Reaction of Zn(II) with a BINOL-amino-acid Schiff base: An unusual off-on-off fluorescence response

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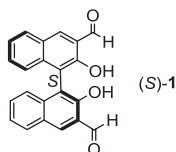[b] Department of Chemistry, University of Virginia, Charlottesville, Virginia 22904-4319, USA

ABSTRACT

An amino-acid based Schiff base (*S*)-**2** is prepared from the condensation of (*S*)-3,3′-diformyl BINOL (BINOL = 1,1′-bi-2-naphthol) with ʟ-valine in the presence of tetrabutylammonium hydroxide in methanol. This compound is found to exhibit off-on-off fluorescence response toward Zn^{2+}. The spectroscopic studies reveal that (*S*)-**2** reacts with 1 equiv Zn^{2+} to form a dimeric [2+2] complex with greatly enhanced fluorescence. Excess amount of Zn^{2+} might cause dissociation of this dimeric complex to give significantly reduced fluorescence.

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Previously, we reported that the 1,1′-bi-2-naphthol (BINOL)-based aldehyde (*S*)-**1** in combination with Zn^{2+} shows highly enantioselective fluorescent response toward certain chiral amino acids and other functional chiral amines.[1] Enantioselective fluorescent recognition of amino acids is potentially useful for high throughput chiral assay or biological imaging.[2] When (*S*)-**1** is used to interact with amino acids, we found that the fluorescence response can be significantly influenced by the amount of Zn^{2+} used. In order to gain a better understanding on this fluorescent recognition process, we have synthesized an amino acid-based Schiff base from (*S*)-**1** and studied its fluorescence responses toward Zn^{2+}. An unusual off-on-off fluorescence response toward Zn^{2+} is discovered. Our spectroscopic investigation has shed new light on the mechanism of this process. Herein, these results are reported.
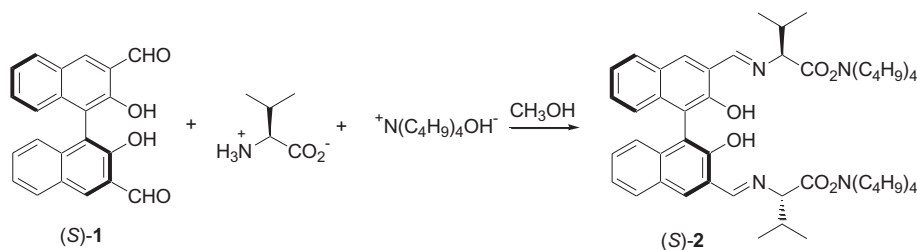
We carried out the reaction of (*S*)-**1** with ʟ-valine (2 equiv) and tetrabutylammonium hydroxide [$^+N(C_4H_9)_4OH^-$, 2 equiv] in methanol at 0 °C for 12 h (Scheme 1).[3,4] After removal of the solvent, the product (*S*)-**2** was obtained as an orange solid quantitatively. The ^1H NMR spectrum of this compound in CD_3OD solution gives two singlets at δ 8.68 and 8.11 for the two imine protons and the two 4,4′-protons of the BINOL unit respectively.

We studied the fluorescence response of (*S*)-**2** toward Zn^{2+} in methanol solution. (*S*)-**2** shows little fluorescence in methanol. When it was treated with $Zn(OAc)_2$, this compound exhibited greatly enhanced fluorescence at λ = 495 nm which reached maximum at 1 equiv of Zn^{2+} (I/I_0 = 55) (Fig. 1). When more than 1 equiv Zn^{2+} was added, a sharp decrease in the fluorescence intensity was observed. In addition, the emission maximum also underwent a red shift to λ = 524 nm in the presence of excess amount of Zn^{2+}. When the added Zn^{2+} was over 4 equiv, the fluorescence intensity did not undergo further change with increasing amount of Zn^{2+}.

We conducted a ^1H NMR spectroscopic study on the reaction of (*S*)-**2** with Zn^{2+} (Fig. 2). When (*S*)-**2** was treated with 1.0 equiv Zn^{2+}, it was completely converted to a new compound whose NMR signals suggest a symmetric structure. Two unusually upfield signals were observed at δ 0.16 (d, *J* = 6.8 Hz, 3H) and −0.24 (d, *J* = 6.8 Hz, 3H) for the diastereotopic methyl groups of the valine units. The original signals of (*S*)-**2** at δ 3.64 (d, *J* = 6.8 Hz, 1H) and 2.35 (m, 1H) for the two —CH— protons of the valine units are also shifted upfield upon treatment with 1.0 equiv Zn^{2+}. This indicates that both of the valine units of (*S*)-**2** have been moved to a shielding

(*S*)-**1**

Scheme 1. Condensation of (*S*)-**1** with Valine to Form the Schiff Base (*S*)-**2**.
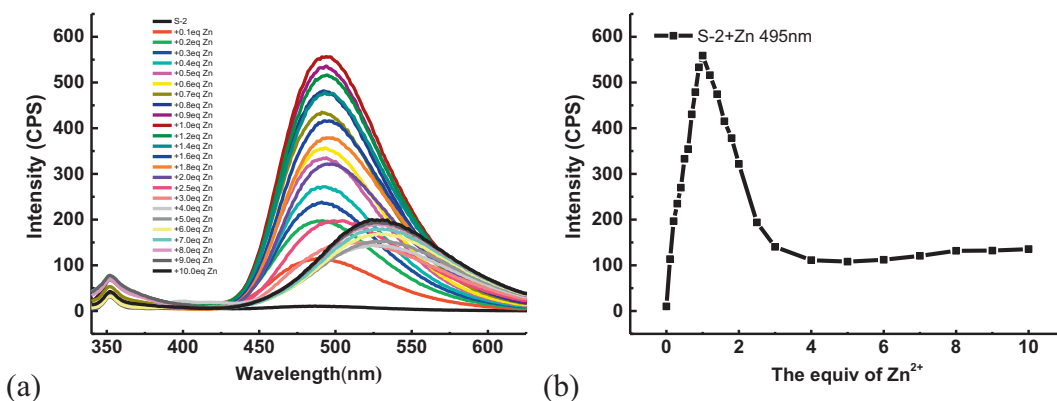

Fig. 1. a) Fluorescence spectra of (*S*)-**2** (1.0×10^{-5} M in CH$_3$OH) in the presence of Zn^{2+}. b) Plots of I$_{495}$ versus the equivalence of Zn^{2+}. (λ_{exc} = 320 nm, slit: 5/5 nm.)
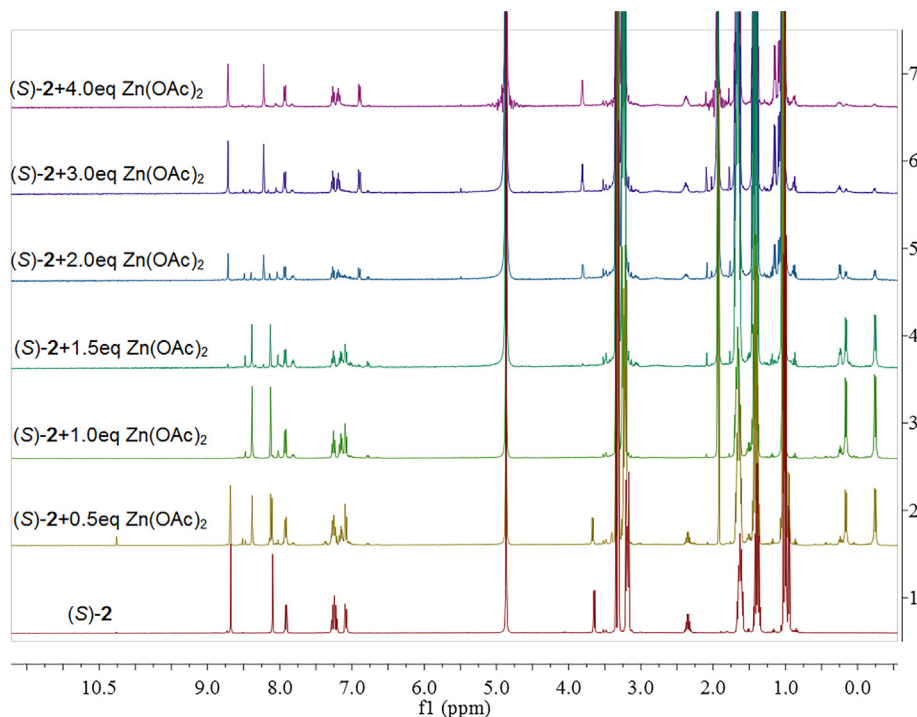

Fig. 2. ^{1}H NMR spectra of (*S*)-**2** (5.0 mM) titrated with Zn(AcO)$_2$ (0–4 equiv) in CD$_3$OD. (The ^{1}H NMR spectra were taken after the solution was allowed to stand at room temperature for 3 h.)

region upon Zn^{2+} coordination. We obtained the MALDI-TOF mass spectrum for the reaction mixture of (*S*)-**2** (1.0×10^{-3} M) with 1 equiv Zn^{2+} in methanol. It gave a prominent signal at m/z = 1689.85 which is consistent with the formation of the [2+2] complex **3** (calculated for **3**-2 N(C$_4$H$_9$)$_4$+H: 1689.86). An approximate molecular modeling structure of **3** (Spartan: Molecular Mechanics

– MMFF) is given in Fig. 3. It shows that in this dimeric structure, an isopropyl group of the valine unit on one BINOL unit could be located in the shielding region of another BINOL unit, leading to the observed upfield signals.

The ^{1}H NMR titration experiment in Fig. 2 further shows that when more than 1 equiv Zn^{2+} were added, the high field two
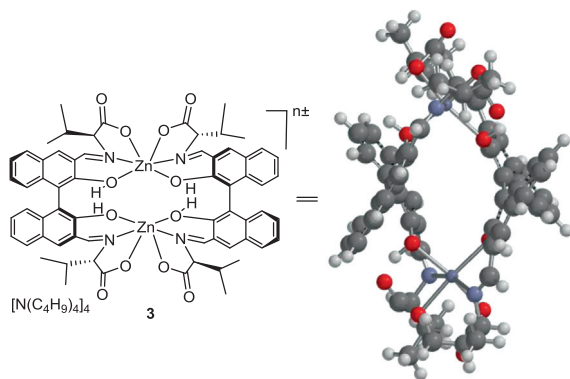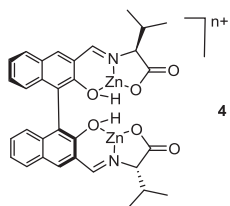
Fig. 3. Proposed complex **3** and its molecular model.

methyl signals were decreasing. At 4 equiv Zn^{2+}, a new compound was generated with the signals of **3** mostly disappeared. All of the upfield signals for the valine units of **3** have returned to the normal region in the newly formed compound. The aromatic signals are also almost the same as those of (S)-**2**. In the mass spectrum of the reaction mixture of (S)-**2** (1.0×10^{-3} M) with 4 equiv Zn^{2+} in methanol, a prominent peak at $m/z = 916.37$ is observed which supports the formation of **4** (calculated for **4**+HN(C$_4$H$_9$)$_3$+2CH$_3$OH: 916.34). In the above ^{1}H NMR titration experiment in CD$_3$OD, formation of a light yellow precipitate was also observed when (S)-**2** was treated with 4 equiv Zn^{2+}. When the isolated precipitate was dissolved in DMSO-d_6, it gave a ^{1}H NMR spectrum very similar to that of (S)-**2** with 1 equiv Zn^{2+} in either CD$_3$OD or DMSO-d_6 still with the two upfield doublets. This indicates that in the presence of excess amount of Zn(OAc)$_2$, part of the dimeric complex **3** dissociates to form the monoBINOL complex **4** and part of it precipitates out due to reduced solubility. As shown in Fig. 2, the ^{1}H NMR signals of **4** are very similar to those of (S)-**2** without the shielding effect of a second BINOL unit in **3**. No precipitate formation was observed in either the fluorescence experiments shown in Fig. 1 or the mass spectroscopic analyses when (S)-**2** (at 1.0×10^{-5} M and 1.0×10^{-3} M respectively) was treated with excess amount of Zn^{2+} which is attributed to the much lower concentration of (S)-**2** in these experiments than that in the NMR experiment. In the mass spectrum of (S)-**2** with 4 equiv Zn^{2+}, signals corresponding to **3** were also observed. Formation of the dimeric **3** from the amino acid-based Schiff base is similar to that observed for the reaction of an amino alcohol-based Schiff base with Zn^{2+}.[5] However, when the amino alcohol-based dimeric complex is treated with excess Zn^{2+}, no dissociation of the dimeric structure or fluorescence quenching is observed.[5] Thus, the dimeric structure from the reaction of the BINOL-amino acid Schiff base with Zn^{2+} is much more susceptible to dissociation than the corresponding BINOL-amino alcohol Schiff base.

On the basis of the above NMR and mass analyses, we propose the following explanation for the observed fluorescence response of (S)-**2** toward Zn^{2+}. Compound (S)-**2** is almost nonfluorescent because of (1) an intramolecular excited state proton transfer between the BINOL hydroxyl groups with the adjacent imine groups[6] and (2) the excited state isomerization of its imine double bond.[7] Upon coordination with a Zn^{2+}, the above two processes should be inhibited to give fluorescence enhancement. In addition, the reaction of (S)-**2** with 1 equiv Zn^{2+} forms the [2+2] complex **3** which could further increase its fluorescence due to the increased structural rigidity of this dimeric complex. When more than 1 equive Zn^{2+} is added, complex **3** could dissociate to form the monomeric complex **4** with lower fluorescence intensity due to the structural flexibility of the monomeric complex via rotation around the 1,1'-binaphthyl bond. This study provides a better understanding on the interaction of Zn^{2+} with the BINOL-based fluorescent sensor and should be useful for further development of this class of molecular receptors.

Acknowledgments

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.04.069.

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3. Synthesis and characterization of (S)-**2**: L-valine (69.1 mg, 0.59) and tetrabutylammonium hydroxide (0.59 mL, 1.0 M in methanol) were stirred for 10 min. Then methanol (20 mL) and (S)-**1** (100.0 mg, 0.29 mmol) were added. The reaction mixture was stirred at 0 °C for 12 h. After evaporation of the solvent, (S)-**2** was obtained as an orange solid quantitatively (297.3 mg). ^{1}H NMR (400 MHz, CD$_3$OD) δ 8.68 (s, 1H), 8.11 (s, 1H), 7.92 (d, J = 7.6, 1H), 7.30–7.21 (m, 2H), 7.08 (d, J = 8.2, 1H), 3.64 (d, J = 6.8, 1H), 3.17–3.10 (m, 8H), 2.39–2.31 (M, 1H), 1.63–1.54 (m, 8H), 1.41–1.32 (m, 8H),1.01–0.94(m, 18H). ^{13}C NMR (101 MHz, CD$_3$OD) δ 178.64, 166.59, 156.04, 136.57, 134.40, 129.90, 129.07, 128.78, 125.95, 124.08, 122.82, 117.76, 83.79, 59.44, 32.81, 24.74, 20.69, 20.54, 19.16, 13.96. HRMS: m/z calcd for C$_{64}$H$_{103}$N$_4$O$_6$: 1023.7872 [M+H$^+$]; found: 1023.8169. [α]$_D$ = −51.0 (c = 1.0 mg mL^{-1}, CH$_3$OH). Mp 154–156 °C.
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