Efficient Lanthanide Catalysis in Aminoacyl-Transfer from the Bipyridine-Functionalized Amide-Substrate to Alcohols at Ambient Temperature

Koji Araki,* Takeshi Kajikawa, and Satoshi Kawaguchi
Institute of Industrial Science, University of Tokyo, 7-22-1 Roppongi, Minato-ku, Tokyo 106

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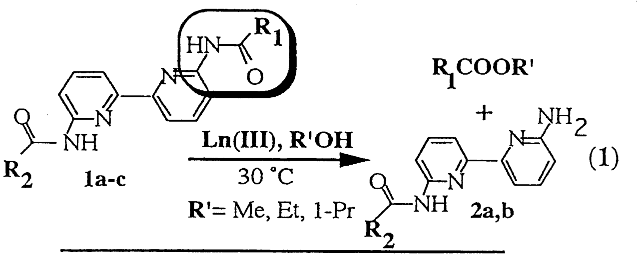
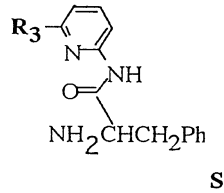
Lanthanide cations showed high catalytic activities in aminoacylation of alcohols by the amide-substrates having bipyridine as a metal chelation site at 30°C (first-order rate constants were 10^{-4} s^{-1} range at Ce^{3+}/substrate = 0.2), yielding corresponding amino acid esters almost quantitatively.

Transition metals show variety of physiological activities, many of which are ascribed to their high catalytic activities.[1] However, studies on the metalloenzyme-like activities of transition metals are mostly limited to the first and second transition series, and relatively few have been known as to the biological implication of lanthanides. Recently unique features of lanthanide catalysis have been reported,[2] and catalytic activities of lanthanides have become recent topics. In this letter, we report high catalytic activities of lanthanide cations in efficient aminoacylation of alcohol hydroxy groups at 30 °C as a model for aminoacyl-transfer reaction in biological systems.

Aminoacylation of hydroxy groups of biologically important molecules is not well understood yet, though it is the essential process in protein synthesis. Metal-catalyzed amide hydrolysis has been the subject of continuing interest, and large rate-enhancement was reported recently for the ligand functionalized amide substrates.[3] We previously found that one of the amide bonds of the Cu^{2+} complex of bis(aminoacylamino)-2,2'-bipyridine was efficiently cleaved in methanol to form amino acid ester under mild conditions.[4] Since the complex has the amide-O coordinated structure, use of lanthanide cations having high O affinity might be effective for the aminoacylation of alcohol hydroxy groups by solvolysis of amide bond. Based on this assumption, we tested the effect of lanthanides on the substrate **1a** having phenylalanyl group at one side of diaminobipyridine.



	R_1	R_2
1a	$-CH(NH_2)CH_2Ph$	-Ph
1b	$-CH(NH_2)CH_2Ph$	$-CH(NH_2)CH_2Ph$
1c	$-(CH_2)_2NH_2$	$-(CH_2)_2NH_2$



	R_3
3	-H
4	$-NHCOCH(CH_2Ph)NH_2$

Scheme 1.

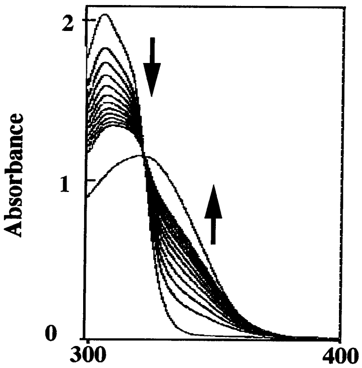


Figure 1. Spectral change of substrate **1a** ($1.0x10^{-4}$mol dm^{-3}) in methanol in the presence of $CeCl_3$ ($2.0x10^{-5}$ mol dm^{-3}) at 30 °C (H_2O content: 0.01 v/v%), the spectra were recorded every 1.5 min, though the last spectrum was that of **2a**.

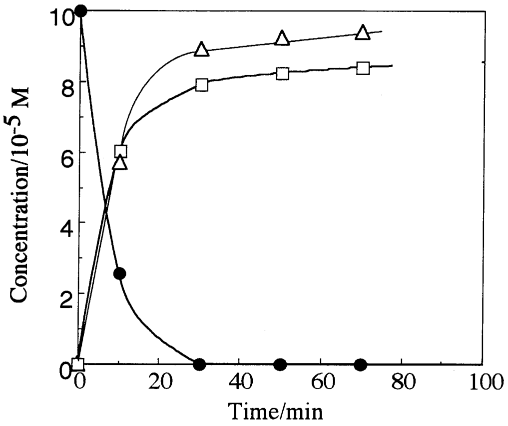


Figure 2. Time course of the reaction of the substrate **1a** (1 x 10^{-4} mol dm^{-3}) in methanol in the presence of $CeCl_3$ (2 x 10^{-5} mol dm^{-3}) at 30 °C (H_2O content:0.01 v/v%); ●: substrate **1a**; △: **4a**; and □: phenylalanine methyl ester.

The reaction of **1a** was carried out in methanol at 30°C.[5] Addition of catalytic amounts of $CeCl_3$ (Ce^{3+}/substrate molar ratio = 0.2) caused rapid spectral change of the solution with an isosbestic point at 322 nm (Figure 1), and the final spectrum became identical to that of **2a**. HPLC analysis of the reaction mixture (Figure 2) confirmed disappearance of the substrate **1a** within half an hour and concomitant formations of phenylalanine methyl ester and **2a**. Therefore, the amide bond with amino acid but not with benzoic acid was cleaved by methanolysis to yield phenylalanine methyl ester (88%) and **2a** (94%) almost quantitatively (Scheme 1), showing high catalytic activity of

Table 1. Rate constants(k_o) of solvolysis of **1a**

Solvent	Ln^{3+}	k_ox10^4/s^{-1}	Relative rate
Methanol[a]	Ce	4.80	=1
	Ce[b]	6.48	1.35
	La	5.38	1.12
	Eu	3.48	0.73
	Y	2.72	0.57
	Yb	3.24	0.67
	Sc	0	0
Ethanol[c]	Ce	5.96	1.24
	La	1.92	0.41
	Eu	5.28	1.10
	Y	3.04	0.63
	Yb	0.98	0.21
	Sc	0	0

[a]Water content 0.02 v/v%. [b]Water content 0.01 v/v%.

[c]Water content 0.01 v/v%. Substrate **1a** 1.0x10^{-4}mol dm^{-3}, $LnCl_3$ 2.0x10^{-5}mol dm^{-3}.

$CeCl_3$ in phenylalanyl-transfer from **1a** to methanol. However, no amide solvolysis of **1a** occurred at all in the presence of more than 4v/v% of water [6] (pH 6.0) under the similar conditions. Rate of decrease of the substrate **1a** (v)was linearly dependent on the substrate concentration, and the first-order rate constant (k_0) was determined to be 4.8 x 10^{-4} s^{-1} at 30 °C. It is worth noting that the rate constant obtained here for the Ce^{3+}-catalyzed methanolysis is even larger than those reported for the water-catalyzed hydrolysis of the ligand-functionalized substrates in the presence of Cu^{2+} or Zn^{2+}.[7] The rate (v) was also linearly dependent on the Ce^{3+} concentration at low Ce^{3+}/substrate molar ratio (0 - 0.5).

The reaction proceeded not only in methanol but also in ethanol and 1-propanol to give corresponding phenylalanine esters. Effects of other lanthanides including Y and Sc were also studied, and results are summarized in Table 1. Though Sc showed no catalytic activities at all, other lanthanides tested in this study showed excellent catalytic activities. Thus, it is shown that the system serves as a model for aminoacyl-transfer reaction in biological systems.

To clarify the role of metal chelation site in the substrate, substrates having different structures were studied in methanol in the presence of $CeCl_3$. In the case of substrate **1b** having two phenylalanyl groups, only one of the amide bond reacted to give ester and **2b**. Substrates **2a-c** bearing one amide bond or substrates **3** and **4** having pyridine instead of bipyridine did not react at all (Table 2). Therefore, bis(acylamino)-substituted bipyridine structure is indispensable as the ligand-functionalized amide-substrate for aminoacylation of alcohol by lanthanide ions.

Table 2. Reaction of various substrates in methanol at 30 °C

Substrate	k_ox10^4/s^{-1}	Relative rate
1a	4.80	= 1
1b	6.32	1.3
1c	0.05	0.01
2a-c	0	0
3	0	0
4	0	0

Substrate 1.0x10^{-4} mol dm^{-3}, $CeCl_3$ 2.0x10^{-5} mol dm^{-3}, water content 0.02 v/v%.

Low reactivity of **1c** having β-amino group indicated that presence of α-amino group on the acyl side chain is also essential for the reaction. No reactivity observed for CBZ-protected **1a** under the same conditions further supported the necessity of the α-amino group. Detailed studies on the catalytic activities of lanthanides are currently underway in our laboratory. The results presented here demonstrated that lanthanide metal ions served as an efficient catalyst in aminoacyl-transfer from the bipyridine-functionalized amide-substrate to alcohols at physiological temperature.

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5 Spectroscopic and elemental analyses established structure and purity of the substrates. Lanthanide chlorides were purchased from Aldrich Chem. Co. Alcohols were dried prior to use. The methanolic solution containing substrate (1x10^{-4} mol dm^{-3}) and $CeCl_3$ (2x10^{-5}mol dm^{-3}) was kept at 30°C, and periodically sampled solutions were analyzed by HPLC.

6 In the case of the Cu^{2+}-catalyzed reaction,[4] the reaction proceeded even in the presence of more than 40v/v% of water.

7 Rate constants for water-catalyzed hydrolysis of the ligand-functionalized tertiary amides or anilides in the presence of Cu^{2+} or Zn^{2+} were 10^{-4}-10^{-5} s^{-1} range at 50-70°C.[3]