Accepted Manuscript
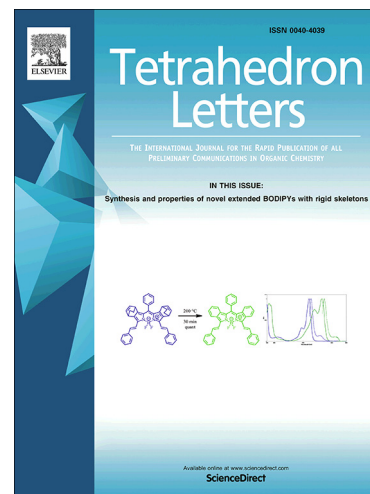
Synthesis of a new metal chelating amino acid: Terpyridyl-alanine

Tobias Schneider, Ivana Gavrilova, Nediljko Budisa

Please cite this article as: Schneider, T., Gavrilova, I., Budisa, N., Synthesis of a new metal chelating amino acid: Terpyridyl-alanine, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.02.037
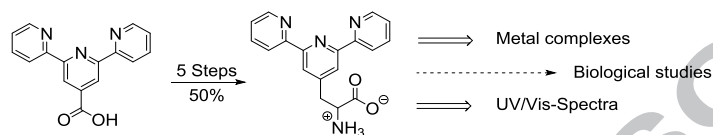
Graphical Abstract

Synthesis of a new metal chelating amino acid: Terpyridyl-alanine

Tobias Schneider, Ivana Gavrilova, and Nediljko Budisa

5 Steps
50%

⟹ Metal complexes

------► Biological studies

⟹ UV/Vis-Spectra

Synthesis of a new metal chelating amino acid: Terpyridyl-alanine

Tobias Schneider[a], Ivana Gavrilova[a,] and Nediljko Budisa[a,b*]

[a]Institute of Chemistry, Technical University of Berlin, Müller-Breslau-Str. 10, Berlin, 10623, Germany
[b]Department of Chemistry, University of Manitoba, 144 Dysart Rd, 360 Parker Building, R3T 2N2 Winnipeg, MB, Canada

ARTICLE INFO

ABSTRACT

In past years, terpyridine-containing substances have been found useful in polynucleotide chemistry and enzymatic engineering applications. Therefore, the construction of a noncanonical amino acid with a terpyridine side chain may offer promising features for *in vitro* and *in vivo* applications, such as the direct bio-expression of proteins with these substances as building blocks. The first step towards these goals is to establish a synthetic protocol for a terpyridine analog bearing an amino acid moiety. Here, we demonstrate the synthesis of terpyridyl-alanine for the first time in 5 steps and an overall yield of 50%. A metal complex with Fe(II) ions was prepared by crystallization of a protected terpyridyl-alanine derivative and analyzed by X-ray crystallography. Complex formation in aqueous solution was studied by ^{1}H-NMR, UV/Vis and fluorescence spectroscopy. The comparison of 5 transition metal ions revealed a metal dependent shift in the UV-absorption and a strong fluorescence in the presence of Zn(II) ions.

* Corresponding author. Tel.: +49-30-314-28960; fax: +49-30-314-28279; e-mail: budisa@chem.tu-berlin.de

1. Introduction

Terpyridines are a class of nitrogen-containing heterocycles consisting of three monocyclic pyridine rings. The most prominent terpyridine is 2,2':6',2''-terpyridine (terpy), which has attracted attention as promising functional moiety, particularly as tool for introducing many new chemical reactions and functions into biological systems. For example, the use of terpyridine derivatives as tridentate ligands for transition metals has been well documented in numerous studies[1]. Particular attention was paid to the catalytic properties of terpyridine-metal complexes especially to Ru(II) complexes [2], which act as photo- or electro-catalysts in economically important reactions like water oxidation[3] and CO_2 reduction[4], artificial photosynthesis[5] as well as in photodynamic therapy[6]. Additionally, terpy complexes are often used as a structural unit in the formation of artificial supramolecular frameworks.[7]
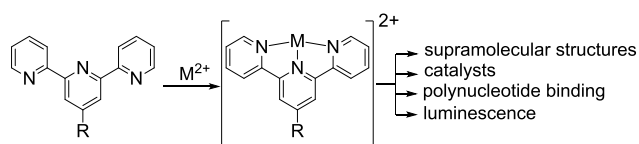
Figure 1. Applications of terpyridine-metal complexes

Complexes with a large variety of transition metal cations have been synthesized, some of which can be used as catalysts in reactions like [3+2]-cycloaddition, cyclopropanations (both Cu(II)[8]) and hydrosylilations (Fe(II)[9]). Furthermore, some complexes are known for their luminescent properties.[10]

Many applications of terpyridine-based complexes are found in (poly)nucleotide chemistry. A terpyridine based Zn(II) complex has been demonstrated to act as a catalyst for adenosine triphosphate (ATP) hydrolysis[11]. Zn-terpy complexes can be used as detectors for pyrophosphate by change in their fluorescence spectra.[12] Other complexes are potent RNA cleavage[13] and DNA binding agents[14]. For example, complexes with Ru(II)[15] and Pt(II)[16] were used to bind to DNA fragments and enable its detection due to shifts in their UV/Vis-absorption and luminescent properties.

In recent years, numerous studies have exploited terpy compatibility with biological systems for the production of artificial metalloenzymes, and remarkable results have been reported.[17] In the course of these experiments a terpy analogue was incorporated into a protein scaffold by means of strain-promoted azide-alkyne cycloaddition and was subsequently used as an enantioselective catalyst.[18] However, this method requires the use of a bulky linker, which might impair the formation of a defined binding pocket in those proteins.

An alternative to this approach would be a direct incorporation by orthogonalized protein translation[19], which uses non-canonical amino acids to directly integrate them into the amino acid sequence during ribosomal synthesis.[20] This approach has a great advantage of being efficient in living cells (*in vivo*) and avoids the use of linkers, as well as post-translational modifications. Orthogonalized translation has already enabled the *in vivo* incorporation of a small number of amino acids with metal chelating side chains without affecting the vitality and growth of the host cells. In particular, two derivatives of 8-hydroxyquinoline (1[21] and 2[22]), bipyridine (3)[23] and a pyrazole modified tyrosine (4)[24] were inserted into various functional proteins during *in vivo* biosynthesis.
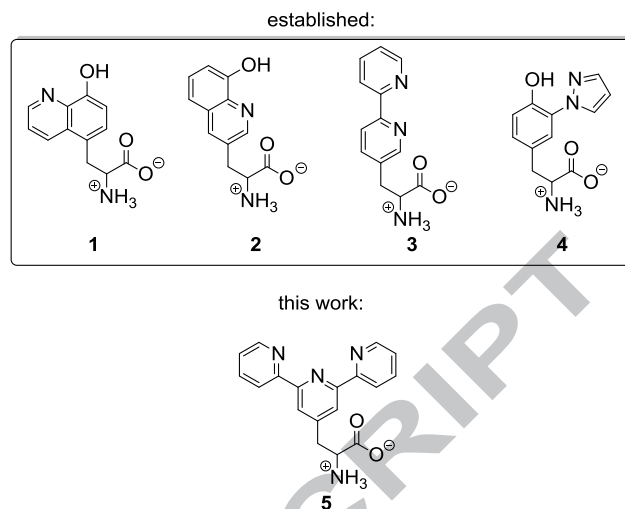
Figure 2. Genetically encoded amino acids (**1**-**4**) and terpyridyl-alanine (**5**)

This approach can be extended to terpy as a side chain of amino acids. The use of the above-mentioned, much-explored catalytic and functional properties of terpy-complexes in different protein scaffolds would allow us to expand the toolkit of genetically encoded amino acids for further applications (e.g. development of biocompatible catalysis) in complex protein structures.[25] In addition, it should offer an option to sustainably alter the chemical composition of whole cells and their structures, especially those that are not readily available for classical chemical modifications. The first step in this direction is certainly the reliable synthetic path for a terpyridine-containing amino acid. In this context, the aim of this work is to establish a synthetic protocol for the synthesis of terpyridylalanine (**5**) to support further microbiological and cell biological studies.

2. Results and discussion

To achieve the synthesis of terpyridyl-alanine (**5**) we envisioned the following synthetic strategy.
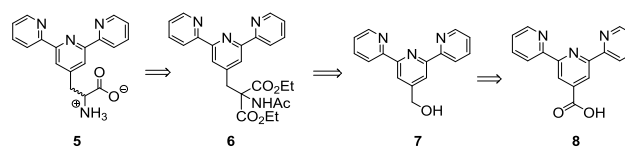
Scheme 1. Retrosynthetic approach for the synthesis of **5**

The amino acid moiety should be constructed by hydrolysis of the diethylacetamidomalonate group in **6**. The introduction of this group is commonly achieved by nucleophilic substitution, which requires a leaving group at the 4'-CH_2 position. The leaving group should be installed by conversion of alcohol **7**. Remarkably, we were not able to find a synthetic protocol for this compound. Therefore, we aimed to produce **7** from by reduction of acid **8**.

Carboxylic acid **8** was synthesized according to well established procedures described in the literature.[26] Alkylation to methyl ester **9** was performed in order to make the subsequent reduction more facile. The reaction was achieved using

SOCl₂/MeOH in a good yield. Reduction of **9** to alcohol **7** proved difficult at first. Attempts with LiAlH₄ in THF gave a green solution, which turned orange during workup and produced heterogeneous product with no significant amount of **7** present.

NaBH₄ is usually regarded as unsuitable for the reduction of esters but is known to be able to react with electron deficient esters.[27] Interestingly, under mild conditions NaBH₄ in ethanol only led to transesterification to the ethyl ester **10** (see scheme 2).
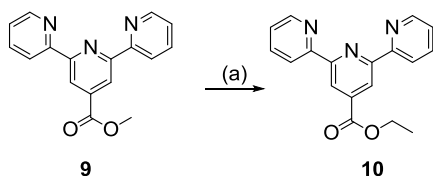

Scheme 2. Reagents & conditions (a) NaBH₄ (1 equiv), EtOH, 57%

Refluxing **9** with 3 equiv. NaBH₄ in EtOH for several hours led to partial conversion to alcohol **7**, while addition of LiCl to the mixture proved to be superior, producing alcohol **7** in excellent yields (Scheme 3).

PBr₃ was then used to convert alcohol **7** to bromide **11**. When anhydrous DCM was used as a solvent the reaction mixture turned blue and precipitation was observed. The desired product was detected after workup, albeit in a low yield (< 30%). The addition of water to the reaction mixture significantly improved this result and gave bromide **11** in a good yield of 83%. Addition of water produces HBr in the mixture due to its reaction with PBr₃. This will lead to the protonation of the nitrogen atoms in **7**. We suspect that this is necessary to suppress nucleophilic substitution on the freshly produced bromide. Therefore, insufficient amounts of acid will lead to multimers with *N*-alkyl-pyridinium units. These are known to show absorbance in the visible part of the electromagnetic spectrum[28], which would explain our observation of a deep blue color.

In the next step of our planned strategy, the reaction of bromide **11** with diethyl acetamidomalonate proceeded as anticipated to give compound **6** in a good yield (Scheme 3). Single crystals of this compound were prepared and analyzed using X-ray crystallography and confirmed our presumed structure (See supporting information).
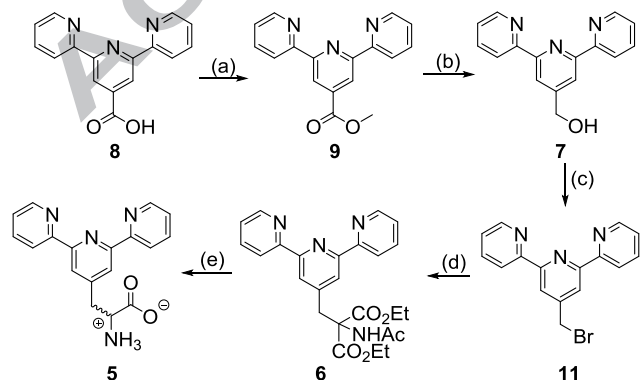
Scheme 3. Reagents & conditions (a) SOCl₂, MeOH, 89%; (b) NaBH₄, LiCl, EtOH, 96%; (c) PBr₃, H₂O, DCM, 83%; (d) Diethyl acetamidomalonate, NaH, DMF, 79% (e) 32% HCl, 90%

Racemic terpyridyl-alanine **5** was then produced by acidic hydrolysis of **6** (32% HCl, reflux, 4h) and purified by isoelectric precipitation. The amino acid was produced on a one gram scale with an overall yield of 50%.

Additionally, the synthesis of the enantiomericaly pure (*S*)-terpyridyl-alanine was attempted starting from the partial hydrolysis of **6**. Basic hydrolysis of the ethyl esters followed by decarboxylation under acidic conditions gave racemic *N*-acetyl amino acid **13**. Unfortunately, enzymatic resolution of this compound with acylase I from *A. melleus* and porcine kidney acylase was unsuccessful.
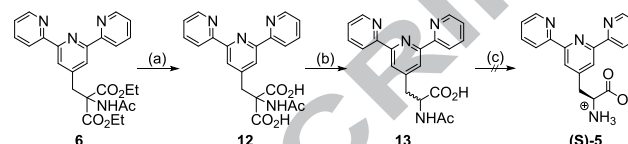

Scheme 4. Reagents & conditions (a) KOH, EtOH, H₂O, not isolated (b) 0.2 M HCl, 62%, (c) amino acylases, H₂O (pH 8)

Possibly, the binding pocket of these enzymes might be simply unsuitable for compound **13**. However, amino acylases are known to use metal cofactors (usually Zn²⁺) and to be inhibited by metal-chelating agents.[29] Nonetheless, even the addition of 0.5, 1 and 2 equiv. of ZnBr₂ into the reaction mixture did not improve enzyme activity.

The solubility of racemic terpyridyl alanine in water is relatively low; we determined the value of 56±8 μmol/L at pH 7. However, the solubility can be greatly increased by addition of acid or base, as well as suitable transition metal ions like Fe(II) or Ni(II) as a result of complex formation.

In addition, we have synthesized *rac-N*-acetyltepyridylalanine-methylester **14** to perform crystallization of this compound with a small number of transition metal salts. Acetyl and methyl protective groups at the amino acid moiety were installed to suppress its metal complexation and to create a peptide-like environment. We were able to obtain X-ray crystallographic data from crystals of **14** and of **14** with Fe(II) ions.
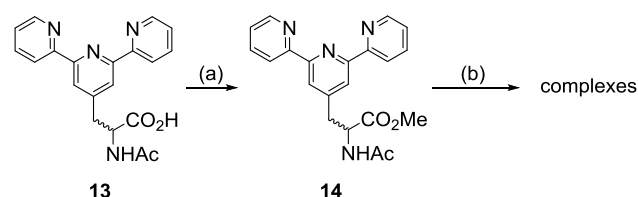
Scheme 5. Reagents & conditions (a) SOCl₂, MeOH, 59% (b) Metal salts, H₂O/MeCN
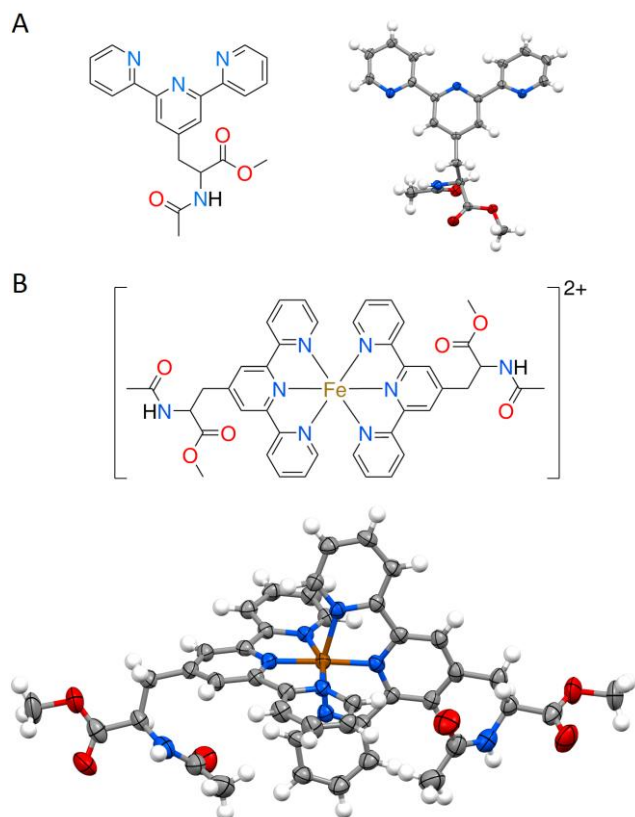
Figure 3. X-ray crystal structures for compound **14** A) and its Fe(II) complex (B). Carbon – grey; hydrogen – white; oxygen – red; nitrogen – blue; iron – brown. Sulfate (counter ion) and solvent molecules are not shown in B.

Co-crystallization of **14** with $FeSO_4 \cdot 7 \, H_2O$ led to dark red needles. As expected, a mononuclear bis complex was formed; the Fe(II) atom is coordinated by a distorted octahedral arrangement of six nitrogen atoms from two terpyridyl side chains. Additionally, we obtained light-brown needles when we co-crystallized 14 with $Ni(NO_3)_2 \cdot 6 \, H_2O$ or $Co(NO_3)_2 \cdot 6 \, H_2O$. The general structure of those complexes is very similar to the Fe(II) complex. However, their structures were not completely resolved (see supporting information).

We followed the stepwise addition of Zn(II) into a solution of **14** by ^{1}H-NMR spectroscopy. When less than 0.5 equiv. of Zn(II) were added, new signals for the bis complex ($[(14)_2Zn]^{2+}$) were detected without concurrent observation of signals for a mono-complex($[(14)Zn]^{2+}$). When more than 0.5 equiv. of Zn(II) were added, a set of signals for a mono-complex emerged and gained intensity with rising Zn(II) concentration. This assignment was further affirmed by additional DOSY experiments. The relative signal intensity of **14**, $[(14)Zn]^{2+}$ and $[(14)_2Zn]^{2+}$ with varying Zn(II)-concentration is shown in table 1.
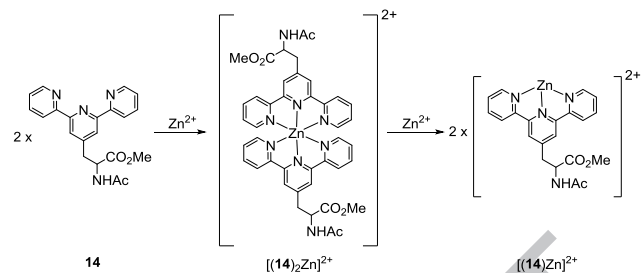
Scheme 6. Subsequent formation of $[(14)_2\text{-}Zn]^{2+}$ and $[(14)\text{-}Zn]^{2+}$ by addition of Zn(II) ions.

Compound	Equivalents of Zn(II)						
	0.2	0.4	0.5	0.6	0.8	1.0	1.5
Free **14**	61%	20%	0%	0%	0%	0%	0%
$[(14)Zn]^{2}$	0%	0%	0%	10%	22%	31%	39%
$[(14)_2Zn]^{2+}$	39%	80%	100%	90%	78%	69%	61%

Table 1. Relative signal intensity of **14** in unbound state, bound in $[(14)Zn]^{2+}$and $[(14)_2Zn]^{2+}$ with increasing concentration of Zn(II) ions determined by ^{1}H-NMR spectroscopy in a 1:1 D_2O:MeCN-d3 mixture. This data is consistent with previous values collected for other terpyridines.[30]

We recorded UV/Vis spectra of **5** and **14** with a small selection of transition metal ions to study the optical properties of the formed complexes. Previous studies reported a metal dependent absorbance of terpyridine complexes[31], which was fully confirmed in our experiments as well.
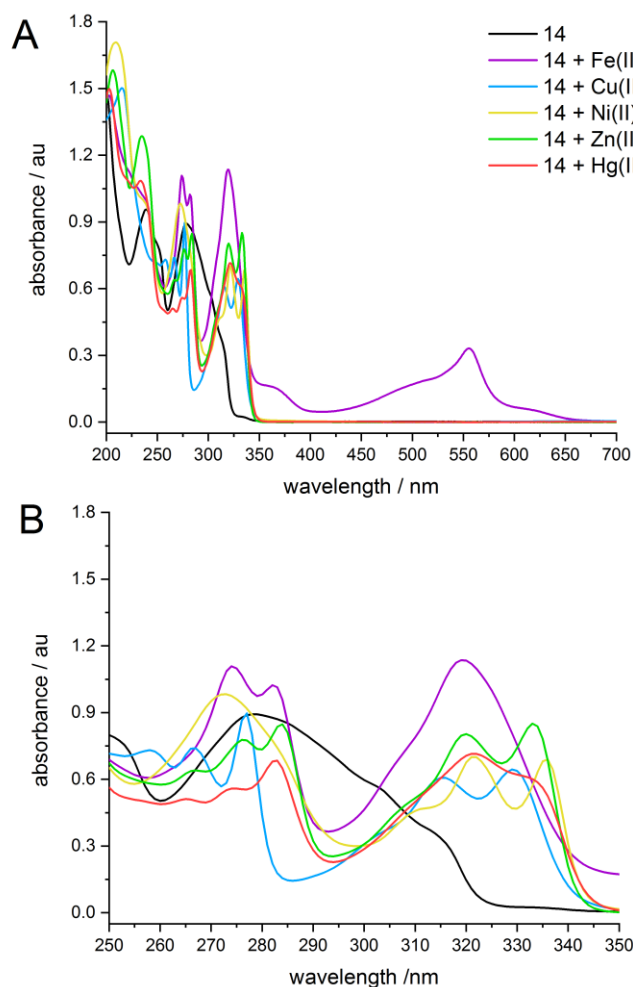
Figure 4. UV/Vis absorbance spectra of compound **14** alone and with addition of 5 transition metal ions recorded in 50/50 (v %) MeCN/aqueous phosphate buffer (pH 7). Ligand and metal ion concentration = $5 \cdot 10^{-5}$ mol/L. (A) Spectrum from 200 nm - 700 nm (B) Enlarged section between 250 nm - 350 nm

Addition of Fe(II) ions produced a deep purple color with a maximum absorption in the visible region at 555 nm (see figure **4** A), which is a well described reaction of terpyridines with Fe(II) ions and has been used for the colorimetric detection of ferrous ions.[32] The addition of Ni(II), Cu(II), Zn(II) and Hg(II) did not lead to absorbance in the visible region. However, in contrast to the free ligand, they exhibit one or multiple local absorbance maxima between 310 nm and 340 nm (See figure **4** B). For a given metal, the wavelength of these maxima was identical for compounds **14** and **5** (see supporting information). Metal specific shifts in absorbance were also observed in the spectral regions below 310 nm.

The recording of UV/Vis spectra with different metal:ligand ratios enabled us to qualitatively follow the complex formation by observing the gradual change in the absorbance profile. The concentration of **14** was held fixed at 50 μM, while the concentration of metal ions was raised progressively. We found that spectra with all metal cations continued to change from 0 μM to 25 μM. For Zn(II), there was only little change associated with the addition of more metal salt, which suggests the complete formation of a bis complex at a 2:1 ratio in solution (see Figure 5), which is consistent with our ^{1}H-NMR experiments. The slightly higher ratio of Zn(II) ions to **14** in the UV/Vis

experiments, which is required to form a bis complex, can be attributed to the lower absolute concentration, which disfavors complex assembly (50 μM in UV/Vis vs. 2.2 mM in ^{1}H-NMR). A further increase in concentration did not significantly alter the absorption curves, which suggests that the absorption profiles of $[(\mathbf{14})Zn]^{2+}$ and $[(\mathbf{14})_2Zn]^{2+}$ are fairly similar. Fe(II) and Hg(II) showed an analogous behavior to Zn(II), while Ni(II) absorption profiles already seized to change when a 25μM concentration was reached. However, for Cu(II), this process took up to 50μM (for more information see SI). All measurements were also performed with **5** and gave similar results.
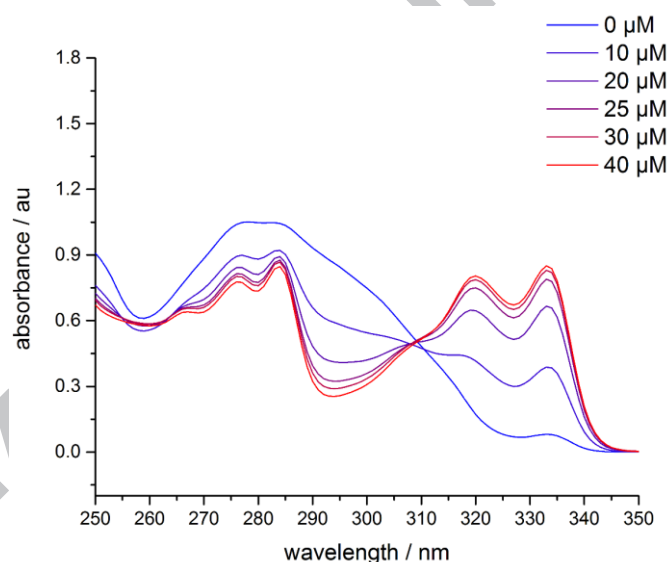

Figure 5. UV/Vis absorbance spectra of compound **14** with varying concentration of Zn(II) ions. Spectra show no significant changes after a Zn(II) concentration of 30 μM is exceeded.

We also found that samples of 5 and 14 show fluorescent properties when Zn(II) ions are added, which has been reported for other types of terpyridines as well.[12] This property could be of particular importance for noninvasive biological imaging in various microscopic settings. In particular, when exited at 275 nm, emission-maxima were detected at 342 and 355 nm. On the other hand, no fluorescence was observed for other metal ions under the identical experimental conditions. However, addition of Cu(II) ions to a solution of 5 and Zn(II) instantly led to a complete suppression of fluorescence. When Ni(II) was added instead of Cu(II), the fluorescence decreased at a slower pace, resulting in complete suppression after 1 hour.
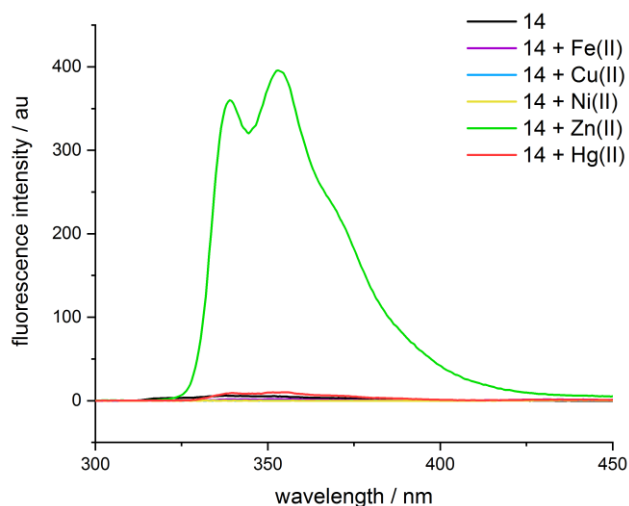
Figure 6. Fluorescence profiles of sole compound **14** (terpy-alanine with protected amino and carboxy functions) and with addition of **5** transition metal ions recorded in 50/50 (v %) MeCN/aqueous phosphate buffer (pH 7) upon excitation at 275 nm. Ligand and metal ion concentration = $1 \cdot 10^{-5}$ mol/L for Zn(II) and $5 \cdot 10^{-5}$ mol/L in all other cases.

Conclusion

We have found for the first time a synthetic route for the metal chelating amino acid terpyridyl-alanine. Our synthesis involves 5 steps with an overall yield of 50%. The structure of Fe (II) complexes obtained by co-crystallization of the protected terpyridyl-alanine derivative with $FeSO_4 \cdot 7\ H_2O$ revealed mononuclear bis complex. ^{1}H-NMR spectroscopy showed strong evidence for a concentration depended formation of bis and mono complexes of Zn(II). Complex formation was further studied by a UV/Vis spectroscopic investigation of 5 transition metal ions, which showed strong metal-specific features of absorption profiles. Finally, we also observed that Zn(II) complexes of terpyridyl-alanine exhibit fluorescent properties with the spectral emission maxima located at 340 and 360 nm. Microbial studies are ongoing and will be published elsewhere.

Crystallographic data

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC. CCDC-Deposition Numbers: 1881433 (**14**); 1881434 (**6**); 1881435 (**14+FeSO₄**)

Acknowledgements

References

[1]   J. P. Sauvage, J. P. Collin, J. C. Chambron, S. Guillerez, C. Coudret, V. Balzani, F. Barigelletti, L. de Cola, L. Flamigni, *Chem. Rev.* **1994**, *94*, 993.

[2]   a) G. Chelucci, R. P. Thummel, *Chem. Rev.* **2002**, *102*, 3129; b) A. Winter, G. R. Newkome, U. S. Schubert, *ChemCatChem* **2011**, *3*, 1384.

[3]   B. Mondal, M. G. Walawalkar, G. Kumar Lahiri, *J. Chem. Soc., Dalton Trans.* **2000**, 4209.

[4]   a) T. Yoshida, K. Tsutsumida, S. Teratani, K. Yasufuku, M. Kaneko, *J. Chem. Soc., Chem. Commun.* **1993**, *32*, 631; b) C. M. Bolinger, B. P. Sullivan, D. Conrad, J. A. Gilbert, N. Story, T. J. Meyer, *J. Chem. Soc., Chem. Commun.* **1985**, 796.

[5]   a) N. S. Lewis, D. G. Nocera, *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 15729; b) J. H. Alstrum-Acevedo, M. K. Brennaman, T. J. Meyer, *Inorg. Chem.* **2005**, *44*, 6802.

[6]   a) A. Frei, R. Rubbiani, S. Tubafard, O. Blacque, P. Anstaett, A. Felgenträger, T. Maisch, L. Spiccia, G. Gasser, *J. Med. Chem.* **2014**, *57*, 7280; b) F. Heinemann, J. Karges, G. Gasser, *Acc. Chem. Res.* **2017**, *50*, 2727.

[7]   a) H. Hofmeier, U. S. Schubert, *Chem. Soc. Rev.* **2004**, *33*, 373; b) R. Sakamoto, K.-H. Wu, R. Matsuoka, H. Maeda, H. Nishihara, *Chem. Soc. Rev.* **2015**, *44*, 7698.

[8]   a) T. Suzuka, K. Ooshiro, K.'y. Kina, *Heterocycles* **2010**, *81*, 601; b) H.-L. Kwong, W.-S. Lee, *Tetrahedron: Asymmetry* **2000**, *11*, 2299.

[9]   K. Kamata, A. Suzuki, Y. Nakai, H. Nakazawa, *Organometallics* **2012**, *31*, 3825.

[10] a) L. Flamigni, B. Ventura, F. Barigelletti, E. Baranoff, J.-P. Collin, J.-P. Sauvage, *Eur. J. Inorg. Chem.* **2005**, *2005*, 1312; b) G. Arena, G. Calogero, S. Campagna, L. Monsù Scolaro, V. Ricevuto, R. Romeo, *Inorg. Chem.* **1998**, *37*, 2763.

[11] C. Bazzicalupi, A. Bencini, A. Bianchi, A. Danesi, C. Giorgi, C. Lodeiro, F. Pina, S. Santarelli, B. Valtancoli, *Chem. Commun.* **2005**, 2630.

[12] L. J. Liang, X. J. Zhao, C. Z. Huang, *The Analyst* **2012**, *137*, 953.

[13] B. Linkletter, J. Chin, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 472.

[14] A. McCoubrey, H. C. Latham, P. R. Cook, A. Rodger, G. Lowe, *FEBS Letters* **1996**, *380*, 73.

[15] M. M. Milutinović, Ž. D. Bugarčić, R. Wilhelm, *New J. Chem.* **2018**, *42*, 7607.

[16] D. R. McMillin, J. J. Moore, *Coord. Chem. Rev.* **2002**, *229*, 113.

[17] T. K. Hyster, T. R. Ward, *Angew. Chem. Int. Ed. Engl.* **2016**, *55*, 7344.

[18] H. Yang, P. Srivastava, C. Zhang, J. C. Lewis, *ChemBioChem* **2014**, *15*, 223.

[19] a) C. C. Liu, P. G. Schultz, *Annu. Rev. Biochem.* **2010**, *79*, 413; b) R. A. Mehl, J. C. Anderson, S. W. Santoro, L. Wang, A. B. Martin, D. S. King, D. M. Horn, P. G. Schultz, *J. Am. Chem. Soc.* **2003**, *125*, 935.

[20] F. Agostini, J.-S. Völler, B. Koksch, C. G. Acevedo-Rocha, V. Kubyshkin, N. Budisa, *Angew. Chem. Int. Ed. Engl.* **2017**, *56*, 9680.

[21] X. Liu, J. Li, C. Hu, Q. Zhou, W. Zhang, M. Hu, J. Zhou, J. Wang, *Angew. Chem. Int. Ed. Engl.* **2013**, *52*, 4805.

[22] H. S. Lee, G. Spraggon, P. G. Schultz, F. Wang, *J. Am. Chem. Soc.* **2009**, *131*, 2481.

[23] a) J. Xie, W. Liu, P. G. Schultz, *Angew. Chem.* **2007**, *119*, 9399; b) H. S. Lee, P. G. Schultz, *J. Am. Chem. Soc.* **2008**, *130*, 13194.

[24] X. Liu, J. Li, J. Dong, C. Hu, W. Gong, J. Wang, *Angew. Chem. Int. Ed. Engl.* **2012**, *51*, 10261.

[25] P. J. Almhjell, J. H. Mills, *Curr. Opin. Struct. Biol.* **2018**, *51*, 170.

[26] E. M. Hahn, N. Estrada-Ortiz, J. Han, V. F. C. Ferreira, T. G. Kapp, J. D. G. Correia, A. Casini, F. E. Kühn, *Eur. J. Inorg. Chem.* **2017**, *2017*, 1667.

[27] a) N. Boechat, J. C. S. da Costa, J. de Souza Mendonça, P. S. M. de Oliveira, M. Vinícius Nora De Souza, *Tetrahedron Lett.* **2004**, *45*, 6021; b) H.-J. Zhu, C. U. Pittman, *Synth. Commun.* **2003**, *33*, 1733.

[28] M. Pal, S. Bagchi, *J. Chem. Soc., Faraday Trans. 1* **1985**, *81*, 2323.

[29] S. V. Story, A. M. Grunden, M. W. Adams, *Journal of bacteriology* **2001**, *183*, 4259.

[30] R. Shunmugam, G. J. Gabriel, K. A. Aamer, G. N. Tew, *Macromol. Rapid. Commun.* **2010**, *31*, 784.

[31] H. Hofmeier, G. R. Newkome (Eds.) *Modern terpyridine chemistry*, Wiley-VCH, Weinheim, **2006**.

[32] a) G. T. Morgan, F. H. Burstall, *J. Chem. Soc.* **1932**, 20; b) N. O. Laschuk, I. I. Ebralidze, S. Quaranta, S. T. W. Kerr, J. G. Egan, S. Gillis, F. Gaspari, A. Latini, O. V. Zenkina, *Mater. Des.* **2016**, *107*, 18.

Synthesis of a new metal chelating amino acid: Terpyridyl-alanine

Tobias Schneider[a], Ivana Gavrilova[a,] and Nediljko Budisa[a,b*]

[a]*Institute of Chemistry, Technical University of Berlin, Müller-Breslau-Str. 10, Berlin, 10623, Germany*
[b]*Department of Chemistry, University of Manitoba, 144 Dysart Rd, 360 Parker Building, R3T 2N2 Winnipeg, MB, Canada*

Highlights:

Terpyridine-containing compounds have higher compatibility with living cells

Amino acids with terpyridine side chains are potentially useful tools for the design of metalloenzymes

Reliable synthesis of terpyridyl-alanine for the first time in 5 steps and an overall yield of 50% is achieved

Various terpyridyl-alanine metal complexes are analyzed structurally and spectroscopically

---

* Corresponding author. Tel.: +49-30-314-28960; fax: +49-30-314-28279; e-mail: budisa@chem.tu-berlin.de