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Synthetic, Spectroscopic and X-ray Crystallographic Studies of Bivalent Metal Complexes with Amino Acids Having a Thiazolidine Ring.
II. Properties of Bivalent Metal Complexes with Racemic 4-Thiazolidinecarboxylic Acid

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Abstract

Complexes of the type $ML_2 \cdot nH_2O$ (M = Co, Ni, Zn, Cd) and $ZnCl_2(HL)_2$ have been prepared, where HL is racemic 4-thiazolidinecarboxylic acid ($\overline{\underline{CH_2-S-}}$$\underline{CH_2-NH-CH}$–COOH). Each complex was characterized by elemental analysis, powder diffuse reflection, infrared absorption, NMR spectroscopy magnetic susceptibility, thermal analysis and powder X-ray diffraction. These measurements suggest that in the first type of complex the ligand coordinates to a metal with a nitrogen atom and an oxygen atom, while in the second type of complex, the zinc atom is ligated with a carboxyl oxygen atom of this ligand which has a zwitterion structure, and two chlorine atoms. The IR spectrum of racemic 4-thiazolidinecarboxylic acid is the same as that of (*S*)-4-thiazolidinecarboxylic acid, but the IR spectra of the metal complexes are different from those of the corresponding metal complexes with (*S*)-4-thiazolidinecarboxylic acid.

Introduction

Recently (*S*)-4-thiazolidinecarboxylic acid has been reported as a new type of anticancer agent which can induce reverse transformation [1–4]. Many studies have been reported about metal complexes with this ligand in aqueous solution and the solid state [5–8]. In our previous investigation on bivalent metal complexes with (*S*)-4-thiazolidinecarboxylic acid (HL′) in the solid state, two types of complexes were found: $ML'_2 \cdot nH_2O$ and ZnClL′(HL′) [9]. In the former, the ligand coordinates to a metal with a nitrogen atom and an oxygen atom. The results of single X-ray diffraction in the latter, ZnClL′(HL′), show that the zinc atom is pentacoordinated, being ligated with a carboxyl oxygen atom of (*S*)-thiazolidinium-4-carboxylate which has a zwitterion structure, with two carboxyl oxygen atoms and a nitrogen atom of (*S*)-4-thiazolidinecarboxylate anion, and with a chlorine atom.

In this work we prepared the bivalent metal complexes of racemic 4-thiazolidinecarboxylic acid (HL) and systematically investigated their spectral properties. We discuss how the differences between the optically active ligand and the racemic one influence the properties and the structures of the complexes.

Experimental

Preparation of Racemic 4-Thiazolidinecarboxylic Acid

This was prepared by Rather and Clarke's method [10]. Formaldehyde (36 g of 37%) was added to an aqueous solution containing 60 g of DL-cysteine hydrochloride. After this solution was stirred, it was left standing overnight at room temperature. As soon as 200 cm^3 of pyridine was added to this solution, the colorless crystals were precipitated. After ethanol was added to this solution and it was stirred, the crystals were filtered, recrystallized from water and dried in a desiccator.

Preparation of Complexes

$CoL_2 \cdot 2H_2O$ was prepared by adding 0.01 mol of cobalt(II) hydroxide to the hot aqueous solution containing 0.02 mol of racemic 4-thiazolidinecarboxylic acid. After the solution was stirred for 1 h, the precipitate which formed was filtered, washed with water and dried *in vacuo* for 6 h at room temperature. $NiL_2 \cdot 2H_2O$, $ZnL_2 \cdot 2H_2O$ and CdL_2 were prepared from the corresponding metal hydroxide by the same procedure as the cobalt(II) complex.

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Physical Measurements

The powder diffuse reflection and infrared absorption spectra, magnetic moments, thermal analysis and powder X-ray diffraction patterns were obtained by the methods described in a previous paper [9]. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL GX-270 FT-NMR spectrometer with dioxane as internal standard in D_2O at 65 °C.

Results and Discussion

The results of elemental analyses for racemic 4-thiazolidinecarboxylic acid and its metal complexes are listed in Table I. These results and the infrared spectra suggest that there are two types of complexes: the first type includes $ML_2 \cdot nH_2O$, and $ZnCl_2(HL)_2$ is the second type. To distinguish between these zinc(II) complexes, we call the first type zinc(II)-A and the second one zinc(II)-B for convenience.

TABLE I. Elemental Analyses of Racemic 4-Thiazolidinecarboxylic Acid (HL) and its Metal Complexes

Compounds	Found (calc.) (%)				
	H	C	N	M	Cl
HL	5.25 (5.30)	35.15 (36.07)	9.99 (10.52)		
$CoL_2 \cdot 2H_2O$	4.52 (4.49)	26.44 (26.74)	7.64 (7.80)	17.05 (16.40)	
$NiL_2 \cdot 2H_2O$	4.39 (4.49)	26.40 (26.76)	7.62 (7.80)	16.84 (16.35)	
$ZnL_2 \cdot 2H_2O$	4.44 (4.41)	26.02 (26.27)	7.42 (7.66)	18.1 (17.88)	
CdL_2	3.23 (3.21)	25.29 (25.50)	7.22 (7.44)	29.8 (29.84)	
$ZnCl_2(HL)_2$	3.41 (3.50)	23.15 (23.86)	6.57 (6.96)	16.3 (16.24)	18.07 (17.61)

Powder Diffuse Reflection Spectra and Magnetic Moments

These results and assignments are listed in Table II. The assignments of the reflection spectra have been made by referring to refs. 11–13. These assignments suggest that these complexes have an octahedral configuration in an O_h approximation, like that of diaqua((*S*)-4-thiazolidinecarboxylato)zinc(II), the structure of which was determined by single crystal X-ray analysis [6]. The magnetic moment of the cobalt(II) complex is within the range expected for a high-spin complex.

TABLE II. Magnetic Moments and Powder Diffuse Reflection Spectra of Metal Complexes with Racemic 4-Thiazolidinecarboxylic Acid

	Co(II)-A	Ni(II)-A
Magnetic moment μ_{eff} (BM)	4.85 (3.87)^a	3.21 (2.83)^a
Reflection spectra λ (nm)	1060 ($^4T_{2g} \leftarrow {}^4T_{1g}$) 524 ($^4A_{2g} \leftarrow {}^4T_{1g}$) 449 ($^4T_{1g}(P) \leftarrow {}^4T_{1g}$)	910 ($^3T_{2g} \leftarrow {}^3A_{2g}$) 610 ($^3T_{1g} \leftarrow {}^3A_{2g}$) 387 ($^1A_{1g} \leftarrow {}^3A_{2g}$) 357 ($^3T_{1g}(P) \leftarrow {}^3A_{2g}$)

^{a}Spin-only value.

Thermal Analysis

The reaction temperature ranges with mass loss obtained from TG and DTA curves of the complexes are summarized in Table III. In the first step cobalt(II), nickel(II) and zinc(II)-A complexes give endothermic reactions with mass losses as shown in Table III. The percentages of the mass loss for these complexes in this step are in good agreement with the values which have been calculated by assuming that two molecules of water have been released.

TABLE III. Temperature Range of Decomposition and Mass Loss of Racemic 4-Thiazolidinecarboxylic Acid Complexes

Complex	Temperature range (°C)	Thermal reaction	Mass loss (%)	
			observed	calculated
$CoL_2 \cdot 2H_2O$	162–219	*endo*	11	10.0
	258–309	*exo*	68	79.1^a
$NiL_2 \cdot 2H_2O$	192–249	*endo*	10	10.0
	276–312	*exo*	66	79.2^a
$ZnL_2 \cdot 2H_2O$	108–159	*endo*	10	9.84
	222–636	*exo*	73	77.5^a
CdL_2	141–245	*endo*		
	245–650	*exo*	65	61.7^b
	650–	*exo*		65.9^a
$ZnCl_2(HL)_2$	174–201	*endo*		
	201–249	*exo*		
	480–633	*exo*	85	79.8^a

^{a}As metal oxide. ^{b}As metal sulfide.

The cadmium(II) complex gives two exothermic reaction steps with mass loss. In the first step, the cadmium(II) complex becomes cadmium sulfide, and then this sulfide seems to change to cadmium oxide in the second step.

For the zinc(II)-B complex, an endothermic peak without mass loss is observed below about 200 °C. The peak is assigned to the melt of this complex. Similar behavior has been observed for dichlorobis-

(L-proline)zinc(II), whose structure was previously determined by single crystal X-ray diffraction in our laboratory [14].

For all the complexes, the residual materials yielded by the final exothermic reactions seem to be the corresponding metal oxides, as found by comparison with residual masses.

NMR Spectra

The ^1H NMR spectra lines of racemic 4-thiazolidinecarboxylic acid and the zinc(II)-A complex have been assigned by referring to the results of Tatarowski *et al.* [6] and to refs. 15–18. These chemical shifts are listed in Table IV along with those of (*S*)-4-thiazolidinecarboxylic acid and its zinc(II) complex.

TABLE IV. ^1H NMR Data for Racemic 4-Thiazolidinecarboxylic Acid (HL), (*S*)-4-Thiazolidinecarboxylic Acid (HL') and their Zinc(II)-A Complexes (ppm)

Compound	H_a	H_b	H_c	H_d	H_e
HL^a	4.46	4.34	3.41	3.31	4.41
HL^b	4.46	4.34	3.31	3.20	4.40
$ZnL_2 \cdot 2H_2O$ ^{b}	4.17	4.07	3.27	3.14	4.09
HL' ^{a}	4.46	4.34	3.41	3.32	4.41
HL' ^{b}	4.48	4.34	3.41	3.31	4.40
$ZnL'_2 \cdot 2H_2O$ ^{b}	4.19	4.03	3.28	3.19	4.15

^{a}0.1 mol dm^{-3}. ^{b}8.5 × 10^{-3} mol dm^{-3}.

TABLE V. ^{13}C NMR Data of Racemic 4-Thiazolidinecarboxylic Acid (HL) and its Zinc(II)-A Complex (ppm)

Compound	C_{COO^-}	C_2	C_4	C_5
HL	172.4	49.6	64.9	33.8
$ZnL_2 \cdot 2H_2O$	178.4	52.4	66.0	35.2

8.5 × 10^{-3} mol dm^{-3}.

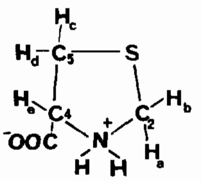

Fig. 1. Notation of hydrogen and carbon atoms.

Since the chemical shift variation due to changes in the concentration of the ligand is less than that due to complex formation, the solvent effect seems to be small.

^{13}C NMR spectra have been measured for 0.1 mol dm^{-3} of the ligand solution. The numbering scheme is shown in Fig. 1 and the chemical shifts are listed in Table V. The carbon shift changes upon zinc ion coordination are equal to 6.0 (COO^-), 2.8 (C_2), 1.1 (C_4) and 1.4 ppm (C_5) downfield. This result strongly suggests that the zinc atom binds nitrogen and carboxyl oxygen atoms as well as the zinc(II) complex with (*S*)-4-thiazolidinecarboxylic acid.

Infrared Absorption Spectra

The infrared spectral data are listed in Table VI. The assignments of the observed frequencies have been made by referring to L-proline [19], 4-hydroxy-L-proline, their metal complexes [12], and (*S*)-4-thiazolidinecarboxylic acid and its metal complexes [5,9].

Racemic 4-thiazolidinecarboxylic acid

The spectrum of this ligand is identical to that of (*S*)-4-thiazolidinecarboxylic acid. There are some bands which shift to lower frequency regions on deuteration. They are assigned to NH_2^+ stretching and bending vibrations. The antisymmetric and symmetric vibrations of the carboxyl group are observed at 1625 and 1378 cm^{-1}, respectively. Therefore this ligand has a zwitterion structure.

Complexes

The spectra of the cobalt(II), nickel(II) and zinc(II)-A complexes are similar to each other, except

TABLE VI. Assignments of Infrared Absorption Spectra of Racemic 4-Thiazolidinecarboxylic Acid (HL) and its Complexes (cm^{-1})

HL	Co(II)-A	Ni(II)-A	Zn(II)-A	Cd(II)-A	Zn(II)-B	Assignments
	3275	3265	3230	3200		NH str.
3030					3135	NH_2^+ str.
2920					2725	
1625	1627	1613	1600	1573	1636	COO^- asym. str.
1547					1545	NH_2^+ scissors
1450					1427	NH_2^+ wagging
1378	1357	1366	1385	1400	1376	COO^- sym. str.
859					839	NH_2^+ rocking
624	673	668	664	665	618	C–S str.

in the region from about 1300 to 1600 cm^{-1}. The cadmium(II) complex shows a spectrum different from those of the above complexes because it contains water molecules.

In the above four complexes, some absorption bands which can be observed in the ligand disappear and new bands which shift to lower frequency regions on deuteration can be observed. These are assigned to NH stretching and bending vibrations.

The antisymmetric and symmetric stretching vibrations of the carboxyl group shift to lower or higher frequency regions as compared with that of the ligand. Therefore in the cobalt(II), nickel(II), zinc(II)-A and cadmium(II) complexes, each metal is coordinated through a carboxylato oxygen atom and a nitrogen atom of the thiazolidine ring. This is supported from NMR spectra.

Tatarowski *et al.* [6] have reported from the results of X-ray analysis that diaquabis((*S*)-4-thiazolidinecarboxylato)zinc(II) has an octahedral configuration with two water molecules occupying the *cis*-positions and with nitrogen and oxygen atoms in both ligand molecules. The spectrum of zinc(II)-A in this work is different from that of the corresponding zinc(II) complex with (*S*)-4-thiazolidinecarboxylic acid. In addition, the powder X-ray diffraction pattern suggests that the zinc(II)-A complex is different from the zinc(II) complex with (*S*)-4-thiazolidinecarboxylic acid in its crystal system. Therefore, zinc(II)-A seems to have a structure different from that of the zinc(II) complex with (*S*)-4-thiazolidinecarboxylic acid.

Thus, it is well known that L- or D- and DL-forms of amino acids have different configurations when they are coordinated with metals; in the case of the copper(II) complex with proline, L-proline forms *cis*-bis(L-prolinato)copper(II) [20] and DL-proline forms *trans*-diaquabis(DL-prolinato)copper(II) [19]. So the zinc(II)-A complex probably has a *trans*-octahedral configuration similar to that of the DL-proline copper(II) complex.

As the powder X-ray diffraction patterns of cobalt(II) and nickel(II) complexes are similar, they have the same crystal systems. But these two complexes and the cadmium(II) complex are different from those of the corresponding complexes with (*S*)-4-thiazolidinecarboxylic acid. Therefore the structure of each complex with racemic 4-thiazolidinecarboxylic acid is different from that of the corresponding metal complex with (*S*)-4-thiazolidinecarboxylic acid.

The zinc(II)-B complex, $ZnCl_2(HL)_2$

The infrared absorption spectrum of the zinc(II)-B complex is different from that of the zinc(II)-A complex. Some absorption bands due to NH_2^+ vibrations are observed at the same region as those of the free ligand.

The antisymmetric stretching vibration of the carboxyl group shifts to a higher frequency region, while the symmetric one is observed in the same region as that of the free ligand. The similar tendency of the shift about the stretching vibrations of the carboxyl group has been observed for dichlorobis(L-proline)zinc(II) [14], which has a tetrahedral configuration with two oxygen atoms of the carboxyl groups and two chlorine atoms.

Therefore this zinc(II)-B complex has a tetrahedral configuration with two chlorine atoms and two oxygen atoms of the carboxyl groups in racemic 4-thiazolidinecarboxylic acid, which has the zwitterion structure.

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