Formation of Lanthanide Complexes with Bipyridine-Functionalized Amide Compounds and Their Unusually High Amide Reactivity

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In the presence of a catalytic amount of lanthanide cations (Ln^{3+}), the amide of 6-benzoylamino-6′-L-phenylalanylamino-2,2′-bipyridine (**1a**) was efficiently cleaved at 30 °C to give L-phenylalanine ester in methanol almost quantitatively. The reaction proceeded in the manner of the Michaelis–Menten type via the 1 : 1 **1a**–Ln^{3+} complex ([**1a**]/[Ln^{3+}] molar ratio = 1); the half-life time of the scissile amide bond of the complex was as short as 2 min for the **1a**–Dy^{3+} system. The reactions were highly specific to the structure of the substrates, requiring 2,2′-bipyridine having two acylamino side chains at the 6,6′-positions and an amino group at the α-position of the scissile carbonyl. The formation and structures of the less-reactive 6,6′-bis(benzoylamino)-2,2′-bipyridine (**1d**) with lanthanide cations were studied spectrophotometrically. They formed 1 : 1 complexes, and the formation constants (K_a) were on the order of 10^3—10^5 mol^{-1} dm^3 in methanol at 30 °C. Coordination of the bipyridine nitrogens and the carbonyl oxygens was indicated in chloroform. However, coordination of the carbonyl oxygens was not observed in methanol. Detailed structures of the complexes are discussed in relation to their reactivity.

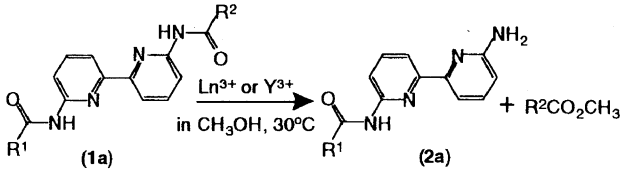
Amide bonds are the key connecting units for biologically important small molecules, like amino acids, and are sufficiently stable under physiological conditions.[1] In biological systems, however, the amide bonds are efficiently formed or cleaved under mild conditions. Ribosomal peptide synthesis[2] and hydrolysis by peptidases[3] are typical examples. In order to understand and mimic highly efficient biological systems, model reactions have been extensively studied, though model reactions are mostly limited to amide hydrolysis. Transition metal-promoted amide hydrolysis has been studied for several decades.[4—6] Though it has been noted that the coordination of transition-metal cations to an amide oxygen promotes amide hydrolysis,[7] the rate enhancement of the metal-catalyzed amide hydrolysis was relatively small compared to that observed for ester hydrolysis.[8]

Recently, several groups have reported efficient cleavage of the amide bond by introducing transition-metal coordination sites on the proximity to the scissile amide bonds.[9—15] For example, Kostić and his group reported that the hydrolysis of methionine-containing dipeptide was greatly enhanced by methionine-coordinated Pd^{2+}, whose half-life period has been reported to be shorter than 30 min at 40 °C.[15]

During our study on developing novel functional ligands, we found efficient Cu^{2+}- or lanthanide (Ln^{3+})-catalyzed alcoholysis of the amide bond between L-amino acids and 6,6′-diamino-2,2′-bipyridine (**dabp**).[16,17] The reaction took place efficiently in methanol at ambient temperature. The Cu^{2+}-catalyzed reaction was shown to proceed via metal complexes,[16] but the role and structure of the complex were not clearly identified. In the case of the lanthanide-catalyzed reaction, however, nothing has been known concerning the interaction between the lanthanide and the substrate. Unique catalytic activities of lanthanides have been recent topics,[18—24] but relatively few have been known regarding the biological or metalloenzyme-like implication of lanthanides. We report here on the formation of the lanthanide complexes with bipyridine-functionalized amide substrates (Fig. 1) and the unusually high reactivity of their amide bond under mild conditions.

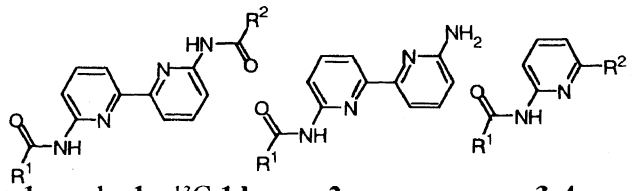
Results

The Efficient Amide Alcoholysis and the Reactive Intermediate. The bisamide ligand **1a** has two amide substituents at both sides of the bipyridine ring (Fig. 1); one is the amide with L-phenylalanine and the other is with benzoic acid. A catalytic amount of a series of lanthanide cations ([Ln^{3+}]/[**1a**] molar ratio = 0.2) caused selective cleavage of the amide at the phenylalanyl side in dehydrated methanol (H_2O content : 0.01—0.02 w/w%) at 30 °C to give **2a** and L-phenylalanine methyl ester within one hour (Scheme 1). A HPLC analysis of the solutions confirmed quantitative ester formation (e.g. 94, 93, 95, 91, 97, and 97 mol % for Ce^{3+}, Sm^{3+}, Pr^{3+}, Dy^{3+}, Gd^{3+}, and Ho^{3+}-catalyzed reactions, respectively) under mild conditions. The catalytic activities of Sc^{3+} and Y^{3+} were also examined under the same conditions,



(R¹=Ph; R²=CH(NH₂)CH₂Ph)

Scheme 1. Methanolysis of the substrate.



1a-e, cbz-1a, ^{13}C-1d **2a-c** **3, 4**

molecule	R^1	R^2
1a	-Ph	$-CH(NH_2)CH_2Ph$
1b	$-CH(NH_2)CH_2Ph$	$-CH(NH_2)CH_2Ph$
1c	$-CH(NH_2)CH_3$	$-CH(NH_2)CH_3$
1d	-Ph	-Ph
1e	-p-hexylphenyl	-p-hexylphenyl
cbz-**1a**[a)]	-Ph	$-CH(NH\text{-cbz})CH_2Ph$
^{13}C-**1d**[b)]	-Ph	-Ph
2a	-Ph	-
2b	$-CH(NH_2)CH_2Ph$	-
2c	$-CH(NH_2)CH_3$	-
3	$-CH(NH_2)CH_2Ph$	-H
4	$-CH(NH_2)CH_2Ph$	$-NHCOCH(NH_2)CH_2Ph$

a) cbz=$-COOCH_2Ph$

b) the substrate having ^{13}C-enriched carbonyl carbons

Fig. 1. Molecular structures.

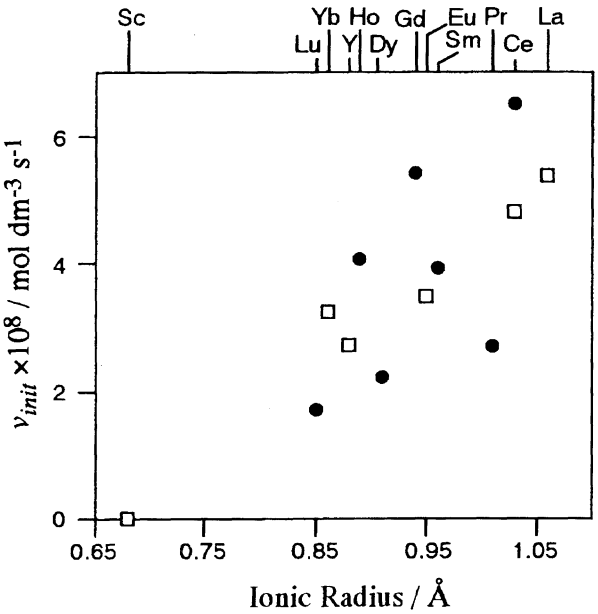


Fig. 2. Initial rate (v_{init}) of the methanolysis (H_2O content: ●: 0.01 w/w%; □: 0.02 w/w%) of **1a** (1×10^{-4} mol dm^{-3}) catalyzed by metal ions (2×10^{-5} mol dm^{-3}) at 30 °C as a function of ionic radii.

since their chemical behaviors are frequently discussed in relation to the lanthanides. Interestingly, Y^{3+} showed similar catalytic activity for the amide cleavage of **1a**, whereas Sc^{3+} had no catalytic activity. It has been pointed out that the chemical behavior of Sc^{3+} is not truly the same as those of the other lanthanides.[25] The initial reaction rates (v_{init}) were determined from the decrease of **1a** of the electronic spectra, and were in the order of 10^{-8} mol dm^{-3} s^{-1}; they are shown in Fig. 2 as a function of the ionic radii of metal cations.

The substrate structure was found to be important for the reaction (Fig. 1). As presented in Table 1, Ce^{3+} and Lu^{3+} showed similar substrate selectivity. The substrates **1a**, **1b**, and **1c**, having amide bond(s) of L-phenylalanine or L-alanine at one or both side(s) of the bipyridine unit, were highly susceptible to cleavage of the amide bond at the L-amino acid side to yield the L-amino acid esters and **2a**, **2b**, and **2c**, respectively. However, no further reaction was observed at all, and the amide bonds of **2a**, **2b**, and **2c**, having one acylamino side chain, were not susceptible to methanolysis. The substrates **1d** and cbz-**1a** were much less, or not, reactive compared to the reactive substrates **1a**, **1b**, and **1c**, indicating the importance of the amino group at the α-position of the scissile amide bond. The reactivity of substrates **3** and **4**, having pyridine instead of the bipyridine unit, was much smaller than that of **1a**, **1b**, or **1c**. Thus, the bipyridine unit and two acylamino side chains are essential for efficient cleavage of the amide bonds.

Table 1. Initial Rates (v_{init}) of Methanolysis of the Amide Substrates (1×10^{-4} mol dm^{-3}) Catalyzed by Ce^{3+} or Lu^{3+} (2×10^{-5} mol dm^{-3}) in Methanol (H_2O Content: 0.02 w/w%) at 30 °C

Substrate	$v_{init}\times10^8$ / mol dm^{-3} s^{-1}			
	Ce^{3+}		Lu^{3+}	
1a	4.8	(=1)	1.2	(=1)
1b	6.3	(1.3)	—[d)]	
1c	2.3	(0.47)	—[d)]	
1d	0	(0)	0.03[a)]	(0.02)
1d[b)]	—[d)]		0.13	(0.11)
cbz-**1a**[c)]	0.07	(0.01)	0.34	(0.28)
2a	0	(0)	0	(0)
3	0.05	(0.01)	0	(0)
4	0.06	(0.01)	0.04	(0.03)

a) H_2O content: 0.03 w/w%. b) In the presence of NaOH (2×10^{-5} mol dm^{-3}). The H_2O content was not determined. c) Reaction products were not identified yet. d) Not determined.

Though the reactions catalyzed by lanthanides were similar to each other, the electronic spectra of the solutions during the reaction were somewhat different for the later lanthanides after Eu^{3+}. In Fig. 3, the electronic spectra of the reactions catalyzed by Ce^{3+} and Lu^{3+} are shown as representative examples of the early and late lanthanide-catalyzed reactions. In each spectrum, **1a** (1×10^{-4} mol dm^{-3}) showed an absorption peak at 307 nm ($\varepsilon = 2.30\times10^4$ dm^3 mol^{-1} cm^{-1}) due to the π–π^* transition of the bipyridine moiety.[26] During the course of the reactions, a decrease of the band at 307 nm and an increase at 350 nm were observed with an isosbestic point at 322 nm. The spectral change was due to the conversion of **1a** to **2a**, since the absorption maximum of **2a** was about 320 nm with an extended absorption tail at the longer wavelength side. However, a new absorption band appeared at around 360 nm for reactions catalyzed by the late lanthanides (Fig. 3b). This new absorption band was indicative of the formation of the **1a**–lanthanide complex, since the first-row transition metal complexes of 6,6′-bis(acylamino)-

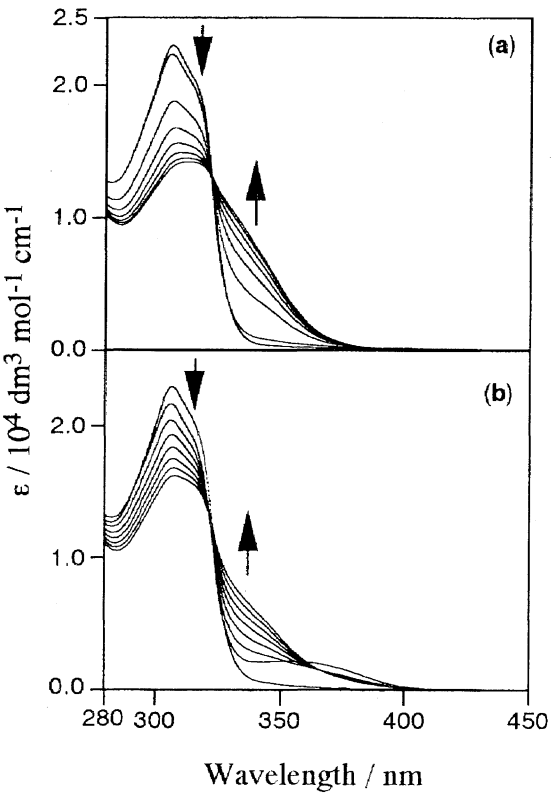


Fig. 3. Electronic spectra of **1a** (1×10^{-4} mol dm^{-3}) in methanol (H_2O content: 0.01 w/w%) before (first spectrum of each figure) and after addition (every 10 min) of (**a**) Ce^{3+} or (**b**) Lu^{3+} (2×10^{-5} mol dm^{-3}) at 30 °C.

2,2′-bipyridine showed absorption bands in a similar region (about 300—400 nm).[27,28]

Kinetic Analysis of the Reaction. Figure 4 shows the rate of the reaction as a function of the Lu^{3+} concentration. The rate increased as the Lu^{3+} concentration increased up to $[Lu^{3+}]/[\mathbf{1a}]=1$, but any further increase of the Lu^{3+} concentration resulted in a slight decrease of the rate. These results suggested that the 1 : 1 complex was the active species of the reaction. To clarify the role of the complex, kinetic analyses of the reactions were carried out. The kinetics of the reactions catalyzed by early lanthanides, e.g. La^{3+} or Ce^{3+}, was not performed because of high sensitivity of the reactions to the H_2O content in the solutions (Table 2). For example, a Ce^{3+}-catalyzed reaction was totally suppressed by 0.03 w/w% of H_2O, though no hydrolysis took place at all. Therefore, the reactions of the **1a**–Lu^{3+} and $-Dy^{3+}$ systems were analyzed by a Lineweaver–Burk plot[2] according to

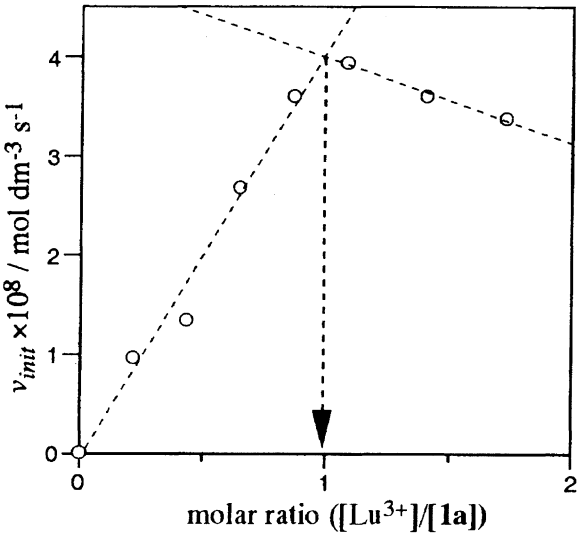


Fig. 4. Initial rate (v_{init}) of the methanolysis of **1a** (initial conc.: 1×10^{-4} mol dm^{-3}, H_2O content: 0.03 w/w%) as a function of molar ratio $[Lu^{3+}]/[\mathbf{1a}]$ at 30 °C.

$$\mathbf{1a}+Ln^{3+} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{complex} \xrightarrow{k_2} \mathbf{2a}+\text{L-phenylalanine methyl ester}+Ln^{3+},$$

$$1/v_{init} = (K_M/v_{max})(1/[\mathbf{1a}]_0)+1/v_{max}$$

$$(\text{where}, K_M = (k_{-1}+k_2)/k_1, k_2 = v_{max}/[M]_{total}), \quad (1)$$

where, $[M]_{total}$, v_{max}, k_2, and K_M represent the total concentration of the lanthanide cation, the maximum rate, the rate constant for cleavage of the scissile amide of **1a**–Lu^{3+} intermediate, and the Michaelis constant, respectively.

In Fig. 5, the Lineweaver–Burk plots gave satisfactory linear lines, suggesting that the reactions proceeded in the manner of the Michaelis–Menten type via the **1a**–Ln^{3+} intermediates ($[\mathbf{1a}]/[Ln^{3+}]$ molar ratio=1). The results are summarized in Table 3.

Electronic Spectral Analysis of 6,6′-Bis(acylamino)-2,2′-bipyridine–Lanthanide Complexes. Complex formations between lanthanides and the 6,6′-bis(acylamino)-2,

Table 2. Effect of H_2O Content in Methanol on the Initial Rates (v_{init}) of the Methanolysis of **1a** (1×10^{-4} mol dm^{-3}) in the Presence of Ce^{3+} or Lu^{3+} (2×10^{-5} mol dm^{-3}) at 30 °C

Metal	H_2O/w/w%	$v_{init}\times10^8$/mol dm^{-3} s^{-1}	(Relative rate)
Ce^{3+}	0.01	6.5	(= 1)
Ce^{3+}	0.02	4.8	(0.74)
Ce^{3+}	0.03	0.52	(0.08)
Ce^{3+}	3.7	0.06	(0.01)
Lu^{3+}	0.01	1.7	(= 1)
Lu^{3+}	0.02	1.2	(0.71)
Lu^{3+}	0.03	1.1	(0.64)
Lu^{3+}	4.0	0.21	(0.12)

Table 3. The v_{max}, k_2 and $1/K_M$ Values of the Methanolysis of **1a** Catalyzed by Dy^{3+} or Lu^{3+} at 30 °C

Metal	H_2O/w/w%	v_{max}/mol dm^{-3} s^{-1}	k_2/s^{-1}	$1/K_M$/dm^3 mol^{-1}
Dy^{3+}	0.03	1.2×10^{-7}	5.9×10^{-3}	1.9×10^{3}
Lu^{3+}	0.03	2.2×10^{-8}	1.1×10^{-3}	8.9×10^{3}
Lu^{3+}	0.12	7.0×10^{-9}	3.5×10^{-4}	4.3×10^{3}
Lu^{3+}	0.2	4.7×10^{-9}	2.3×10^{-4}	4.1×10^{3}

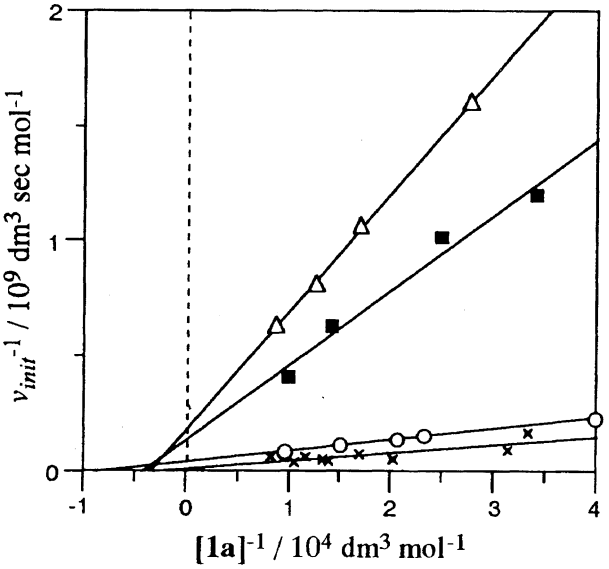


Fig. 5. Lineweaver–Burk plots for the methanolysis of **1a** catalyzed by Lu^{3+} (H_2O content ○: 0.03 w/w%, ■: 0.12 w/w%, △: 0.2 w/w%) and Dy^{3+} (H_2O content ×: 0.03 w/w%) at 30 °C.

2′-bipyridine substrate were studied using less-reactive substrate **1d**. Though **1d** has no α-amino group on its acylamino side chain, it is expected to offer similar metal coordination sites. The addition of lanthanides to a methanolic solution of **1d** caused a red shift of the π–π^* band of the substrate from 307 nm to around 330—380 nm (Fig. 6a), indicating formation of the complex.[26—28] The continuous-variation method was applied to the absorption at around 341 nm and confirmed the composition of the complex to be 1 : 1 (Fig. 7). The association constants (K_a) were determined by the least-squares curve-fitting method, and are summarized in Fig. 6b as a function of the ionic radii of the lanthanide cations. Except for Sc^{3+}, which had no catalytic activity, the K_a values are in the order of 10^3—10^5 mol^{-1} dm^3, and are smaller for the earlier lanthanide complexes.

We examined the electronic spectra of the complexes in more detail. Figure 8 indicates the electronic spectra of **1a**, cbz-**1a**, and **1d** in the presence or absence of Lu^{3+}. Regardless of the substrate structure, the absorption bands due to the complexes were observed in the region around 330—400 nm when Lu^{3+} was present in the solution. However, the absorption bands of the less-reactive cbz-**1a**–Lu^{3+} (**a-3**) and **1d**–Lu^{3+} (**b-2**) were not exactly the same as that of the reactive **1a**–Lu^{3+} (**a-2**), appearing at a slightly shorter wavelength side. Interestingly, the addition of NaOH to the **1d**–Lu^{3+} system caused a small red shift of the bands (**b-3**), appearing at a

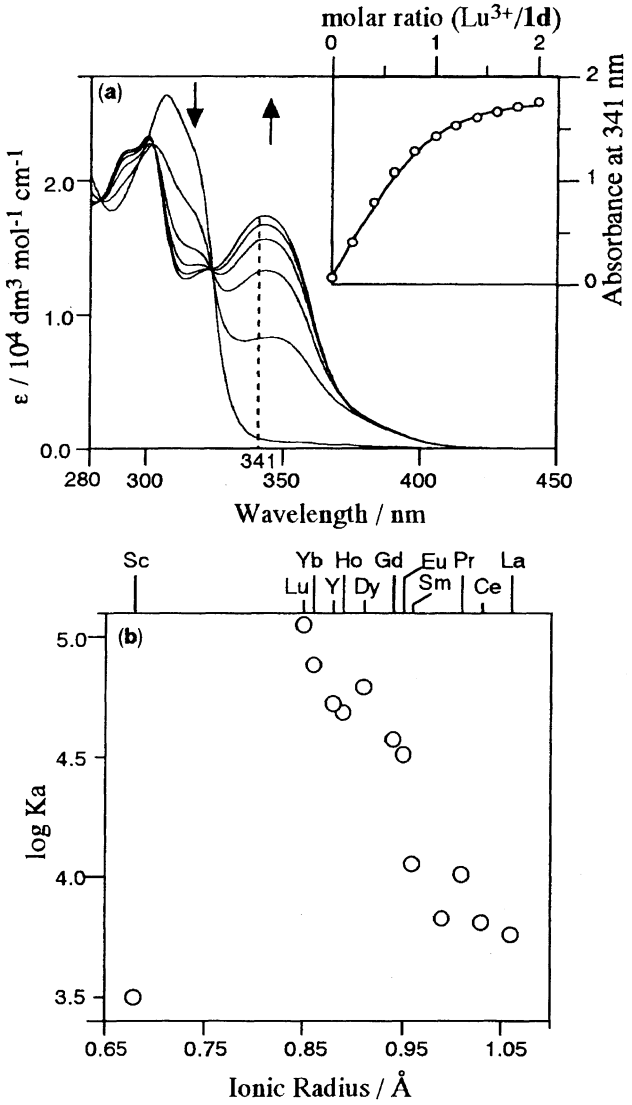


Fig. 6. (a) Spectral change of **1d** (1×10^{-4} mol dm^{-3}) on addition of Lu^{3+} (Lu^{3+}/**1d** molar ratio: 0—2) in methanol (H_2O content: 0.01—0.02 w/w%) at 30 °C. The inset represents the absorbance at 341 nm as a function of Lu^{3+}/**1d** molar ratio (circles) and simulated curve by least-square curve-fitting method based on the complex formation of **1d** and Lu^{3+} in 1 : 1 stoichiometry.
(b) Complex formation constants (log K_a) for **1d** and Ln^{3+} in methanol (H_2O content: 0.01—0.02 w/w%) at 30 °C plotted against ionic radii.

similar region as that of the reactive **1a**–Lu^{3+}. These spectral features are discussed later. Cleavage of the amide bond of **1d** was accelerated by the addition of NaOH, and the rate became 5-times larger. The mode of the reaction was similar

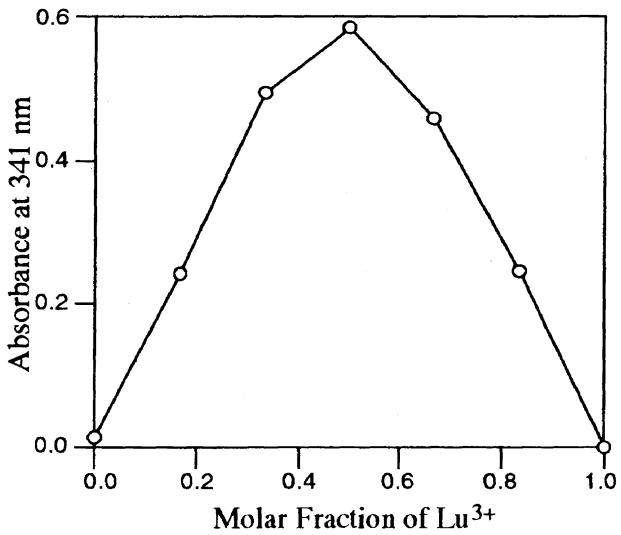


Fig. 7. The plot for continuous variation method for **1d**–Lu^{3+} (341 nm) in methanol (H_2O content: less than 0.08 w/w%, [**1d**]+[Lu^{3+}]=9.1×10^{-4} mol dm^{-3}) at 30 °C.

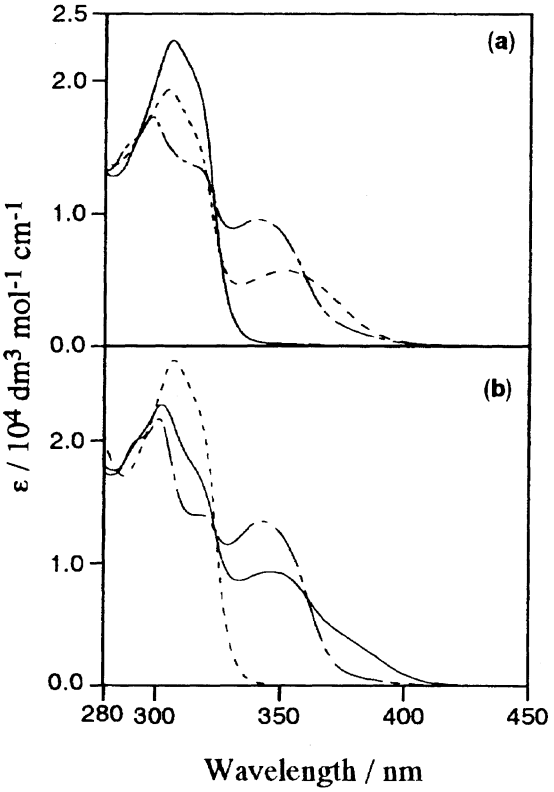


Fig. 8. Electronic spectra of substrates and lanthanide complexes (**1a**, **1a**–Lu^{3+}, cbz-**1a**–Lu^{3+}, **1d** and **1d**-Lu^{3+}) in methanol at 30 °C. Sample conditions are as follows: (a) (**a-1**) **1a** alone (—); (**a-2**) [**1a**] : [Lu^{3+}]=1 : 1 (- - -); (**a-3**) [cbz-**1a**] : [Lu^{3+}]=1 : 1 (-·-), (b) (**b-1**) **1d** alone (- - -); (**b-2**) [**1d**] : [Lu^{3+}]=1 : 1.1 (-·-); (**b-3**) [**1d**] : [Lu^{3+}] : [NaOH]= 1 : 1.1 : 1.1 (—), initial concentration of the substrates [**1a**]= [cbz-**1a**]=1.0×10^{-4} mol dm^{-3}; [**1d**]=8.8×10^{-5} mol dm^{-3}.

to the reaction of **1a** yielding methyl benzoate as one of the products (Fig. 9). The results are also included in Table 1.

NMR Analysis of 6,6′-Bis(acylamino)-2,2′-bipyridine–Lanthanide Complexes. The formation and structure of the complex were also analyzed by ^{13}C NMR. In this experiment, we used hexyl-substituted **1e** (Fig. 1) and chloroform-*d* as a substrate and solvent, respectively, because of the low solubility of **1a** and **1d** in methanol-d_4 or chloroform-*d*. As the lanthanide cation, Lu^{3+} was also selected for NMR experiment due to its diamagnetic property and the largest complexability to the bipyridine substrate (Fig. 6).

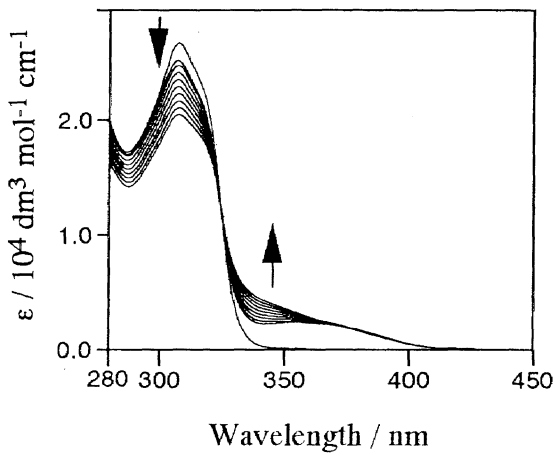


Fig. 9. Electronic spectra of **1d** (1×10^{-4} mol dm^{-3}) in methanol (H_2O content: 0.02—0.03%) before (first spectrum) and after addition of Lu^{3+} (2×10^{-5} mol dm^{-3}) and NaOH (2×10^{-5} mol dm^{-3}) at 30 °C (every 1 h).

Figure 10 shows the NMR spectra in the presence of different amounts of Lu^{3+} in chloroform solution of **1e** (3×10^{-2} mol dm^{-3}) at 30 °C. Upon the addition of a methanolic solution of Lu^{3+}, a set of ligand signals disappeared and different sets of signals were observed. As the [**1e**]/[Lu^{3+}] molar ratio increased, one set of signals became prominent and other signals practically disappeared above about [**1e**]/[Lu^{3+}]=1. Since a further increase of the [**1e**]/[Lu^{3+}] ratio little affected the spectra, we concluded that the observed set of signals was due to the 1 : 1 complex of **1e** and Lu^{3+}. The additional signals observed at lower concentration of Lu^{3+} were suggestive of the presence of a complex having lower Lu^{3+} composition. The changes in the bipyridine-carbon signals of the 1 : 1 complex ($|\Delta\delta|$) were about 0.59—4.58 ppm compared to those of the ligand alone. Also, the carbonyl-carbon signal also shifted from 165.70 to 169.22 ppm ($|\Delta\delta|$=3.52 ppm) upon complexation. These results indicated the coordination of the carbonyl oxygens and bipyridine nitrogens to the metal center in chloroform. To test the carbonyl-metal interaction further, we used ^{13}C-**1d** having ^{13}C-enriched carbonyl carbons, which allowed us to observe the carbonyl carbon signals in methanol-d_4 at low concentration (4×10^{-4} mol dm^{-3}). The carbonyl signals of the ligand and the complex were observed at 168.85 and 168.86 ppm, respectively, indicating that practically no interaction was observed between the carbonyl oxygens and the metal center in methanol. The electronic spectrum of the complex in methanol was confirmed to be identical to that in Fig. 8 (**b-2**). Unfortunately, the NMR spectra in the presence of NaOH could not be obtained due to relatively fast solvolysis and the

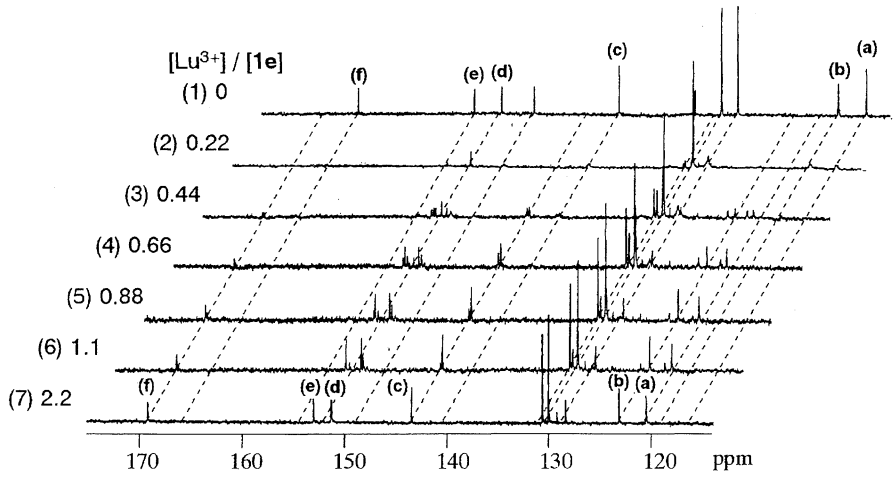


Fig. 10. ^{13}C NMR spectra ((1)—(6): 100.40 MHz, (7): 125.65 MHz) of **1d** in the absence and presence of Lu^{3+} (molar ratio) in $CDCl_3$ at 30 °C. A small amounts of methanolic Lu^{3+} was added stepwise to a chloroform solution of **1d** (3×10^{-2} mol dm^{-3}). Signals were assigned as follows; bipyridine carbons (**a**) 5,5′; (**b**) 3,3′; (**c**) 4,4′; (**d**) 6,6′; (**e**) 2,2′, and the carbonyl carbon (**f**).

low S/N (signal/noise) ratio.

Discussion

The Lanthanide-Catalyzed Amide Cleavage. Amide bonds are generally stable under physiological conditions, and the half-life of amide hydrolysis of glycylglycine at 25 °C was estimated to be 350 years or more.[1] However, the results presented here demonstrated that the amide bond of the substrate **1a** was cleaved within a few hours in the presence of a 0.2 equimolar amount of lanthanides in methanol at 30 °C to yield **2a** and L-phenylalanine methyl ester almost quantitatively. The reaction was exclusively the alcoholysis of the scissile amide bond, but no hydrolysis took place at all in the presence of appreciable amounts of water. Metal-promoted amide hydrolysis generally required a higher temperature in order to attain an appreciable rate,[8] and the amide cleavage reported here is comparable, or even faster, compared with those reported recently by Kostić et al.,[12,14,15] Mortellaro et al.,[13] or Yashiro et al.[18] Since the reaction of substrate **1a** in the absence of metal ions was found to be negligibly small, the scissile amide bond of the reactive substrate, itself, is not readily reactive. Therefore, an unusually fast reaction-rate and high specificity to the substrate structure should be ascribed not to the increased susceptibility of the scissile amide bond, itself, but to the high catalytic activity of the lanthanide cations.

Except for the reaction of **1a—c** with earlier lanthanides like Ce^{3+}, La^{3+}, and Sm^{3+}, the electronic spectra of the reaction mixture indicated the formation of the complex. Satisfactory Lineweaver–Burk plots for Lu^{3+} and Dy^{3+} confirmed the reaction to be the Michaelis–Menten type and that the rate-limiting step was the cleavage of the amide bond of the complex.

In the case of the earlier lanthanides, no clear absorption assignable to the complex was observed during the reaction of **1a**. The presence of the absorption of **2a** in the same region made it difficult to identify the absorption due to the complex. However, the less-reactive substrate **1d** showed clear absorption of the complex upon the addition of these metal ions. Furthermore, the reactions catalyzed by these metals and other lanthanide metals showed little difference in their substrate specificity, products, and other features. Since these metals have relatively fast reaction rates and smaller association constants with the model substrate **1d**, difficulty in assigning the absorption of the complex during the reaction of **1a** with these metals might be due to the low steady-state complex concentration in the system. Thus, it is quite likely that the reactions catalyzed by the earlier lanthanides also proceeded by formation of the complex.

The reactivity of the scissile amide bond of the complex was unusually high. The half-life times of the reaction were estimated from the k_2 values to be 2.0 and 10.5 min for the **1a**–Dy^{3+} and –Lu^{3+} system, respectively, at 30 °C (water content 0.03 w/w%). However, small amounts of water strongly suppressed the reaction. Lanthanide cations generally show high water affinity, and the presence of water may suppress complexation with the substrate. Indeed, the $1/K_M$ value of the Lu^{3+}-catalyzed reaction became smaller as the water content increased (Table 3). However, the rate constant of the methanolysis of the complex (k_2) also decreased. Therefore, the inhibitory effect of water cannot be explained simply by suppression of the complex formation, and the effect on the reactivity of the scissile amide bond of the complex must be considered.

Structure of the Complexes and Their Reactivity. To understand the high reactivity of the amide bond in the complex, the structure of the complex was examined. Since the bipyridine unit and the amide side chains were essential for the reaction, the amide units should play some role in the complex. The composition of the complex of the less-reactive substrate **1d** with lanthanide was shown to be 1 : 1, and a hyperchromic shift of the bipyridine-centered absorption upon complexation confirmed coordination of the bipyridine unit in methanol. The shifts of the ^{13}C NMR signals of the bipyridine unit upon complexation also confirmed the coordination of the bipyridine. However, coordination of the

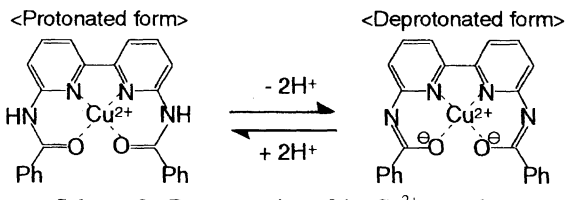
amide oxygens was indicated only for the **1e**–Lu^{3+} system in chloroform-*d*, but not in methanol-d_4 based on the ^{13}C NMR spectra. Though **1d** was shown to serve as a N_2O_2 quadridentate ligand by coordination of the two carbonyl oxygens and the two bipyridine nitrogens in methanol for the first-row transition metal cations, such as Cu^{2+} and Ni^{2+},[27—29] coordination of the amide units was not observed in the case of lanthanide cations in methanol.

However, the absorption band of these complex appeared at a slightly shorter wavelength side compared to that of the reactive substrate **1a** in methanol (Fig. 8a). The addition of NaOH to the less-reactive substrate **1d**–Lu^{3+} system induced a small red shift of the band (Fig. 8b), which also caused a large rate acceleration. Therefore, the active form of the complex might be different from that of the less reactive **1d**–Lu^{3+} complex. The amide protons of the Cu^{2+} complex of **1d** were highly acidic (acid dissociation constant pK_a=5.1 in H_2O),[27] and the amide-deprotonation (Scheme 2)[27] induced a slight red-shift of the absorption band.[27,28] The presence of an α-amino group further increased the acidity of the amide protons of the complex (acid dissociation constant pK_a for **1c**–Cu^{2+} complex was 3.1 in H_2O);[30] also, the α-amino group in the reactive substrate might enhance deprotonation of the complex. These results suggest that the amide-deprotonated complex is the active form of the complex, which nicely explains the role of the α-amino group in the reactive substrate, and the effect of NaOH on the less-reactive substrate **1d**. In the amide-deprotonated complex, a strong interaction of the negatively charged amide oxygens with lanthanide was expected. Coordination of the negatively charged carbonyl oxygens also explains the role of the two acylamino side chains observed in the substrate selectivity of the reaction. Lastly, it is worth noting that Yamada and other groups have reported efficient alcoholysis of highly distorted amide to form ester as a product, similar to what is reported in this paper.[31—35] Cyclic amides or amides having large substituents suffer considerable steric distortion of the amide moiety, which increase the reactivity of the amide bond.

Experimental

Materials. All solvents and chemicals were obtained commercially and were purified by routine methods if necessary. Dehydrated methanol was purchased from Kanto Chem. Ind. Co., Ltd. and was used without further purification or dehydration. Lanthanides were purchased from Aldrich Chem. Co. or Wako Pure Chem. Co. as hexahydrated chloride salts with the exception of Sc ($ScCl_3 \cdot H_2O$), La ($LaCl_3 \cdot 7H_2O$), and Ce ($CeCl_3 \cdot 7H_2O$).

Measurements. The electronic absorption spectra were measured with a Shimadzu UV-2200 spectrometer at 30 °C. The ^1H NMR spectra were recorded on a JEOL JNM-LA500 (500.00 MHz), a JNM-LA400 (399.65 MHz), or a JNM-GX270 (270.05 MHz) spectrometer in $CDCl_3$, CD_3OD, or $(CD_3)_2SO$, and ^{13}C NMR on the JNM-LA500 (125.65 MHz), the JNM-LA400 (100.40 MHz), or the JNM-GX270 (67.80 MHz) at 30 °C.



Scheme 2. Deprotonation of **1e**–Cu^{2+} complex.

Reactions. The reactions were carried out at 30 °C in quartz-made UV-cells or test vials prewashed by concentrated nitric acid, and were monitored spectrophotometrically. Unless specified, the sample solutions contained 1.0×10^{-4} mol dm^{-3} of the substrate and 2.0×10^{-5} mol dm^{-3} of lanthanide salts. The water content of the solutions, which was found to be critical to the reaction, was measured by a Hiranuma aquacounter AQ-7 and was controlled at the level of 0.01 w/w%. The amounts of the substrates, amino acids, and amino acid esters in the solutions were determined by HPLC. The amino acid esters were detected as their fluorescent derivatives by postcolumn OPA (Reagent: *o*-phthalaldehyde and 2-mercaptoethanol) method. The conditions were as follows: Hitachi L-6000 HPLC system with a ODS column (Merck LiChrospher RP-18 or Kanto Mightysil RP-18 GP: ϕ 4.6×150 mm, particle size 5 μm) and a Hitachi F-1080 fluorescence detector (*Ex*=350 nm, *Em*=500 nm)

Preparation of the Substrates. 6,6′-Diamino-2,2′-bipyridine (**dabp**) was prepared by two steps from 2,6-diaminopyridine according to the reported method.[36] The reaction of **dabp** with benzoyl chloride gave **2a** and **1d** after extraction and recrystallization from methanol–H_2O. Substrates **1a**–**1e**, ^{13}C–**1d**, **3**, and **4** were synthesized by the reaction of **2a**, **dabp**, 2-aminopyridine, and 2,6-diaminopyridine, respectively, with excess amounts of corresponding acids or *N*-benzyloxycarbonyl (cbz)-protected L-amino acids and subsequent deprotection with HBr/AcOH. Benzoic-carboxy-^{13}C acid (99 atom% ^{13}C) was purchased from Sigma Chemical Company. The structures and purity of the synthesized substrates were established by spectroscopic methods and analyses. The molecular structures are summarized in Fig. 1.

6-Amino-6′-benzoylamino-2,2′-bipyridine (2a). Yield 21%. Mp 152.7—155.0 °C. IR (KBr) ν (amide) 1294, 1531, 1675, ν_{N-H} 3335, 3444 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ=4.55 (s, 2H), 6.56 (d, 1H), 7.45—7.65 (5H), 7.86 (t, 1H), 7.97 (d, 2H), 8.02 (d, 1H), 8.38 (d, 1H), 8.65 (s, 1H). Found: C, 70.48; H, 4.85; N, 19.38%; *m/z* 290.1158. Calcd for $C_{17}H_{14}N_4O$: C, 70.33; H, 4.86; N, 19.30%; M^+, 290.1168.

6-Benzoylamino-6′-[*N*-(benzyloxycarbonyl)-L-phenylalanyl]-amino-2,2′-bipyridine (cbz-1a). Yield 89%. Decomp 160 °C. IR (KBr) ν (amide) 1258, 1297, 1524, 1670, ν_{N-H} 3304 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ=3.22 (d, 2H), 4.63 (1H), 5.13 (2H), 5.32 (1H), 7.2—7.4 (10H), 7.53 (t, 2H), 7.59 (t, 1H), 7.8—7.9 (2H), 7.92—8.01 (3H), 8.04 (d, 1H), 8.21 (d, 1H), 8.31 (s, 1H), 8.41 (d, 1H), 8.63 (s, 1H). Found: C, 71.66; H, 5.17; N, 12.05%. Calcd for $C_{34}H_{29}N_5O_4$: C, 71.44; H, 5.11; N,12.25%.

6- Benzoylamino- 6′- L- phenylalanylamino- 2, 2′- bipyridine (1a). Yield 92%. Mp 164.6—165.9 °C. IR (KBr) ν (amide) 1253, 1294, 1520, 1650, 1671, ν_{N-H} 3319, 3387 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ=2.83 (m, 1H), 3.40 (m, 1H), 3.81 (m, 1H), 7.2—7.3 (3H), 7.34 (t, 2H), 7.53 (t, 2H), 7.59 (t, 1H), 7.86 (2H), 7.97 (d, 2H), 8.04 (d, 1H), 8.08 (d, 1H), 8.32 (d, 1H), 8.40 (d, 1H), 8.65 (s, 1H), 9.97 (s, br, 1H). Found: C, 71.20; H, 5.30; N, 16.03%. Calcd for $C_{26}H_{23}N_3O_2$: C, 71.38; H, 5.30; N,16.01%.

6,6′-Bis(L-phenylalanylamino)-2,2′-bipyridine (1b). IR ν (amide) 1291, 1512, 1683, ν_{N-H} 3300, 3386 cm^{-1}. ^1H NMR (DMSO) δ=2.73 (2H), 3.10 (2H), 3.71 (2H), 7.20—7.28 (10H), 7.94 (2H), 8.01 (2H), 8.18 (2H). Found: C, 70.00; H, 5.87; N, 17.26%. Calcd for $C_{28}H_{28}N_6O_2$: C, 69.98; H, 5.87; N,17.49%.

6,6′-Bis(L-alanylamino)-2,2′-bipyridine (1c). IR ν (amide)

1292, 1521, 1680, ν_{N-H} 3346 cm^{-1}. ^1H NMR (DMSO) δ=1.25 (6H), 3.22 (4H), 3.52 (2H), 7.93 (2H), 8.02 (2H), 8.17 (2H). Found: C, 58.21; H, 6.00; N, 25.71%. Calcd for $C_{16}H_{20}N_6O_2$: C, 58.52; H, 6.14; N, 25.59%.

6,6′-Bis([carboxy-^{13}C]benzoylamino)-2,2′-bipyridine (^{13}C-1d). Yield 25%. Mp 283.1—284.5 °C. IR (KBr) ν (amide) 1247, 1521, 1625, ν_{N-H} 3303 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ=7.54 (t, 4H), 7.61 (t, 2H), 7.91 (t, 2H), 7.98 (m, 4H), 8.07 (d, 2H), 8.43 (d, 2H), 8.65 (s, 2H). ^{13}C NMR (125 MHz) δ=165.75 (carbonyl in $CDCl_3$), 168.83 (carbonyl in CD_3OD).

2-(L-Phenylalanylamino)pyridine (3). Mp 112.8—113.5 °C. IR (KBr) ν (amide) 1296, 1528, 1679, ν_{N-H} 3230, 3337 cm^{-1}. ^1H NMR (400 MHz, DMSO) δ=2.70 (m, 1H), 3.05 (m, 1H), 3.33 (s, 2H), 3.66 (m, 1H), 7.10 (t, 1H), 7.15—7.24 (1H), 7.24—7.32 (4H), 7.79 (t, 1H), 8.12 (d, 1H), 8.30 (d, 1H), 10.32 (s, br, 1H). Found: C, 69.89; H, 6.30; N, 17.24%; *m/z* 241.1220. Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41%; M^+, 241.1215.

2,6-Bis(L-phenylalanylamino)pyridine (4). Yield 49%. Mp 171.2—174.8 °C. IR (KBr) ν (amide) 1294, 1523, 1665, ν_{N-H} 3287, 3359 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ=2.75 (m, 2H), 3.38 (m, 2H), 3.74 (m, 2H), 7.10—7.50 (11H), 7.75 (t, 1H), 8.01 (d, 2H), 9.76 (s, 2H). Found: C, 68.65; H, 6.26; N, 17.46%; *m/z* 403.2023. Calcd for $C_{23}H_{25}N_5O_2$: C, 68.47; H, 6.24; N, 17.36%; M^+, 403.2008.

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