Thermochimica Acta, 219 (1993) 115–120
Elsevier Science Publishers B.V., Amsterdam

A calorimetric study of the protonation of vitamin D_3 and of three other ligands and their formation of binary and ternary complexes with Cd(II)

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(Received 13 July 1992; accepted 31 August 1992)

Abstract

The heats of protonation of vitamin D_3 (VD_3) and of glycine (gly), 2,2′-bipyridyl (bipy) and ethylenediamine (en), and their coordination with Cd(II) to form binary and ternary complexes have been determined at 37°C and $I = 0.1$ M (KNO_3) in 70% (v/v) ethanol, using a model RD-1 automatic conduction calorimeter. The entropies of formation of these systems were calculated. The results show that all the ternary systems have large positive entropy values. It seems that the stacking effect between the alkyl residue, which is far removed from the coordination atom (O) in the VD_3 molecule, and the aromatic ring of bipy or the carbon linkage of gly (or en) plays a very important role in the entropy increase of the ternary complex compounds. Furthermore, the magnitude of the stacking effect may be in the order aryl–aryl > aryl–alkyl ring > alkyl ring–alkyl ring > alkyl ring–carbon linkage.

INTRODUCTION

When cadmium is ingested, it concentrates in the liver and poisons the system. It has been found that vitamin D_3 (VD_3) can reduce the concentration of Cd(II) in the liver. It is therefore a good antidote. A study of the stability constants of the Cd(II)–VD_3 (and –gly, –bipy, –en) binary and Cd(II)–VD_3–gly (and –bipy, –en) ternary system has been published [1]; however, no calorimetric study of these systems has been reported in the literature.

Here we report the calorimetric investigation of these systems and try to explain the extra-stabilities of ternary and binary systems that include VD_3.

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EXPERIMENTAL

Instruments and reagents

An improved model RD-1 automatic conduction calorimeter with a precision of ±0.5% [2] was used to measure the heat effects. The instrumental constant K was found to be $(3.00 \pm 0.01) \times 10^{-3}$ J mm^{-2} ($n = 12$, where n denotes the number of measurements) by electrical power calibration. A Beckmann model 71ϕ, 0.001 pH meter was used to measure the pH values of the solutions. The reagents used were vitamin D_3 (VD_3) (Merck Co., Germany), glycine (gly) (biochemical reagent, Tianjin Reagent Institute), 2,2′-bipyridly (bipy) (A.R., Shanghai First Reagent Factory), ethylenediamine (en) (Merck Co., Germany), cadmium nitrate (A.R., Tianjin Second Reagent Factory), potassium nitrate (C.P., Beijing Hongxing Chemical Factory) and anhydrous ethanol (A.R., Tianjin Second Reagent Factory).

All the reaction solutions were prepared with stock solution of KNO_3 (1 M) and anhydrous ethanol and redistilled water. The design and operation of the calorimetric experiment were as described previously [3]. The heat of neutralization ($HNO_3 + KOH$) at 37°C, $I = 0.1$ M (KNO_3) in 70% (v/v) ethanol was first determined so that the heat of formation of water in the actual reaction vessel could be calibrated. The result was a ΔH_N value of -44.5 ± 0.2 kJ mol^{-1}. Using the densities of both water and ethanol at 20°C, we can convert the volume percent of ethanol (70%) into a mole fraction value, 0.419. Then a value of $\Delta H^{\ominus}_{25}$ (-40.83 kJ mol^{-1}) can be calculated by interpolating the literature value [4]. Comparing both values, it can be seen that the former is larger than the latter by about 4 kJ mol^{-1}. If we consider only the effect of ionic strength, this follows the same trend as that in aqueous solution [5]. The heats of protonation of the ligands and the heats of formation of the binary and ternary systems were determined under the same conditions. All the data obtained are tabulated in Tables 1–3.

RESULTS AND DISCUSSION

All the thermodynamic parameters obtained for the binary and ternary systems from the data of the heats and the stability constants in Tables 2 and 3 are shown in Table 4.

From Table 4, we see that, comparing the free energies and enthalpies of the binary and ternary systems, the free energy change (ΔG_{MAB}) for the ternary system is much greater than the sum of the free energy changes (ΔG_{M1} and $\Delta G'_{M1}$) for the corresponding two binary systems. However the enthalpy change (ΔH_{MAB}) is almost equal to the sum of the enthalpy changes (ΔH_{M1} and $\Delta H'_{M1}$) for the corresponding two binary systems within

TABLE 1

Determination of the heats of protonation (kJ mol^{-1}) of some ligands at 37°C, $I = 0.1$ M (KNO_3) in 70% (v/v) ethanol

Ligand	n[a]	pK_1[b]	pK_2	$[L] \times 10^3$/M	$\mathrm{pH_i}$	$\mathrm{pH_f}$	Q_c/J	ΔH_{N1}	ΔH_{N2}
VD_3	1	12.36		9.433	13.253	7.850	−7.34	−43.0	
gly	3	4.02	9.60	9.284	10.997	7.448	−5.78 ± 0.02	−32.3 ± 0.2	
	4			4.646	6.454	2.763	−0.25		−2.5 ± 0.2
bipy	5	3.16	3.96	9.286	6.801	3.041	−0.917 ± 0.024	−4.35 ± 1.08	
	4			4.643	6.578	2.754	−0.461 ± 0.020		−0.23 ± 1.45
en	1	6.97	9.61	9.284	10.495	7.767	−6.44	−33.0 ± 0.2	
	3			4.642	10.447	5.280	−5.40 ± 0.02		−25.0 ± 0.2

[a] n is the number of experiments. [b] Values from ref. 5.

TABLE 2

Determination of the heats of formation (kJ mol^{-1}) of Cd(II)–Ligand binary systems at 37°C, $I = 0.1$ M (KNO_3) in 70% (v/v) ethanol

L	n[a]	log K_1[b]	log K_2	$[M] \times 10^3$/M	$[A] \times 10^3$/M	$\mathrm{pH_i}$	$\mathrm{pH_f}$	Q_c/J	ΔH_{M1}	ΔH_{M2}
VD_3	2	6.46	7.18	2.184	1.723	12.389	8.300	−0.49 ± 0.01	−38.5 ± 2.9	
	2				3.419	12.615	10.765	−0.79 ± 0.01		−31.2 ± 3.8
gly	2	5.36	4.88	4.368	4.642	10.058	7.268	−1.63 ± 0.02	−34.7 ± 0.8	
	2				9.284	9.790	7.748	−2.38 ± 0.02		−35.7 ± 2.1
bipy	4	3.96	3.50	4.368	4.644	6.502	5.558	−2.20 ± 0.04	−22.4 ± 0.7	
	4				9.287	6.665	5.934	−3.91 ± 0.04		−23.1 ± 0.3
en	5	5.96	5.11	4.368	4.642	9.722	7.201	−1.91 ± 0.02	−35.6 ± 1.5	
	5				9.284	9.306	7.217	−3.88 ± 0.02		−36.7 ± 1.6

[a] n is the number of experiments. [b] Values from ref. 1.

TABLE 3

Determination of the heats of formation (kJ mol^{-1}) of Cd(II)–VD_3–Ligand ternary systems at 37°C, $I = 0.1$ M (KNO_3) in 70% (v/v) ethanol

L	n [a]	$\log K_{MAB}$ [b]	$[M] \times 10^3$/M	$[VD_3] \times 10^3$/M	$[L] \times 10^3$/M	pH_i	pH_f	Q_c/J	ΔH_{MAB}
gly	2	12.72	2.184	1.534	1.601	11.011	8.981	−0.96 ± 0.01	−71.1 ± 0.6
bipy	3	12.03	2.184	1.704	1.970	11.021	8.894	−0.72 ± 0.02	−57.8 ± 0.7
en	2	13.48	2.184	1.607	1.567	11.103	9.510	−0.96 ± 0.02	−72.9 ± 0.7

[a] n is the number of experiments. [b] Values from ref. 1.

TABLE 4

The apparent thermodynamic functions of formation of Cd(II)–Ligand binary and Cd(II)–VD_3–Ligand ternary systems at 37°C, $I = 0.1$ M (KNO_3) in 70% (v/v) ethanol

Ligand	ΔG_{M1}	ΔG_{M2}	ΔG_{MAB}	ΔH_{M1}	ΔH_{M2}	ΔH_{MAB}	ΔS_{M1}	ΔS_{M2}	ΔS_{MAB}
VD_3	−40.8	−45.4		−38.5 ± 2.9	−31.2 ± 3.8		7.0	43	
gly	−33.9	−30.9		−34.7 ± 0.8	−35.7 ± 2.1		−2.4	−14.5	
bipy	−25.0	−22.1		−22.4 ± 0.7	−23.1 ± 0.3		7.9	−3.0	
en	−37.7	−32.2		−35.6 ± 1.5	−36.7 ± 1.6		6.4	−13.3	28.2
VD_3–gly			−80.4			−71.1 ± 0.6			55.2
VD_3–bipy			−76.0			−57.8 ± 0.7			37.3
VD_3–en			−85.2			−72.9 ± 0.7			

ΔG and ΔH values in kJ mol^{-1}; ΔS values in J K^{-1} mol^{-1}.

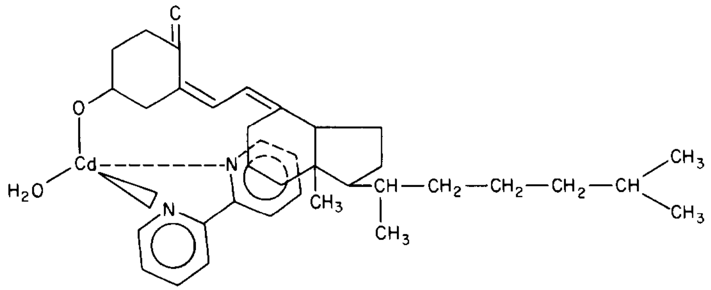

Fig. 1. Schematic structure of the Cd(II)–VD$_3$–bipy ternary system.

experimental error, as reported previously [2, 5, 6]. Evidently, the extra-stability of the ternary system is most probably owing to the contribution of the corresponding entropies of the binary systems. That is, all the entropy terms of the ternary systems have large positive values.

Considering the structure of the ternary complex compound, the increase of entropy may be due to the stacking effect of the alkyl ring of VD$_3$ with the aromatic ring in bipyridyl or with the carbon linkage in glycine and ethylenediamine. The supposed stacking interaction of the Cd(II)–VD$_3$–bipy system, as an example, is shown schematically in Fig. 1. Because the alkyl ring, which is far removed from the coordination atom O^{2-} in the VD$_3$, can stack with the aromatic ring located on the N–Cd(II)–N′ plane which is perpendicular to the plane of H_2O–Cd(II)–O^{2-}, the ternary system Cd(II)–VD$_3$–bipy shows a very high stability. It is interesting to note that the second entropy term ΔS_{M2} of the binary system Cd(II)–VD$_3$ has a very large positive value which can also be ascribed to the stacking effect of both alkyl rings in the ligand molecule.

The magnitude of the stacking effect decreases in the order aryl–aryl > aryl–alkyl ring > alkyl ring–alkyl ring > alkyl ring–carbon linkage. However, for the binary system Cd(II)–bipy, the second entropy term ΔS_{M2} is negative ($-3.0\ \mathrm{J\ K^{-1}\ mol^{-1}}$). This means that there is no stacking effect between the ligand molecules because the aromatic rings are on two mutually perpendicular planes of N–Cd(II)–N′.

This stacking effect of non-polar groups of solute molecules in aqueous solution is largely a result of the hydrophobic bonding between non-polar groups [7, 8]. A first solvation shell is held around the hydrophobic groups by van der Waals forces. The water molecules in the first solvation shell interact with water molecules in the solvent by hydrogen bonding. This interaction increases the fraction of tetra-coordinated or "ice-like" molecules, i.e. it increases the ordering of water and causes a partial cage to form. The hydrophobic groups have a tendency "to escape" from the polar solvent, because the presence of hydrophobic groups in aqueous solution is equivalent to their transfer from a non-polar solvent into a dilute aqueous solution. This process has a very large negative entropy change over the entropy of ideal mixing and it is a non-spontaneous process. Therefore these hydrophobic groups in dilute aqueous solution have a tendency to stack with each other as much as possible. This process is equivalent to the escape of these groups from dilute aqueous solution. The formation of hydrophobic bonding can be considered to be accompanied by the disordering of water, i.e. a partial melting of the "ice-like" regions that were produced when the separate non-polar groups were first introduced into the water, thereby resulting in a very large positive entropy change. This is probably the main cause of the extra-stability attained by the ternary systems and by Cd(II)–VD_3 binary complex compounds.

The fact that ΔG_{MAB} of the Cd(II)–VD_3–gly system shows a large negative value ($-80.4\,kJ\,mol^{-1}$) indicates that the mixed complex compound is very stable, which makes it difficult to remove Cd(II) by VD_3 in biological systems. Therefore it is advisable to administer an appropriate amount of ethylene diamine with the VD_3; this may act as an antidote for Cd(II), because the ΔG_{MAB} value of the Cd(II)–VD_3–en ternary system is larger than that of the Cd(II)–VD_3–gly system.

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