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The Thermodynamics of Lanthanide-Pipecolinate Complexation in an Aqueous Solution

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The need to understand and develop novel complexes based on lanthanide ions with biologically active ligands has increased interest in them.[1] The thermodynamics for the complexation and coordination environment of the complexes in solution are of utmost important in these systems to explain the biological activity of the species.[2] For example, the coordination number and the presence of coordinated water molecules in complexes can affect the stability of the resulting complexes and the interaction between the lanthanide ions and ligands in an aqueous solution.[3]

With this in mind, we reported the thermodynamics of the complexation of trivalent lanthanide ions with cyclo-pentanecarboxlate,[4] L-proline[5] and substituted L-proline ligands.[6-8] Based on the measured thermodynamic parameters, we proposed that lanthanide ions could be used in the resolution of racemic α-aminoacids.[9] In this work, we have extended these studies to pipecolinate complexes in order to investigate the effect of the heterocyclohexyl ring in pipecolinate ligand on complexation in an aqueous solution. Potential and calorimetric titration were used to determine the stability and the enthalpy changes on complexation, and the nature of the binding behaviour was explained in terms of enthalpy and entropy changes.

Experimental Section

Stock solutions of lanthanide perchrolates were prepared and standardized by the previously described method.[4-8] The working solutions were adjusted to give a total ionic strength of 0.1 M $NaClO_4$.

A Fisher 520 digital pH meter in conjunction with a Fisher standard combination electrode was used for the pH titrations. The calorimetric titrations were performed using a Tronac model 450 solution calorimeter. The calorimeter was tested by measuring the amount of the heat of the protonation of THAM (trishydroxymethylaminomethane).

The stability constants of the lanthanide pipecolinate complexes were determined at 25.0 ± 0.1 °C using a jacked titration vessel. The lanthanide solutions were titrated with a pipecolinate buffer solution. The pipecolinate buffer solution was prepared by half neutralizing the pipecolinic acid solution with a standard NaOH solution. The initial pH of the lanthanide and the pipecolinate solutions were adjusted

to approximate the value of pKa of the ligand. To form a 1 : 1 complex in the experiments, the total concentration of the ligand was limited to less than half of the lanthanide concentration. The amount of heat produced in forming the lanthanide pipecolinate complexes was examined by adding increments of the pipecolinate buffer solution (2.0 mL) to the lanthanide solutions (50.0 mL). The procedure for calorimetric titration has been described elsewhere.[10,11] The heat produced by dilution was measured by a blank titration of the pipecolinate buffer solution into the 0.10 M $NaClO_4$ solution.

Results and Discussion

The acid constant and the heat of the protonation of pipecolinic acid were determined respectively by a pH and a calorimetric titration method using a standard NaOH solution in an aqueous medium of 0.1 M $NaClO_4$ ionic strength at 25.0 °C. The results are summarized in Table 1. A typical set of pH titration data of the europium(III) pipecolinate complex is listed in Table 2. The average number of ligands per cation, n, was calculated based on the pH titration data. The plot of $\bar{n}/1-\bar{n}$ versus [L] (where [L] is a concentration of free ligand) shows a good linear relationship, and the stability constant (β_1) was obtained from the slope by a linear-least square analysis of the equation of $\bar{n}/1-\bar{n} = \beta_1$ [L].[12] The concentrations used did not result in the formation of ML_2.

Figure 1 represents the relationship between the sum of the acid constants (ΣpKa) and the stability constants ($\log\beta_1$) of the europium(III) complexes with some bidentate ligands. The selected complexes followed the linear relationship, and the pipecolinate complex matched this relationship well. This result indicates that the interaction between the lanthanide cations and the selected ligands is primarily electrostatic, and that the pipecolinate anion acts as a bidentate

Table 1. Thermodynamic parameters of pipecolinic acid at 25.0 °C and at 0.1 M $NaClO_4$ ionic strength

pKa	$-\Delta Gp$ (kJmol^{-1})	ΔHp (kJmol^{-1})	ΔSp (JK^{-1}mol^{-1})
2.77 ± 0.04	15.81 ± 0.21	38.86 ± 0.19	183.5 ± 1.6

Table 2. pH titration data for Eu^{3+}-pipecolinate at 25.0 °C and at 0.1 M NaClO$_4$ ionic strength

Volume of titrant (mL)	pH	[L] × 10^4 (M)	$\bar{n}$
0.5	2.773	0.146	0.012
1.0	2.768	0.317	0.022
1.5	2.762	0.435	0.034
2.0	2.757	0.580	0.045
2.5	2.752	0.712	0.057
3.0	2.747	0.834	0.068
3.5	2.740	0.863	0.091
4.0	2.738	1.085	0.086
4.5	2.735	1.257	0.100
5.0	2.732	1.421	0.110
5.5	2.728	1.535	0.121
6.0	2.723	1.598	0.134
6.5	2.721	1.779	0.143
7.0	2.720	1.997	0.150
7.5	2.718	2.166	0.159
8.0	2.716	2.328	0.169
8.5	2.714	2.485	0.178
9.0	2.713	2.679	0.185
9.5	2.711	2.824	0.195
10.0	2.709	2.964	0.204

initial volume = 50.00 mL, initial pH = 2.778, [Eu^{3+}] = 7.006 × 10^{-3} M, [HL] = 5.486 × 10^{-3} M
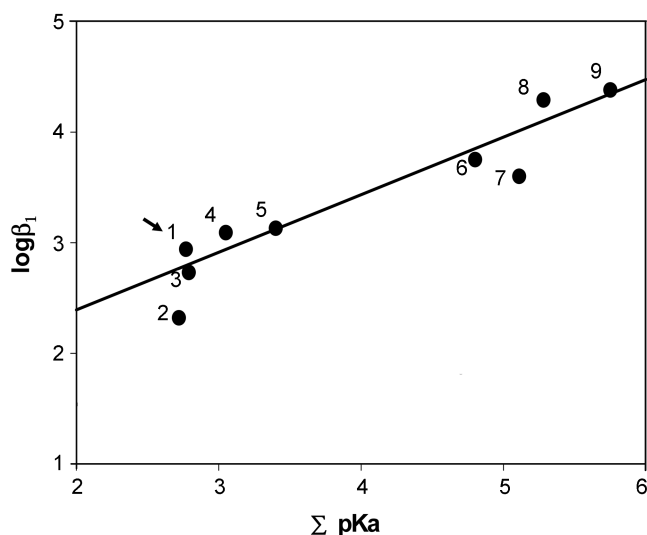
Figure 1. Correlation of the stability constants (logβ_1) of the europium(III) complexes and the acid constants (ΣpKa) of some bidentate ligands; 1. pipecolinate, 2. L-proline, 3. trans-4-hydroxy-L-proline, 4. croconate, 5. α-picolinated N-oxide, 6. glutarate, 7. α-picolinate, 8. malonate, 9. 1,4-cyclohexanedicarboxylate

ligand and forms a chelate complex with lanthanide(III) metal ions.

The calorimetric titration data for the complexation of europium(III) by a pipecolinate ligand is listed in Table 3. The amounts of heat were corrected for the dilution and the deprotonation of the ligand. The heat of water formation was

Table 3. Enthalpy titration data for the complexation of Eu^{3+}-pipecolinate at 25.0 °C and at 0.1 M NaClO$_4$ ionic strength

Volume of titrant (mL)	-Q$_{Total}$ (J)	-Q$_{corrected}$ (J)	[L]$_T$ × 10^3 (M)
1.00	0.588	0.895	2.179
1.10	0.647	0.985	2.396
1.20	0.705	1.074	2.615
1.30	0.764	1.164	2.833
1.40	0.823	1.252	3.051
1.50	0.882	1.343	3.269
1.60	0.941	1.432	3.486
1.70	0.999	1.522	3.705
1.80	1.058	1.611	3.922
1.90	1.117	1.701	4.141
2.00	1.176	1.790	4.385

initial volume = 50.00 mL, [M]$_T$ = 9.945 × 10^{-3} M, initial [H$^+$] = 4.966 × 10^{-4} M final [H$^+$] = 7.186 × 10^{-4} M

Table 4. Thermodynamic parameters for the formation of lanthanide(III)-pipecolinate at 25.0 °C and at 0.1 M NaClO$_4$ ionic strength

Metal	$-\Delta G_1$ (kJmol^{-1})	ΔH_1 (kJmol^{-1})	ΔS_1 (JK^{-1}mol^{-1})
La	16.37 ± 0.39	8.44 ± 0.19	83.2 ± 1.9
Sm	16.96 ± 0.04	10.29 ± 0.05	91.4 ± 0.3
Eu	16.76 ± 0.18	9.43 ± 0.13	87.9 ± 1.0
Gd	16.43 ± 0.47	8.50 ± 0.12	83.7 ± 2.0
Dy	15.92 ± 0.37	9.39 ± 0.17	84.9 ± 1.9
Ho	17.06 ± 11.23	11.23 ± 0.20	94.9 ± 1.1

calculated from a value found in literature (ΔH = -55.81 kJmol^{-1}).[13] The thermodynamic parameters calculated from the calorimetric data for the formation of some 1 : 1 lanthanide pipecolinate complexes in an aqueous solution are summarized in Table 4.

As shown in Table 4, both enthalpy change (ΔH) and entropy change (ΔS) for pipecolinate complexes of the lighter lanthanide ions [La(III) through Eu(III)] increase with decreasing cationic radius. The values increase from Gd(III) to Ho(III), showing minimum value in Gd(III) complex. This S-shaped "gadolinium break" between the lighter and heavier lanthanide series has been observed. The positive values of ΔH and ΔS clearly indicate that the driving force of the complexation is an entropy effect. Figure 2 shows the plot of TΔS against ΔH for some selected europium(III) complexes and shows a good linear relationship. This linear relationship is agrees with the relationship of the enthalpy-entropy compensation effect.[14,15] The enthalpy and entropy terms in complex formation reflect the disruption of the solvent structure as well as the combination of the ions. The elimination of water molecules from both the lanthanide cation and the ligand anion in the complexation results in an endothermic enthalpy change, which is compensated for by a positive entropy contribution. Furthermore, the linear relationship between TΔS and ΔH indicates that the structures of the complexes are similar and that these
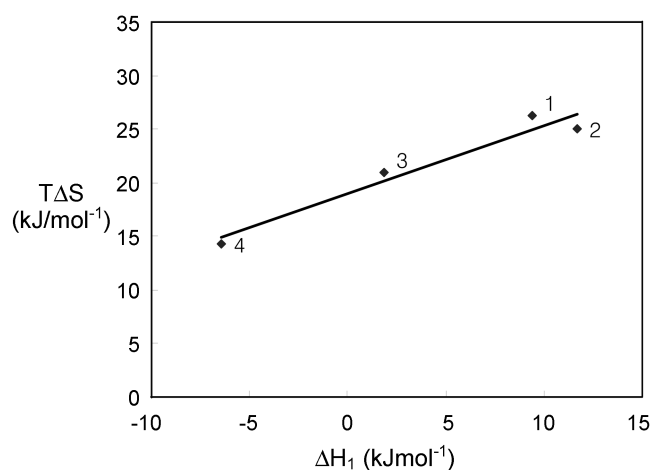
Figure 2. Relationship of TΔS and ΔH for some selected europium(III) complexes; 1. pipecolinate, 2. L-proline, 3. L-thiaproline, 4. α-picolinate.

complexes have similar thermodynamic states. Previously we reported that the inner sphere complexes were formed in lanthanide-prolinate and lanthanide-thiaprolinate complexes, in which the hydration structures were disrupted to a great extent on complexation. Here we propose that stable inner sphere lanthanide-pipecolinate complexes were formed in an aqueous solution. The positive changes of enthalpy and entropy in the reaction support this conclusion. Huskins *et al.*[16] also interpreted a positive entropy change as a formation of an inner sphere complex and a measure for the amount of inner sphere complexation for the monocarboxylate ligand.

It was found that europium(III)-pipecolinate complex (ΔG = −16.76 kJmol^{-1}, ΔH = 9.43 kJmol^{-1}, ΔS = 87.89 JK^{-1} mol^{-1}) is less stable than the reported europium(III)-α-picolinate complex (ΔG = −20.58 kJmol^{-1}, ΔH = −6.4 kJmol^{-1}, ΔS = 48 JK^{-1}mol^{-1})[14] although the pipecolinate complex exhibited a larger entropy change. However, europium(III)-α-picolinate complex was stabilized by the exothermic enthalpy change as well as the entropy effect. The exothermic enthalpy change in europium(III)-α-picolinate complex can be explained by the fact that the basicity of α-picolinic acid (pKa = 5.17)[14] is larger than that of pipecolinic acid (pKa = 2.77). Moreover the COO- group in α-picolinate anion is coplanar with the pyridine ring, so that oxygen is in a sterically more favorable position to coordinate with the metal ion than in the pipecolinate ligand. The heterocyclohexyl ring in a pipecolinate anion causes a steric hindrance compared to α-picolinate when they form chelate complexes,[17] which leads to a more positive enthalpy

change. The more positive entropy effect resulted from the excess dehydration in europium(III)-pipecolinate system. A similar effect was discussed in edta (ethylenediaminetetraacetate) and dcta (trans-1,2-diaminocyclohexane-N,N-tetraacetate) complexes with Ni(II) ion.[18] It was proposed that the steric hindrance of the cyclohexane ring in dcta was responsible for the endothermic enthalpy and the greater entropy change than in the corresponding edta complexes.

In conclusion, pipecolinate ligand forms quite stable chelate complexes with lanthanide cations in an aqueous solution and the driving force for complexation is an entropy effect. The positive entropy effect resulted from the dehydration caused by the ligand anion and the lanthanide cations when they form inner sphere complexes. The heterocyclohexyl ring in pipecolinate ligand causes an excessive dehydration compared to the pyridine ring.

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