Available online at www.sciencedirect.com
SCIENCE DIRECT®
Inorganica Chimica Acta 358 (2005) 947–956
Inorganica Chimica Acta
www.elsevier.com/locate/ica

Mild, rapid and selective alcoholysis of terpyridine-appended amide substrates by Cu^{2+}-catalysis: protonation state and reactivity of the complex

Satoshi Kawaguchi [1], Koji Araki *

Institute of Industrial Science, The University of Tokyo, 4-6-1 Komaba Meguro-ku, Tokyo 153-8505, Japan

Received 7 June 2004; accepted 4 October 2004
Available online 28 October 2004

Abstract

An amide bond of a terpyridine-appended substrate, 6-(L-phenylalanylamino)-2,2′:6′,2″-terpyridine (**2a**), was cleaved to yield phenylalanine methyl ester quantitatively in the presence of catalytic amounts of Cu^{2+} not only in methanol but also in aqueous methanol at 30 °C. The reaction proceeds via formation of an N_3O (three terpyridine nitrogens and one carbonyl oxygen) type 1:1 metal complex **2a**-Cu^{2+}. From spectral titration, the structure of the **2a**-Cu^{2+} complex was confirmed to have three different protonation states, i.e., **A** (non-deprotonated amide with α-ammonium), **D1** (deprotonated-amide with α-ammonium) and **D2** (deprotonated-amide with α-amino) states. Among them, the complex in the **D2** state was exclusively responsible for the observed mild, rapid and selective alcoholysis, showing the first-order rate constant of 6×10^{-3} s^{-1} or half-decay time of 2 min in methanol at 30 °C. Acidity of the amide proton was found to be higher than that of the ammonium proton in the complex, allowing formation of the highly reactive amide-deprotonated **D2** state in methanol even without addition of external bases. Factors contributing to the high reactivity of the complex were discussed.

Keywords: Amide alcoholysis; Aminoacylation; Terpyridine-appended amide; Copper complexes; Protonation states; Highly reactive amide bond

1. Introduction

Amide bond is the key connecting bond for construction of proteins and other biologically important molecules, and is sufficiently stable under physiological conditions [1]. Formation and cleavage of amide bonds are the essential biological reactions, which are efficiently catalyzed by enzymes [2,3]. However, simple acid- or base-catalyzed hydrolysis of unactivated amide bonds is far slower than the enzyme-catalyzed reaction, and development of artificial enzyme-like catalytic systems has been the subject of intense studies [4]. Use of metal ions, especially transition metal ions, as a catalytic center is the most common approach for this purpose. Varieties of metal-catalyzed amide hydrolysis have been reported [4] and role of the metal ions in the reaction has been discussed [5]. Alternative approach is to design novel reactive amide substrates. One such design is to introduce electron-withdrawing groups near the amide bond in order to increase electrophilicity of the amide carbonyl carbon [4e]. Introduction of metal coordination sites in the vicinity of the scissile amide bond has also been reported [4e]. In the latter case, role of the coordinated metal ion is to activate either amide substrate and/or coordinated water as a nucleophile [4c,5].

* Corresponding author. Tel.: +81 3 5452 6363; fax: +81 3 5452 6364.
E-mail address: araki@iis.u-tokyo.ac.jp (K. Araki).
[1] Present address: Technical Research Institute, Japan Society for the Promotion of Machine Industry (JSPMI) 1-1-12 Hachiman-cho, Higashi-Kurume, Tokyo 203-0042, Japan.

0020-1693/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ica.2004.10.008

These designs allowed large increase of the amide hydrolysis rate.

Recently, amide alcoholysis has become the subject of increasing interest partly because of recent reports from several groups on rapid amide alcoholysis under mild conditions [6–9]. For example, Brown and coworkers [6] reported rapid methanolysis of *N*-acetylimidazole and *N*-acetylpyrazole catalyzed by Co^{2+}, Zn^{2+}, and La^{3+} ions in methanol, showing 10^2–10^3 times of rate enhancement. In another case, Berreau et al. [7] reported that the amide methanolysis of Zn^{2+} complex of *N*-bis-2-(methylthio)-*N*-(6-pivaloylamido-2-pyridylmethyl) amine proceeded almost quantitatively over the course of ~2 h at 50 °C in the presence of equimolar amounts of tetramethylammonium hydroxide. Yamada et al. [8] also reported rapid alcoholysis of 3-pivaloyl-1,3-thiazolidine-2-thione having large steric strain, in which the increased reactivity was ascribed to the strain-induced rate enhancement of the amide bond. This twisted amide was also used as selective acylation reagents for primary hydroxyl groups. In the case of serine protease, the amide hydrolysis reaction proceeds in two steps: aminoacylation of the hydroxyl group of the serine residue (aminoacylation), which is the rate determining step, and subsequent hydrolysis of the corresponding ester (deacylation) [2]. Since the aminoacylation is the key step of the protease-catalyzed reaction, studies on the rapid alcoholysis can offer better insight into the enzymatic reaction [2].

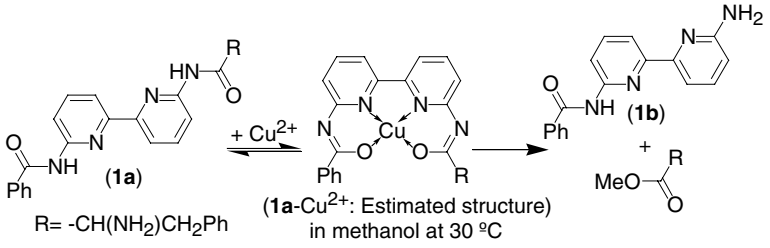
We previously reported that 6,6′-bis(acylamino)-2,2′-bipyridine substrates (**1**) underwent rapid alcoholysis of one of the amide bond under mild conditions [9]. The substrate was required to have 2,2′-bipyridine moiety, two amide bonds at 6,6′-position of the bipyridine, and α-amino group at the scissile amide bond side. In methanol at 30 °C, phenylalanyl side of the amide bond of 6-benzoylamino-6′-phenylalanylamino-2,2′-bipyridine (**1a**) was selectively cleaved within a few hours to yield phenylalanine methyl ester quantitatively in the presence of catalytic amounts of Cu^{2+} ions (Scheme 1). The reaction was shown to proceed via formation of an N_2O_2-type Cu^{2+} complex (**1a**-Cu^{2+}). Since the reaction of **1a** was the aminoacylation of alcohol hydroxyl group and proceeded rapidly under mild conditions, it is worth to extend the study further in order to shed light on the biologically important aminoacylation reaction. However, the presence of the two amide bonds within the substrate (**1**) made the analysis of the reaction systems too complicated for further study.

In this study, we designed new amide substrates and tried to understand the high reactivity of the complex. In the newly designed substrates, 6-acylamino-2,2′:6′,2″-terpyridines (**2**), one of the amide bond of **1** was replaced by the pyridine ring. Thus, the substrates have two structurally and functionally different units: the scissile amide unit with or without the α-amino group and the terpyridine (tpy) unit as a metal coordination site. Through the detailed examination of the alcoholysis of **2**, we will clarify the factors to control efficient cleavage of the amide bond under mild conditions (see Fig. 1).

2. Results

2.1. Alcoholysis of terpyridine-substituted amide substrates

Reaction of 6-L-phenylalanylamino-2,2′:6′,2″-terpyridine (**2a**) was performed in the presence of Cu^{2+} in methanol at 30 °C. Before addition of Cu^{2+}, the electronic spectrum of **2a** showed absorption at 303 nm (log ε = 4.31) due to the π–π* transition of the tpy moiety (Fig. 2). Upon addition of equimolar amounts of Cu^{2+}, this ligand-centered band shifted to 361 nm presumably due to formation of the **2a**-Cu^{2+} complex [9d]. The spectrum underwent rapid change to a slightly different one having the band at 374 nm. An isosbestic point at 361 nm was observed during the spectral change (Fig. 2), suggesting that the change was due to the single-step reaction of **2a** via **2a**-Cu^{2+}. The final electronic spectrum of the solution was identical to that of 6-amino-2,2′:6′,2″-terpyridine (**atpy**) in the presence of equimolar amounts of Cu^{2+}, and almost quantitative formation of phenylalanine methyl ester was confirmed by HPLC analysis (yield > 95 mol%). Therefore, the reaction of **2a** was the fast (half decay time of the substrate: $\tau_{1/2} = 4 \times 10^2$ s) and mild (30 °C in methanol) amide alcoholysis, which is similar to that for the bipyridine substrate **1a** (Scheme 2) [9].



Scheme 1. Methanolysis of bipyridine-type amide **1a** in the presence of Cu^{2+} in methanol.