameters $g_\parallel$ = 2.264 and $A_\parallel$ = 168 for Cu(α-Ala-P)$_2$ and $g_\parallel$ = 2.272 and $A_\parallel$ = 172 for Cu(Phe-P)$_2$, also seem to indicate that two nitrogens are bound to the copper(II) ion.

The complexes MA and MA_2 of aminophosphonates are more stable than the aminocarboxylate complexes (their stepwise stability data are 0.5–2.0 log units larger). This can be explained by the difference in basicity of the $-PO_3^{2-}$ and the $-COO^-$ groups. The equilibrium constants for the processes $M + H_2A \rightleftharpoons MA + 2H^+$ and $MA + H_2A > MA_2 + 2H^+$, which take into account the difference in basicity of the coordinating donor groups ($-PO_3^{2-}$ and $-NH_2$ or $-COO^-$ and $-NH_2$) of the aminophosphonic acids and aminocarboxylic acids, are listed in Table VII.

The data in Table VII clearly show that the relative stability of the aminocarboxylates is about 2–4 orders of magnitude higher. This can be explained in part by the significantly larger size of the PO_3^{2-} group. Accordingly, the relative stability decrease for the complexes of β-Ala-P, which forms six-membered chelate rings, is smaller than those for the other aminophosphonates, which form five-membered chelate rings: the steric hindrance decreases with increasing size of the chelate ring. This presumably appears in the spectral parameters of the metal complexes of α-Ala and β-Ala and their phosphonic analogues (see Table VI): while the energy of the d–d transition is shifted to lower energies in comparison to the metal complexes of α-Ala-P and α-Ala, this energy shift is significantly smaller in

TABLE VII. Derived Equilibrium Constants of the Metal Complexes of some Amino Acids[a] and their Phosphonic Analogues at 25 °C and I = 0.2 mol dm^{-3}

	$\log K_1 - pK_1 - pK_2$		$\Delta \log K^*$[b]	$\log K_2 - pK_1 - pK_2$		$\Delta \log K^*$[b]	$\log(K_1/K_2)$	
	α-Ala-P	α-Ala		α-Ala-P	α-Ala		α-Ala-P	α-Ala
Co(II)	−11.11	−7.79	−3.32	−12.51	−8.62	−3.89	1.40	0.83
Ni(II)	−10.24	−6.71	−3.53	−11.77	−7.61	−4.15	1.53	0.90
Cu(II)	−7.37	−3.99	−3.42	−9.01	−5.34	−3.67	1.64	1.35
Zn(II)	−9.67	−7.67	−2.00		−7.06			0.61
	β-Ala-P	β-Ala		β-Ala-P	β-Ala		β-Ala-P	β-Ala
Co(II)	−11.97	−10.07	−1.90	−13.47	−10.97	−2.50	1.50	0.90
Ni(II)	−11.79	−9.04	−2.75	−13.42	−10.24	−3.18	1.63	1.20
Cu(II)	−8.60	−6.65	−1.95	−10.70	−8.26	−2.44	2.10	1.61
Zn(II)	−11.04	−9.78	−1.26	−12.28	−10.44	−1.84	1.14	0.66
	Phe-P	Phe		Phe-P	Phe		Phe-P	Phe
Co(II)	−10.35	−7.34	−3.01	−11.73	−8.04	−3.69	1.38	0.68
Ni(II)	−9.59	−6.15	−3.44	−11.15	−6.87	−4.28	1.56	0.70
Cu(II)	−6.75	−3.51	−3.24	−8.18	−4.77	−3.71	1.42	0.96
	Tyr-P	Tyr		Tyr-P	Tyr		Tyr-P	Tyr
Co(II)	−10.93	−7.21	−3.72	−11.98	−7.45	−4.53	1.05	0.24
Ni(II)	−9.84	−6.39	−3.45	−11.32	−7.02	−4.30	1.49	0.62
Cu(II)	−6.70	−3.60	−3.00	−8.06	−4.52	−3.54	1.36	0.94

[a]Calculated from data given in ref. 16. [b]$\Delta \log K^*$ is the difference between the $\log K - pK_1 - pK_2$ values for the aminophosphonate and aminocarboxylate complexes.

comparison to the complexes of β-Ala-P and β-Ala. Another factor that may influence the extent of the relative stability decrease is the difference in charge of $-PO_3^{2-}$ and $-COO^-$. The charge neutralization favours the formation of complex MA for aminophosphonates having two negative charges, while for aminocarboxylates having one negative charge the formation of species MA_2 is favoured. This is the reason why the $\log(K_1/K_2)$ values (which express the ratio of the stepwise stability constants) are larger for the aminophosphonate complexes than for the aminocarboxylate ones; for steric and electrostatic reasons, the binding of the second ligand is more hindered in the case of aminophosphonates.

As with the aminocarboxylic acids, the cobalt(II), nickel(II) and copper(II) complexes of the aromatic aminophosphonic acids are more stable than those of the aliphatic Ala-P. This is reflected by the relative stability data and the $\log(K_1/K_2)$ values (see Table VII). This may be explained by the interaction between the empty d orbital of the metal(II) ion and the 6π electron system of the aromatic ring [17].

It can also be seen from the $\Delta \log K^*$ values in Table VII that the extent of the relative stability decrease of the aminophosphonate complexes depends on the metal ion; it varies in the sequence $Zn(II) < Cu(II) \sim Co(II) < Ni(II)$. This is in accord with the results obtained earlier for various catechol derivatives [18], whereas out of the metal ions studied nickel(II) has the lowest affinity for the hard oxygen donor atoms. Hence, it is not surprising that the stability increase due to the higher basicity of the $-PO_3^{2-}$ group is least for the nickel(II) complexes.

Conclusions

The differences in the complex-forming properties of aminophosphonic and aminocarboxylic acids are due to the significant differences in basicity, charge, electron-releasing effect and size of the phosphonate and carboxylate groups. As a result of these effects the stability increase of the metal(II)–aminophosphonate complexes arising from the higher basicity of the $-PO_3^{2-}$ group is compensated to a great extent by steric and electrostatic effects. Because of the more basic character of the $-PO_3^{2-}$ group, however, there is a possibility of monodentate coordination of the ligand via its phosphonate group, which leads to the formation of a protonated MAH complex.

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