Preparation of Bisspirodiimide [2+2] macrocycle (9).

Diazaspiro[5,5]undecane-1,3,7,9-tetraone (210 mg) in acetonitrile (150 mL) was refluxed under nitrogen. To a clear solution was added anhydrous potassium carbonate (0.7 g) and α,α'-dibromo-*m*-xylene (264 mg) and this reaction mixture was refluxed for 2 days. The solvent was removed by evaporation. The residue was dissolved in methylene chloride (100 mL) and filtered to remove insolubles. After the filtrate was dried over $MgSO_4$ and concentrated *in vacuo*. The residue (325 mg) was loaded on column chromatography (silica gel, 1 : 9 hexnane/ethyl acetate). Two products, **9a** and **9b** were isolated.

9a: 81 mg (26%); mp 367-368.5 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (s, Ar, 2H), 7.27 (m, Ar, 6H), 5.05 (d, *J*=14 Hz, 4H), 4.94 (d, *J*=14 Hz, 4H), 2.67 (m, αCH$_2$ to C=O, 8H, and βCH$_2$ to C=O, 4H), 1.85 (m, βCH$_2$ to C=O, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.72, 170.66, 137.0, 128.5, 127.8, 125.9, 50.7, 49.6, 28.5, 25.7; mass spectrum, m/z (rel intensity) 627 (2.4), 626 (3.6), 625 (14.3), 624 (32.8, M$^+$), 568 (100); Anal. Calcd for $C_{34}H_{28}N_4O_8$: C, 65.38; H, 5.16; N, 8.97. Found: C, 65.23; H, 5.02; N, 8.72.

9b: 69 mg (22%); mp >370 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, Ar, 8H), 5.05 (d, *J*=14 Hz, 4H), 4.90 (d, *J*=14 Hz, 4H), 2.8 (m, αCH$_2$ to C=O, 8H, and βCH$_2$ to C=O, 4H), 1.90 (m, βCH$_2$ to C=O, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) (170.64, 170.58, 137.1, 128.1, 127.8, 50.4, 43.5, 28.4, 25.7; mass spectrum, m/z (rel intensity) 626 (5.4), 625 (8.5), 624 (19.0, M$^+$), 568 (100).

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Thermodynamic Parameters on Complexation of Trivalent Yttrium and Lanthanide Ions by L-thioproline

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Recently we have reported the thermodynamic parameters for lanthanide(III) complexation with L-proline[1] and *trans*-4-hydroxy-L-proline[2] in aqueous solution. It was noted that the heterocyclic nitrogen atom in proline ring and the carboxylate were involved in chelate formation and that the complexes were stabilized by the excess entropy effect. Moreover, *trans*-4-hydroxy-L-prolinate complex was more stable than L-prolinate complex. This increased stability was associated with more positive value of enthalpy change on complex formation. The data were interpreted in terms of the hydration sphere structure of the polarizable lanthanide(III)-*trans*-4-hydroxy-L-proline complex in aqueous solutions.

In this study, we have investigated the thermodynamic parameters on the L-thioprolinate complexation with yttrium (III) and lanthanide(III) cations. L-thioproline ligand is similar to L-proline, but 4-carbon atom of proline ring is replaced by sulfur atom in L-thioproline. Therfore, we have focused our interest on the role of 4-sulfur atom in thioproline ring

Notes

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Table 1. Thermodynamic parameters of L-thioproline at 25.0 °C and 0.1 M NaClO₄

pK_a	ΔG_p (kJmol⁻¹)	ΔH_p (kJmol⁻¹)	ΔS_p (JK⁻¹mol⁻¹)
2.45± 0.03	13.98± 0.21	59.42± 0.14	246.15± 0.06

upon complexation. Potentiometry and calorimetry were used to obtain the thermodynamic parameters of complexation.

Experimental

Lanthanide perchlorate solutions were prepared by dissolving the lanthnide oxides (Aldrich Chemical Co.) in perchloric acid. The solutions were evaporated to near dryness to remove excess acid (caution; not to dryness) and diluted to volume with water. The concentration of metal ion was determined by EDTA titration using xylene orange in acetate buffer. The concentration of L-thioproline was determined using the standard NaOH solution. All the working solutions were adjusted to give a total ionic strenth of 0.1 M using NaClO₄.

The stability constants were determined by pH titration method using a Fisher 520 digital pH meter in conjunction with a Fisher standard combination electrode. The initial pH of metal solutions was adjusted to approximately 2.4 with perchloric acid. The calorimetric titration was performed using a Tronac 450 isoperibol solution calorimeter. The accuracy of the calorimeter was tested by measuring the heat of protonation of THAM (*tris*-hydroxymethylaminomethane). The general procedure for the calorimetric titration was followed by the literature method.³ In a typical run, 50.0 mL of a lanthanide solution (~10⁻² M) was titrated with incremental addition of 2.0 mL of the ligand solution (~10⁻¹ M). The heat of dilution was measured by a blank titration of the ligand solution into 0.1 M NaClO₄ solution. The heat of protonation of L-thioproline was also determined by calorimetric titration of the ligand solution with a standard NaOH solution.

Results and Discussion

The acid constant and the thermodynamic parameters for the protonation of L-thioproline determined in aqueous midium of 0.1 M (NaClO₄) ionic strength at 25 °C are given in Table 1.

The stability constants of L-thioprolinate complexes were determined by titration of metal solutions with L-thioprolinate buffer solution. (pH ~2.5) The average number of L-thioproline ligand bound per cation, $\bar{n}$, was calculated from the pH data. A linear least square analysis of the equation, $\bar{n}/(1-\bar{n})=\beta_1$ [L] (where [L] is free ligand concentration) gave the value of β_1. The concentrations used did not results in formation of ML₂. The calculated stability constants (1 : 1) are summarized in Table 3. Figure 1 shows a good linear relationship between $\bar{n}/(1-\bar{n})$ and [L].

The correlation between the stability constant (log β_1) of Eu(III) complexes and the acid constants (pK_a) of some bidentate ligands is shown in Figure 2. The linear correlation
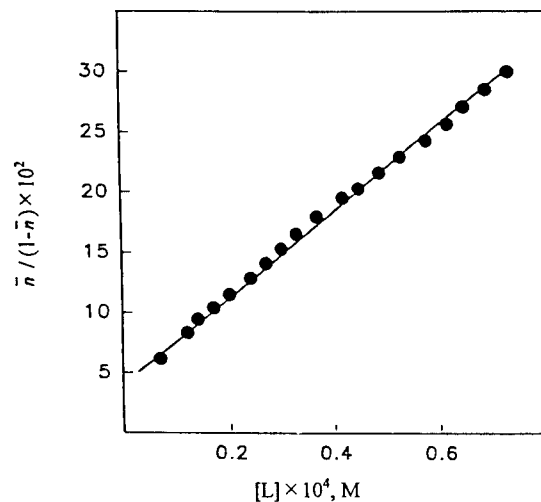
Figure 1. Plot of [L] *vs* $\bar{n}/(1-n)$ for Eu³⁺-L-thioproline.
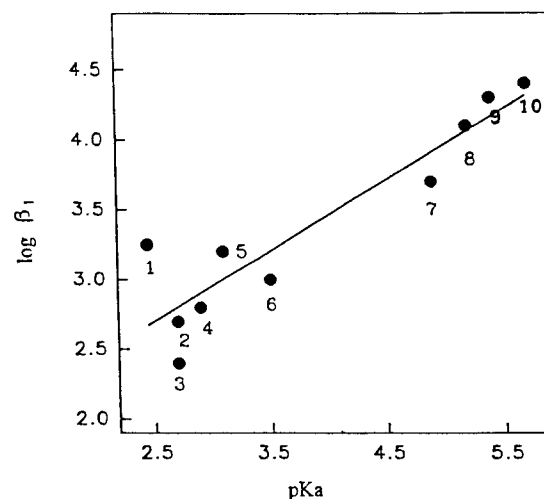
Figure 2. Correlation of logβ_1 the Eu³⁺ complexes and pK_a of the bidentate ligand. 1. L-thioprolinate. 2. trans-4-hydroxy-L-prolinate². 3. L-prolinate¹. 4. pyrazine-2-carboxylate⁴. 5. cronate⁵. 6. α-picolinate-N-oxide⁵. 7. glutarate⁵. 8. α-picolinate⁵. 9. malonate⁵. 10. 1,4-cyclohexanedicarboxylate⁶

reflects the ionic nature of the metal-ligand interaction in lanthanide series.⁷ However, the stability constant of L-thioprolinate complex is somewhat larger than those of L-prolinate complex and trans-4-hydroxy-L-prolinate complex, and somewhat deviated from the linear relationship in Figure 2. It is likely from this observation that the heterocyclic nitrogen atom and the carboxylate group are involved in chelate formation, and that the extra stability of the L-thioprolinate complex is due to the indirect interaction between the lone pair electrons of 4-sulfur atom in L-thioproline and the large lanthanide metal ion. The more detailed disscusion will be performed in terms of the enthalpy and entropy terms on complex formation.

In L-thioprolinate complexes, the stability constant increases gradually from La³⁺ to Eu³⁺, and increases again from Gd³⁺ to a maximum in the vicinity of Ho³⁺, followed by a decrease through the Lu³⁺ ion. This "gadolinium break"

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Table 2. Enthalpy titration data for complexation of Eu^{3+}-L-thioprolinate at 25.0 °C and 0.1 M ionic strength

Volume of titrant (mL)	Q_{total} (mJ)	$Q_{corrected}$ (mJ)
1.0	974	973
1.1	983	982
1.2	991	991
1.3	998	997
1.4	1010	1009
1.5	1022	1020
1.6	1032	1031
1.7	1046	1044
1.8	1054	1051
1.9	1066	1066
2.0	1073	1073

initial volume=50.00 mL $[M]_t = 9.97 \times 10^{-3}$ M. $[L]_t = 1.01 \times 10^{-1}$ M initial $[H^+] = 3.55 \times 10^{-3}$ M

Table 3. Thermodynamic parameters for the formation of lanthanide(III)-L-thioprolinate complexes (25.0 °C and 0.1 M ionic strength)

Metal	$\log\beta_1$	$-\Delta G_1$ (kJmol^{-1})	ΔH_1 (kJmol^{-1})	ΔS_1 (JK^{-1}mol^{-1})
Y	3.29±0.06	18.78±0.32	1.90±0.08	69.36±2.32
La	3.16±0.02	18.04±0.12	1.79±0.09	66.51±1.05
Nd	3.13±0.08	17.86±0.43	2.83±0.10	69.41±3.08
Sm	3.24±0.01	18.49±0.07	2.02±0.06	68.79±0.72
Eu	3.34±0.02	19.06±0.09	1.84±0.05	70.13±0.80
Gd	3.20±0.01	18.26±0.07	1.96±0.03	67.84±0.62
Tb	3.30±0.02	18.84±0.10	2.09±0.08	70.17±0.96
Dy	3.38±0.03	19.29±0.17	2.27±0.08	72.33±1.41
Ho	3.27±0.01	18.66±0.06	2.06±0.10	69.50±0.88
Er	3.16±0.03	18.04±0.18	2.03±0.08	67.28±1.37
Lu	3.15±0.03	18.00±0.16	2.03±0.05	67.12±1.17

between the lighter lanthanides (La^{3+} through Eu^{3+}) and the heavier lanthanides (Gd^{3+} through Lu^{3+}) has been observed in lanthanide series.[8] It has been interpreted as corresponding to either the stability of the half-filled (4f^7) arrangement at the Gd^{3+} ion or two different hydration sphere structure for the two series.

The stability constant of Y^{3+} ion is similar to that of Ho^{3+}. This result is rationalized from the fact that the ionic radius of Y^{3+} ion ($r=0.88$ Å) lies in the region of those of the ions Ho^{3+} ($r=0.894$ Å) and Er^{3+} ($r=0.881$ Å).

Table 2 shows a typical set of calorimetric titration data for the europirm(III)-mono-L-thioprolinate system. All the heats measured were corrected for dilution and deprotonation of the ligand. The thermodynamic parameters for the complexation were calculated from the heat corrected and listed in Table 3. The error limits indicate one standard deviation.

The positive values of enthalpy (endothermic) and the positive entropy change for the complexation of L-thioprolinate

Table 4. Thermodynamic parameters of the europium(III) complexes

ligand	$-\Delta G_1$ (kJmol^{-1})	ΔH_1 (kJmol^{-1})	ΔS_1 (JK^{-1}mol^{-1})	References
L-thioproline	19.06	1.8	70	This work
L-proline	13.23	11.7	84	[1]
trans-4-hydroxy-L-proline	15.58	2.2	60	[2]
pyrazyne-2-carboxylic acid	16.09	−0.3	53	[4]
α-picoline	20.58	−6.4	48	[5]

complex indicate that the inner-sphere complexes are formed in aqueous solution. In inner-shpere complexes, the hydration zone is disrupted to a greater extent which results in a net endothermic enthalpy term. The elimination of water molecules from the inner sphere also results in a net positive entropy effect.[9] The experimental positive values are in agreememt with this relationship.

The thermodynamic parameters for some europium(III) complexes are collected in Table 4. It can be seen from Table 4 that L-thioprolinate as well as L-prolinate and trans-4-hydroxy-L-prolinate are stabilized by excess entropy effect, whereas α-picolinate and α-pyrazine-2-carboxylate are stabilized by both enthalpy and entropy effect. However, ΔH_1 for L-thioprolinate is about 10 kJmol^{-1} less positive than ΔH_1 for L-prolinate complex. It is clear that the increased stability constant for L-thioprolinate compared to L-prolinate is asssociated the less positive enthalpy effect.

It was reported[4] that the decreased stability in the pyrazinecarboxylate complex compared to the picolinate complex was due to the reduced basicity of pyrazinecarboxylate ligand caused by the 4-nitrogen atom of pyrazine ring. It means that the basicity of heterocyclic ring plays an important role to stablilize the complex. But, in L-thioproline ligand, the electronegativity of sulfur atom ($EA=2.5$) is similar to that of carbon atom ($EA=2.4$), and the acidity of L-thioproline ($pK_a=2.45$) is comparable to that of L-proline ($pK_a=2.72$). In spite of the similar acidity, L-thioprolinate complex was found to be more stable than L-prolinate complex. This result seems likely due to the extra interaction of the lone electron pair on the sulfur atom in L-thioproline with the lanthanide cation on complexation, resulting in the relatively exothermic enthalpy change in L-thioprolinate complex compared to in L-prolinate complex. This is coincident with the result of the rather less entropy change in L-thioprolinate complex.

In conclusion, the L-thioproline ligand forms quite stable chelate complexes with lanthanide cations in aqueous solution and that the net driving force for the complexation is the entropy effect. The relatively less positive enthalpy change in L-thioprolinate complex compared to L-prolinate complex indicates that the 4-sulfur atom in thioproline ring interacts with the lanthanide cations indirectly on complexation. The less positive entropy change in L-thioprolinate complex also support the conclusion.

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Ketovinyl Dipeptide Isosteres : A General Synthesis and Conformational Study

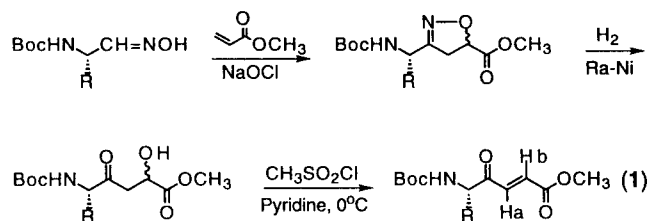Byeang Hyean Kim,* Yong Jun Chung, Hye Jeong Ahn, and Tae-Kyu Ha*†

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Dipeptide isosteres have been well utilized in the synthesis of pharmacologically important enzyme inhibitors. Ketovinyl dipeptide isostere[1] is an interesting dipeptide analog which combines conformational restriction and the ability to undergo conjugate addition upon reaction with nucleophilic species from the respective receptor or enzyme binding sites. In 1985, this isostere was firstly introduced by Hanson and Lindberg[1a] with only one example (Boc-L-Phe-Ψ[COCH=]-Gly-L-Pro-OMe) and very recently Italian chemists[1b] have reported two examples (Boc-L-Val-Ψ[COCH=]-Gly-OEt, Boc-L-Phe-Ψ[COCH=]-Gly-OEt) of ketovinyl dipeptide isostere. However both groups could synthesize the ketovinyl isosteres of limited scope. We have been interested in the development of an efficient and general synthesis of ketovinyl dipeptide isostere. Here, we wish to report a facile synthesis of ketovinyl dipeptide isosteres and conformational analysis results aided with *ab initio* calculations.

Results and Discussion

Ketovinyl dipeptide isosteres were prepared from the corresponding α-amino aldoximes in a three step sequence; (1) 1,3-dipolar cycloaddition with methyl acrylate, (2) reductive cleavage[2] of Δ^2-isoxazoline, and (3) dehydration reaction to the final product (Eq. 1). The synthesis of starting materials, α-amino aldoximes from α-amino acids has already been reported from this laboratory.[3] α-Amino nitrile oxides which were generated *in situ* from the reaction of the corresponding α-amino aldoximes and sodium hypochlorite underwent dipolar cycloadditions with methyl acrylate smoothly to give a diastereomeric mixture of cycloadducts. These cycloadducts were directly subjected under the reductive cleavage conditions [Ra-Ni, H_2(1 atm), $B(OH)_3$, $MeOH : H_2O = 5 : 1$] and a diastereomeric mixture of α-hydroxy ketomethylene isosteres were produced. Dehydration of α-hydroxy ketomethylene isosteres using the Kozikowski conditions[4] afforded *E*-olefinic ketovinyl dipeptide isosteres in good yields. The olefinic geometry was readily assigned as *E* from the inspection of coupling constants between Ha and Hb protons (Ja, b = 15.5-16.2 Hz).

$$\text{BocHN}\underset{\overset{\vdots}{R}}{\diagup}\text{CH=NOH} \quad \overset{O}{\underset{\text{NaOCl}}{\diagdown\diagdown\text{OCH}_3}} \quad \text{BocHN}\underset{\overset{\vdots}{R}}{\diagup}\overset{\text{N}-\text{O}}{\diagdown}\text{OCH}_3 \quad \xrightarrow[\text{Ra-Ni}]{H_2}$$

$$\text{BocHN}\underset{\overset{\vdots}{R}}{\overset{O}{\diagdown}}\overset{\text{OH}}{\underset{O}{\diagdown}}\text{OCH}_3 \quad \xrightarrow[\text{Pyridine, 0°C}]{\text{CH}_3\text{SO}_2\text{Cl}} \quad \text{BocHN}\underset{\overset{\vdots}{R}}{\overset{O}{\diagdown}}\overset{\text{H b}}{\underset{\text{Ha O}}{\diagdown}}\text{OCH}_3 \quad (1)$$

The experimental results are summarized in Table 1. From nine natural and one unnatural (cyclohexylalanine, Cha) amino acids, ten different ketovinyl dipeptides were synthesized efficiently using the three step sequence. Reaction yields in all the steps were very high (mostly, more than 80%). It is noteworthy that *E*-olefinic ketovinyl dipeptide isosteres were formed as major products from diastereomeric mixtures of α-hydroxy ketomethylene dipeptide isosteres. These experimental results can be rationalized by the thermodynamic control of dehydration process under the Kozikowski conditions.[4] Therefore we can employ achiral dipolarophile such as methyl acrylate for the synthesis of ketovinyl dipeptide isosteres and it makes our procedure more efficient and practical.

In order to investigate conformational preference of ketovinyl dipeptide isosteres, *ab initio* calculations of a model system (Gly-Ψ[COCH=]Gly) were carried out. Figure 1 shows four planar conformations and their relative energies at HF/6-31G** and MP2/6-31G** levels. The *s-cis, s-cis* conformer is calculated to be the most stable one and this conformational analysis suggests the utility of ketovinyl dipeptide isostere as a new building block for β-sheet structures.[5]

Experimental section

General Procedure. All commercial chemicals were used as obtained without further purification. Anhydrous solvents were obtained as follows: tetrahydrofuran, distillation from sodium/benzophenone; methylene chloride, toluene, dimethylformamide and pyridine, distillation from CaH_2. Mel-