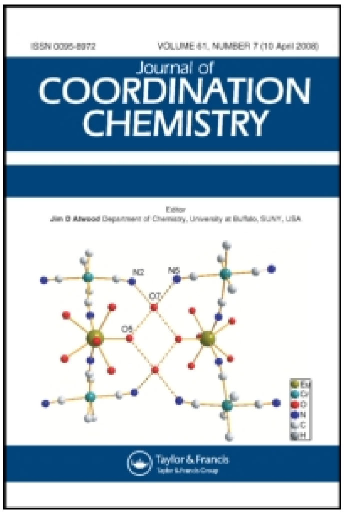

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TERNARY COMPLEXES OF CADMIUM(II) WITH VITAMIN D_3 AND AMINOACIDS: QUANTITATIVE EXPRESSIONS OF RELATIVE STABILITIES*

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The formation and stability of ternary complexes of cadmium(II) with vitamin D_3 (VD_3) and the aminoacids glycine (gly), alanine (ala), histidine (his) and phenylalanine (phe) has been studied by potentiometric pH titrations in 70% (v/v) ethanol–water at 37 ± 0.1°C and at 0.10 ionic strength (KNO_3). All systems give stable ternary complexes, and $\Delta \log K$ values[1] are abnormally high (+0.90, +1.08, +0.85, +1.36, respectively). On the contrary, the $\log X$ values[2] are normal (1.56, 1.59, 1.86, 2.61). The possible reasons that lead to these special results have been discussed in terms of statistical effects and intramolecular ligand–ligand hydrophobic interactions present in the binary and ternary complexes. Some new ideas concerning the stabilities of ternary and the binary complexes have been proposed and discussed.

KEY WORDS: Cadmium, vitamin D, amino acids, ternary complexes

Cadmium is a poisonous metal. When assimilated by animals, it is mainly stored up in the liver and kidney.[3] According to a recent report,[4] the accumulation of cadmium in rat liver can be effectively reduced when the rats are fed with vitamin D_3 (VD_3). It would be instructive therefore to study the coordination of cadmium(II) with VD_3 and other ligands as a model of bioligands. Research on the formation and stability of ternary complexes containing at least one bioligand is still not adequate, especially for the situation when the ML_2 species (L represents the bioligand) is considered. The main reason is that for most metal complexes containing a large bioligand, the second formation constants of species ML_2 is unknown or difficult to determine experimentally.[5,11] Recently, we reported complex formation between cadmium(II) and VD_3 in solution and obtained both the first and the second stability constants for the Cd(II)–VD_3 complexes.[6] In this paper, the formation and stability of the ternary complexes of cadmium(II) with VD_3 and some aminoacid ligands (gly, ala, his, or phe) has been studied by potentiometric pH titrations in 70% (v/v) ethanol–water at 37 ± 0.1°C and at 0.10 ionic strength (KNO_3).

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EXPERIMENTAL

Apparatus and Chemicals

A Radiometer PHM-84 pH meter (accuracy ±0.001 pH unit) and a 2401B compound glass electrode was used for all pH measurements. The temperature was kept at 37 ± 0.1°C, using a jacketted beaker. Cadmium(II) solution was prepared from high purity cadmium (99.99%, dissolved in 1:3 nitric acid) and was calibrated by EDTA titration. VD_3 was a Merck reagent (food grade purity, >99%). The other chemicals used were all A.R. or G.R. grade reagents and were not purified further. The water used in all experiments was doubly distilled.

Method and Calculation

All potentiometric pH titrations were carried out in 70% (v/v) ethanol–water at 37 ± 0.1°C and at 0.10 ionic strength (maintained with KNO_3) under a high purity N_2 flow. Acid formation constants for each aminoacid were determined by preparing a solution (5.00 cm^3 of 5.000 × 10^{-3} M ligand solution, 2.00 cm^3 of 0.04454 M nitric acid, 5.00 cm^3 of 1.0 M KNO_3 and 35.00 cm^3 of ethanol diluted with water to 50.00 cm^3) and titrating with 0.08829 M carbonate-free sodium hydroxide. The same method was used for measurement of stability constants for binary metal complexes of these aminoacids, except for the addition of 5.00 cm^3 of 5.000 × 10^{-3} M cadmium solution. Determination of the constants for VD_3 was the same as reported previously.[6] In the determination of the stability constants for the ternary complexes, mixed solutions were prepared and titrated using the same method. The concentration ratio of Cd^{II} to aminoacid to VD_3 was 1:1:2.

TABLE 1
Acid formation constants for ligands and stability constants for binary and ternary complexes [T = 37°C, I = 0.10 (KNO_3)]

System	$\log \beta_1$	$\log \beta_2$
H^+/VD_3	12.36 ± 0.04	
H^+/phe	8.43 ± 0.02	11.81 ± 0.03
H^+/his	8.65 ± 0.02	14.31 ± 0.02
H^+/ala	9.29 ± 0.03	12.88 ± 0.04
H^+/gly	9.60 ± 0.03	13.62 ± 0.04
Cd^{II}/VD_3	6.46 ± 0.04 (6.45)*	13.64 ± 0.01 (13.61)
Cd^{II}/phe	4.69 ± 0.03 (4.63)	8.77 ± 0.05 (8.78)
Cd^{II}/his	6.59 ± 0.04 (6.45)	12.10 ± 0.07 (12.16)
Cd^{II}/ala	4.71 ± 0.02 (4.73)	9.27 ± 0.04 (9.25)
Cd^{II}/gly	5.36 ± 0.03 (5.40)	10.24 ± 0.05 (10.20)
MAB	$\log \beta_{11}$	
Cd(phe)(VD_3)	12.51 ± 0.05	
Cd(his)(VD_3)	13.80 ± 0.07	
Cd(ala)(VD_3)	12.25 ± 0.04	
Cd(gly)(VD_3)	12.72 ± 0.05	

* The values in parentheses were obtained by a graphical method.[8]

The TITFIT program was used for calculation of acid formation constants of ligands and stability constants of binary complexes, as well as the activity coefficient of the H^+ ion and the ion product of water. Details were as described before.[6] Calculations for ternary complexes were carried out using an Apple II HKC8800A computer, using the method described in the literature.[7] All results are listed in Table 1.

RESULTS AND DISCUSSION

Two common ways of quantitatively expressing relative stabilities of ternary complexes ($\Delta \log K$ and $\log X$) have been widely accepted and used for many years,[5,9–14] and advantages in using $\Delta \log K$ in comparing stabilities of ternary and the binary complexes have been reviewed.[11] For coordination of ligands A and B with solvated metal ion M (omitting the charges), the following apply.

$$\mathrm{M + A + B = MAB} \qquad \beta_{11} = [\mathrm{MAB}]/([\mathrm{M}][\mathrm{A}][\mathrm{B}]) \tag{1}$$

$$\mathrm{M + B = MB} \qquad K^{\mathrm{M}}_{\mathrm{MB}} = [\mathrm{MB}]/([\mathrm{M}][\mathrm{B}]) \tag{2}$$

$$\mathrm{MA + B = MAB} \qquad K^{\mathrm{MA}}_{\mathrm{MAB}} = [\mathrm{MAB}]/([\mathrm{MA}][\mathrm{B}]) \tag{3}$$

$$\mathrm{M + A = MA} \qquad K^{\mathrm{M}}_{\mathrm{MA}} = [\mathrm{MA}]/([\mathrm{M}][\mathrm{A}]) \tag{4}$$

$$\mathrm{MB + A = MBA} \qquad K^{\mathrm{MB}}_{\mathrm{MBA}} = [\mathrm{MBA}]/([\mathrm{MB}][\mathrm{A}]) \tag{5}$$

$$\mathrm{MA + A = MA_2} \qquad K^{\mathrm{MA}}_{\mathrm{MA_2}} = [\mathrm{MA_2}]/([\mathrm{MA}][\mathrm{A}]) \tag{6}$$

$$\mathrm{MB + B = MB_2} \qquad K^{\mathrm{MB}}_{\mathrm{MB_2}} = [\mathrm{MB_2}]/([\mathrm{MB}][\mathrm{B}]) \tag{7}$$

For labile ternary complexes (MAB are identical with MBA), $\Delta \log K$ and $\log X$ have been respectively defined as follows.[1,2,5]

$$\begin{aligned} \mathrm{MA + MB = MAB + M} \qquad \Delta \log K &= \log K^{\mathrm{MA}}_{\mathrm{MAB}} - \log K^{\mathrm{M}}_{\mathrm{MB}} \\ &= \log K^{\mathrm{MB}}_{\mathrm{MBA}} - \log K^{\mathrm{M}}_{\mathrm{MA}} \\ &= \log \beta_{11} - \log K^{\mathrm{M}}_{\mathrm{MB}} - \log K^{\mathrm{M}}_{\mathrm{MA}} \end{aligned} \tag{8}$$

$$\begin{aligned} \mathrm{MA_2 + MB_2 = 2MAB} \qquad \log X &= \log\{[\mathrm{MAB}]^2/[\mathrm{MA_2}][\mathrm{MB_2}]\} \\ &= 2 \log \beta_{11} - (\log \beta_{20} + \log \beta_{02}) \end{aligned} \tag{9}$$

Values of $\Delta \log K$ and $\log X$ for the ternary complexes studied in this paper have been listed in Table 2. For comparison, some literature data are also given. From the data it can be seen that all $\Delta \log K$ values for the ternary complexes of this work are highly positive (higher than typical Cu(II) ternary complexes). Sigel[5,9,10] has noted that statistical values of $\Delta \log K$ should be negative; positive values have been generally considered as evidence of some enhanced stabilities involving the π back donating effects,[5,15] intramolecular ligand–ligand interactions[10,19,20] and hydrophobic effects.[10,21] However, it is very difficult to understand the abnormally high $\Delta \log K$ values for the ternary complexes in this paper ($\Delta \log K = +0.85$–$+1.36$) in such terms. On the other hand, corresponding $\log X$ values are normal ($\log X = 1.56$–2.61).

Obviously, as one of the influencing factors, statistical effects should be considered. Sigel[5,10] pointed out that the statistically expected values of $\Delta \log K$ should be the statistical values of $\log(K_2/K_1)$ of the binary complexes plus 0.3, and calculated those values from considerations of complex configurations for the case of bidentate ligand coordination (−0.4 for the octahedron, −0.6 for the square-plane, −0.8 for the tetrahedron and −0.9– −0.3 for the distorted octahedron). However, since ternary mixed species are coexistent with binary species in solution, the tendency to form ternary complexes MAB from MB and MA will be influenced by that of forming MB_2 and MA_2, respectively, from MB and MA. This means that the actual sizes of $\log K^{MA}_{MAB}$ and $\log K^{MB}_{MBA}$ depend not only on (*3*) and (*5*), but also on (*6*) and (*7*) (*i.e.*, the actual size of $\log K^{MA}_{MA_2}$ and $\log K^{MB}_{MB_2}$). Since the coordination of many binary complexes deviates from statistical regularity and the extent of the deviation is different from various binary complexes,[16] these factors will still influence the actual size of $\Delta \log K$, even though its definition does not include the second equilibrium constants of the binary complexes. Consequently, if the above statistical values of $\Delta \log K$ are used, it seems certain that some confusion or abnormal results may arise when stabilities of various ternary complexes are compared to one another in terms of $\Delta \log K$. Therefore, the statistical application of $\Delta \log K$ is not appropriate, unless the binary constants approximately accord with statistical expectations.

As well known, the statistically expected value of $\log \beta_{11}$ can be expressed by (*10*).[9,13]

$$\log \beta^s_{11} = (\log \beta_{20} + \log \beta_{02})/2 + \log 2 \qquad (10)$$

If $\log \beta_{11} = \log \beta^s_{11}$ is considered in (*8*) and (*9*), statistical values of $\Delta \log K$ and $\log X$ may also be obtained[13] as follows.

$$\Delta \log K^s = (\Delta \log K_A + \Delta \log K_B)/2 + \log 2 \qquad (11)$$

$$\log X^s = 2 \log 2 = 0.60 \qquad (12)$$

Here $\log K_A = \log K^{MA}_{MA_2} - \log K^{M}_{MA}$, $\Delta \log K_B = \log K^{MB}_{MB_2} - \log K^{M}_{MB}$. Equation (*11*) indicates that $\Delta \log K^s$ (similar to $\log \beta^s_{11}$) relates to $\Delta \log K_A$ and $\Delta \log K_B$ of the binary complexes. Thus, on statistical grounds, the greater the opportunities of forming MA_2 or MB_2 from MA or MB, the greater that of forming MAB from the same species (*i.e.*, high values of $\Delta \log K_A$ or $\Delta \log K_B$ will statistically augment the corresponding $\Delta \log K$ values). If both second constants accord with statistical regularities (*i.e.*, $\Delta \log K_A = \Delta \log K^s_A$ and $\Delta \log K_B = \Delta \log K^s_B$), (*13*) is obtained:

$$\Delta \log K^s = (\Delta \log K^s_A + \Delta \log K^s_B)/2 + \log 2$$
$$= \Delta \log K^s_A + \log 2 = \Delta \log K^s_B + \log 2 \qquad (13)$$

This is just the result proposed by Sigel,[5] but from the above, it is obvious that $\Delta \log K^s$ expressed by (*11*) is more practical.

Furthermore, if the $\Delta \log K^s$ of (*11*) is used as the statistical basis of $\Delta \log K$, from the definitions of $\Delta \log K$ and $\log X$, as well as from (*10*)–(*12*), the following will be obtained.

$$\delta_K = \delta_\beta = \delta_X/2 \qquad (14)$$

where $\delta_K = \Delta \log K - \Delta \log K^s$, $\delta_\beta = \log \beta_{11} - \log \beta^s_{11}$, and $\delta_X = \log X - \log X^s$. Equation (*14*) indicates that no matter which of the three δ scales (δ_K, δ_β or δ_X) is used, conclusions about relative stabilities of ternary complexes will be identical.

The results obtained by means of the above approach are presented in Table 2. From these results one can see that although the $\Delta \log K$ values of the four ternary complexes studied in this paper are very positive, the corresponding δ_K values are

TABLE 2
Stability data for some ternary complexes and statistical values of $\Delta \log K$ [$T = 37 \pm 0.1$°C, $I = 0.10$ (KNO_3)]

MAB	$\Delta \log K$	$\log X$	$\Delta \log K^s$	δk	δx	$\delta\beta$	Ref.
Cd(phe)(VD_3)	+1.36	2.61	+0.36	1.00	2.01	1.00	This paper
Cd(his)(VD_3)	+0.85	1.86	+0.22	0.63	1.26	0.63	
Cd(ala)(VD_3)	+1.08	1.59	+0.59	0.49	0.99	0.49	
Cd(gly)(VD_3)	+0.90	1.56	+0.42	0.48	0.96	0.48	
Cu(bipy)(pyr)	+0.43	6.15	−2.35	2.78	5.55	2.78	[15]*
Cu(bipy)(mal)	+0.27	5.49	−2.18	2.45	4.89	2.45	[17]
Cu(bipy)(gly)	−0.35	3.05	−1.58	1.23	2.45	1.23	[15]
Zn(phen)(ala)	−0.02	1.10	−0.27	0.25	0.50	0.25	[18]
Zn(pehn)(leu)	+0.11	1.35	−0.27	0.38	0.76	0.38	[18]
Cu(phen)(ala)	−0.41	3.07	−1.65	1.24	2.47	1.24	[18]
Cu(phen)(leu)	−0.35	3.10	−1.60	1.25	2.50	1.25	[18]
Cu(bipy)(en)	−1.29	1.10	−1.54	0.25	0.50	0.25	[15]
Pb(bipy)(mal)	−0.14	1.98	−0.83	0.69	1.38	0.69	[13]
Pb(bipy)(anth)	+0.66	1.04	+0.44	0.22	0.44	0.22	[14]
Pb(phen)(mal)	−0.37	1.90	−1.02	0.65	1.30	0.65	[13]
Pb(phen)(anth)	+0.20	0.50	+0.25	−0.05	−0.10	−0.05	[14]

* 25°C, I = 0.10, and in aqueous solution for all literature data.

Abbreviations used: pyr, pyrocatecholate; mal, malonate; ala, α-alaninate; leu, leucinate; anth, anthranilate; bipy, 2,2′-bipyridyl; phen, 1,10-phenanthroline.

TABLE 3
Extent of intramolecular ligand–ligand hydrophobic interactions in ternary complex Cd(Aa)(VD_3), where Aa = phe, his, or ala

System	$\Delta\Delta \log K$	$\Delta\delta k$	K_I	K_I^*	Close %	Close %*
Cd(phe)(VD_3)	+0.44	+0.53	1.88	2.39	65	71
Cd(his)(VD_3)	−0.05	+0.15	−0.11	0.41	−12	29
Cd(ale)(VD_3)	+0.18	+0.02	0.51	0.05	34	5

normal. From the above discussion it is expected that the abnormally high $\Delta \log K$ values (statistically) are due to the unusually high $\Delta \log K_B$ value for the Cd(VD_3)$_2$ complex ($\Delta \log K_B = +0.72$), probably caused by intramolecular hydrophobic interactions between the two coordinated VD_3 ligands.[6] The abnormally positive $\Delta \log K$ values of both Pb(bipy)(anth) and Pb(phen)(anth) complexes of Table 2 may also similarly be understood in terms of positive $\Delta \log K_B$ value of Pb(anth)$_2$ binary complexes ($\Delta \log K_B = +1.22$).[14] It is important to note that intramolecular ligand–ligand interactions may occur not only in ternary complexes but also in binary 1:2 complexes.[6,20]

The δ_K values indicate that the four ternary complexes concerned here have the stability order

$$\mathrm{Cd(gly)(VD_3)} < \mathrm{Cd(ala)(VD_3)} < \mathrm{Cd(his)(VD_3)} < \mathrm{Cd(phe)(VD_3)}$$

which corresponds with the order of hydrophobic qualities of the noncoordinating hydrophobic moieties in the aminoacid ligands. Since the four ligands have the same coordinating group and about the same coordinating ability to the same metal ion, and coordinated VD_3 also has a large hydrophobic moiety, it is believed that intramolecular ligand–ligand interactions between VD_3 and the aminoacid are decisive for relative stabilities of the ternary complexes. If $\Delta \log K$ values are directly used, the stability order (his < gly < ala < phe) would be difficult to understand.

Using the approach proposed by Sigel,[19–21] we have also calculated the extent of these hydrophobic interactions, respectively, from $\Delta \log K$ and δ_K values. Results are presented in Table 3, where the symbols have the following meanings.

$$\mathrm{Cd(Aa)(VD_3)_{open}} = \mathrm{Cd(Aa)(VD_3)_{close}} \tag{15}$$

$$K_I = 10^{\Delta\Delta \log K} - 1 \tag{16}$$

$$\Delta\Delta \log K = \Delta \log K_{(Cd/Aa/VD_3)} - \Delta \log K_{(Cd/gly/VD_3)} \tag{17}$$

$$\text{Close\%} = [K_I/(K_I + 1)] \times 100 \tag{18}$$

$$K_I^* = 10^{\Delta^\delta K} - 1 \tag{19}$$

$$\Delta\delta K = \delta K_{(Cd/Aa/VD_3)} - \delta K_{(Cd/gly/VD_3)} \tag{20}$$

$$\text{Close\%}^* = [K_I^*/(K_I^* + 1)] \times 100 \tag{21}$$

Close%* values are obviously more reasonable than the Close%.

From the above discussion, we conclude that, in practice, either directly using $\Delta \log K$ or comparison of $\Delta \log K$ with the $\Delta \log K^s$ to express quantitatively the relative stabilities of ternary complexes is not strictly precise, especially when the actual size of $\Delta \log K_A$ and/or $\Delta \log K_B$ of the binary complexes distinctly deviates from statistical regularity. Use equation *(11)* (*i.e.* δK) seems more reasonable. This means that in quantitatively comparing the stabilities of ternary and binary 1:1 complexes, constants for $\log K^{MA}_{MA_2}$ and $\log K^{MB}_{MB_2}$ are essential. For comparisons of relative stabilities of ternary complexes, this point is particularly important.

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