Sequence-Specific Oxidative Degradation of Tripeptides by a Cobalt(III) Complex Containing a Terpyridine Ligand

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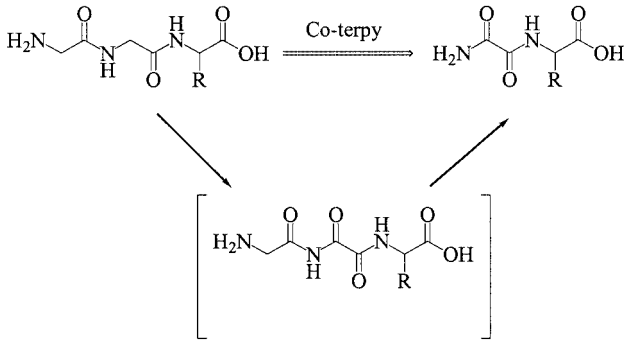
A sequence-specific oxidative degradation of an oligopeptide consisting of aliphatic amino acids was performed with a ternary cobalt(III) complex. Under aerobic conditions the reaction of [Co(CO_3)(OH)(terpy)] and an equimolar amount of tripeptide at 40 °C at pH 8.5 gave two fraction bands (**a** and **b**) with water and then two bands (**c** and **d**) with NaCl solution, respectively, after column separation. In the case of gly-gly-leu (ggl, **1**), [Co(gg′l)(terpy)] [**1a**, gg′l = glycyl(2-oxoglycyl)leucine], [Co(g′l)(terpy)] [**1b**, g′l = *N*-(2-oxoglycyl)leucine], [Co(ggl)(terpy)]$^{+}$ (**1c**), and [Co(terpy)$_2$]$^{3+}$ (**1d**) were obtained. The crystal structure of **1c**, which was the main product, revealed that the starting ggl ligand was cleaved to give a bis-amide compound, g′l, which might be generated by loss of N-terminal glycine and carbonylation of the α-carbon of the N-2 glycine residue. Although the source of the oxygen of the newly generated carbonyl group is not clear, gg′l is supposed to be an intermediate for g′l on the basis of time-dependent HPLC analyses. NMR investigation of other tripeptides [βala-gly-leu (**2**), gly-gly-phe (**3**), and gly-gly-ala (**4**)] containing a bulky C-terminal aliphatic side chain indicated the formation of the corresponding oxidation complexes. On the other hand, peptides containing a C-terminal glycine residue [gly-gly-gly (**5**) and phe-gly-gly (**6**)] or an N-2 β-alanine residue [gly-βala-leu (**7**)] did not give such a transformation product. The crystal structure of [Co(fgg)-(terpy)] (**6c**) revealed that the tripeptide is coordinated to cobalt with a tridentate N-terminal *N*-*N*-*N* geometry. Such sequence specificity demonstrated in the reaction of the aliphatic tripeptide complexes is interpreted by the interligand interaction between the side chain of the C-terminal amino acid residue and terpy.

Introduction

In oxidative transformation of proteins, which plays a major role in many oxidation processes within cells, the radicals generated damage both the peptide backbone and the side chains.[1] In C−N bond dissociation during the peptide degradation, active oxygen species, such as HO$^{\cdot}$, and HOO$^{\cdot}$, attack at the α-position of the amino-acid residues to generate a carbon-centered radical.[2,3] Once formed, this reacts further with molecular oxygen to form peroxy radicals, which expel superoxide species to give carbocations, and are then hydrolyzed to give the corresponding alcohols or are deprotonated to give the corresponding imines.[4,5] Some iron edta complexes attached to cysteine residue of proteins site-specifically cleaved the peptide backbone, in which the iron-hydroperoxo species directly attacked the amide carbonyl moiety.[6] Recently, we have reported selective α-hydroxylation of the C-terminal amino-acid residue of a dipeptide (DP) mediated by a ternary cobalt complex with the 2,2′:6′,2′′-terpyridine (terpy) ligand under aerobic conditions, which is a model reaction for the peptidylglycine α-hydroxylating monooxygenase (PHM) reaction.[7] The terpy ligand is known to accelerate the oxidative transformation of another ligand coordinated *trans* to it,[8] and a ternary complex with the terpy ligand could therefore cause the oxidative degradation of a peptide compound. Herein, we describe a sequence-specific oxidative degradation of tripeptides (TPs), such as GGL (**1**), BGL (**2**), and GGF (**3**), whose reactivities are compared with the cases of GGA (**4**),



Scheme 1. Oxidative cleavage of tripeptides

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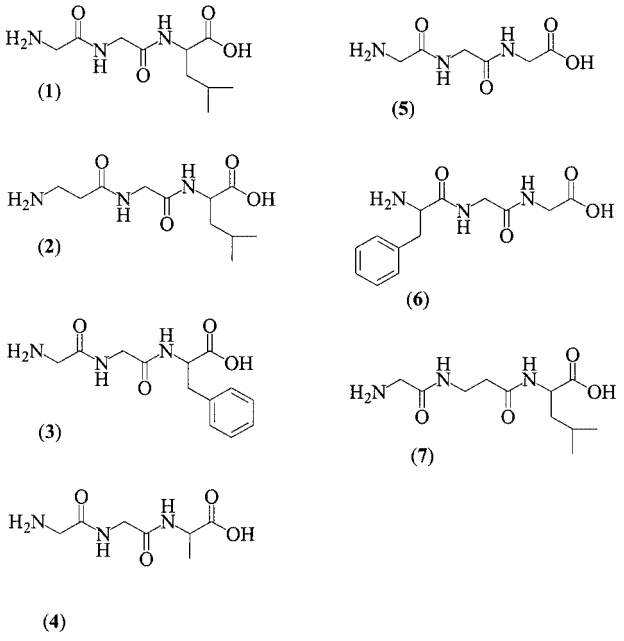
GGG (**5**), FGG (**6**), and GBL (**7**) (Scheme 1 and 2). Upon the formation of the ternary cobalt(III) complexes, some tripeptides containing bulky aliphatic amino acids at the C-terminus are cleaved to give unprecedented dipeptide derivatives on account of the assistance of the terpy ligand.



Scheme 2. Tripeptides employed: gly-gly-leu (GGL; **1**), βala-gly-leu (BGL; **2**), gly-gly-phe (GGF; **3**), gly-gly-ala (GGA; **4**), gly-gly-gly (GGG; **5**), phe-gly-gly (FGG; **6**), gly-βala-leu (GBL; **7**)

Results and Discussion

Characterization of the Ternary Complexes

The reaction of the cobalt carbonyl complex and an equimolar amount of tripeptides **1**−**7** was carried out at pH 8.5 and 40 °C in an aqueous solution for 10 h under aerobic conditions. After passing the reaction mixture through a cation-exchange column, four fractional bands containing cobalt(III) complexes (**a**−**d**) were obtained (see Exp. Sect.). In order to clarify the structure of the cobalt(III) complexes isolated from the column separation a ^{1}H NMR spectroscopic investigation was carried out. Transformation of the TP ligand was observed in the ternary complexes prepared from **1**−**3** (Table 1). Complex **1a** shows α-proton peaks of N-1 (N-terminal) at δ = 2.60 and 2.90 ppm, and that of the C-terminal (N-3) leucine at δ = 5.07 ppm, but no peaks corresponding to those of the N-2 (central) residue. Neither the α-proton peaks corresponding to N-1 nor N-2 glycine residues were detected in the spectrum of complex **1b**, while that of N-3 was detected at δ = 5.07 ppm. In complex **1c**, all α-proton peaks of GGL were detected. The spectroscopic and column behavior of the cobalt complexes prepared from BGL (**2**) and GGF (**3**) was similar to that of GGL (**1**), indicating that transformation of the glycine moieties takes place in the peptide backbone of **1a**, **1b**, **2a**, **2b**, **3a**, and **3b**.

Fortunately, a single crystal of **1b** suitable for X-ray analysis was obtained from the column eluent by allowing it to stand at room temperature. The crystal structure of **1b** (Figure 1)[11] reveals an unprecedented formation of the bisamide compound *N*-(2-oxoglycyl)leucine (G′L), as expected from the NMR spectroscopic data. The crystal data are summarized in the Exp. Sect. In order to determine the species substituted at the α-position of the N-2 residue in G′L, a positive-ion ESI mass spectrum of **1b** was measured. The obtained prominent peaks at *m*/*z* = 492.2 and 514.2 corresponding to the $[\{Co(g'l)(terpy)\} + H]^+$ and $[\{Co(g'l)(terpy)\} + Na]^+$ ions, respectively, indicate that the newly substituted atom is oxygen, although the oxygen source is not yet clear. Formation of a [Co(g′l)(terpy)] complex is also supported by the elemental analysis. Moreover, the relatively short bond length [1.22(2) Å] between the α-carbon [C(16)] and the newly generated atom [O(1)] and the sp^2 character around C(16) [O(1)−C(16)−N(4) = 128(1)° and O(1)−C(16)−C(17) = 119(1)°] in the crystal structure of **1b** indicate the formation of a C=O group at the α-position of the N-2 residue. The cleavage of the amide bond between the N-1 and N-2 residues in the GGL ligand took place in **1b**, but the α-protons of N-1 and N-3 moieties still remain in **1a** and **1c**.

In the case of GGA (**4**), complete column separation of **4a** and **4b** was not accomplished, although their ^{1}H NMR spectra indicated formation of the corresponding cleavage product. Due to the smaller size of the C-terminal side chain in **4** in comparison with the those in **1**−**3**, it is hard to separate complexes **4a** and **4b**. In the cases of some tripeptide ligands, for example GGG (**5**), FGG (**6**), and GBL (**7**), which have either an N-terminal glycine or N-2 β-alanine moiety, the main product was the $[Co(tp)(terpy)]^+$ complex (**5c**, **6c**, or **7c**), accompanied by a small amount of $[Co(terpy)_2]^{3+}$ (**d**).[9] Transformation compounds corresponding to **a** or **b** were not obtained. The ^{1}H NMR spectral patterns of the N1-, N2- and N3-α-proton moieties in **5c**, **6c**, and **7c** are very similar to that of **1c**. On the basis of the spectral analogy among the complexes **1c**−**7c**, the coordination mode of the tripeptide to cobalt is an N-terminal *N*-*N*-*N* form (N-1 terminal amine nitrogen, N-2 amide nitrogen, N-3 amide nitrogen), which agrees well with the empirical rule.[10,11] The tridentate coordination of FGG in **6c** is indicated by the upfield shift of the α-protons of the C-terminal glycine moiety (δ = 2.52 and 2.62 ppm) in comparison with the tetradentate coordination of FGG in $[Co(NH_3)_2(fgg)]$, where the corresponding protons are observed at δ = 4.00 ppm.[12] A complex-formation shift was not observed in the C-terminal α-position of **1c**−**7c**. The single-crystal structure of **6c**, shown in Figure 2, reveals that the cobalt ion is coordinated by two tridentate ligands, terpy and FGG, in which the coordination mode of the FGG to cobalt is an N-terminal *N*-*N*-*N* geometry, as expected from the NMR spectroscopic data. Moreover, the benzene ring of the N-terminal amino-acid side chain is very close to the terpy ring, with a distance of about 3.45 Å (the closest interatomic carbon-carbon distance).

Table 1. NMR spectroscopic data for the ternary complexes

Tripeptide	Column Band	N-terminal α-H	N-terminal β-H	N-2 (center) α-H	N-2 (center) β-H	C-terminal α-H	C-terminal β-H
ggl	**a**	2.60 (d)	–	not detected		5.07 (q)	2.12 (m)
(**1**)		2.90 (d)					2.38 (m)
	b	not detected		not detected		5.07 (q)	2.10 (m)
							2.40 (m)
	c	3.42 (s)	–	5.28 (s)	–	4.00 (q)	1.34 (m)
bgl	**a**	2.30 (m)	1.75 (m)	2.13 (d)	–	4.95 (m)	2.08 (m)
(**2**)			1.85 (m)				
	b	not detected		not detected		5.01 (q)	2.00 (m)
							2.51 (m)
	c	hard to identify					
ggf	**a**	2.31 (d)	–	not detected		5.17 (m)	3.63 (dd)
(**3**)		2.97 (d)					4.43 (dd)
	b	not detected		not detected		5.22 (m)	3.67 (dd)
							4.45 (dd)
	c	3.30 (dd)	–	4.57 (dd)		2.31 (dd)	2.59 (dd)
		3.38 (dd)		4.69 (dd)			2.95 (dd)
gga	**a** + **b**	mixture of complexes (hard to identify)					
(**4**)	**c**	3.50 (dd)	–	4.75 (d)	–	2.50 (b)	0.41 (d)
				4.81 (d)			
ggg	**a**	not isolated					
(**5**)	**b**	not isolated					
	c	3.49 (s)	–	4.68 (s)	–	2.85 (s)	–
fgg	**a**	not isolated					
(**6**)	**b**	not isolated					
	c	3.84 (t)	2.78 (dd)	4.52 (d)	–	2.52 (d)	
			3.39 (dd)	4.72 (d)		2.62 (d)	
gbl	**a**	not isolated					
(**7**)	**b**	not isolated					
	c	3.23 (d)	–	2.65 (t), 4.16 (t)		3.53 (m)	1.17 (m)

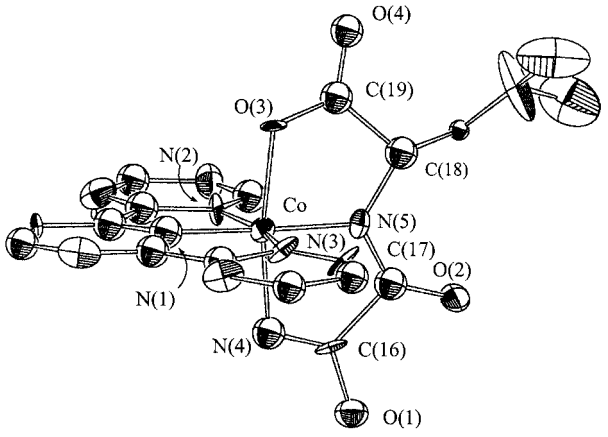


Figure 1. Molecular structure of the transformation compound [Co(g′l)(terpy)] (**1b**); hydrogen atoms are omitted for clarity; selected bond lengths (Å) and angles (°): Co−N(1) 1.87(1), Co−N(2) 1.99(1), Co−N(3) 1.93(1), Co−O(3) 1.92(1), Co−N(4) 1.91(1), Co−N(5) 1.88(2); O(3)−Co−N(4) 168.7(5), O(3)−Co−N(5) 84.0(6), N(1)−Co−N(5) 178.6(6), N(2)−Co−N(3) 162.0(7)

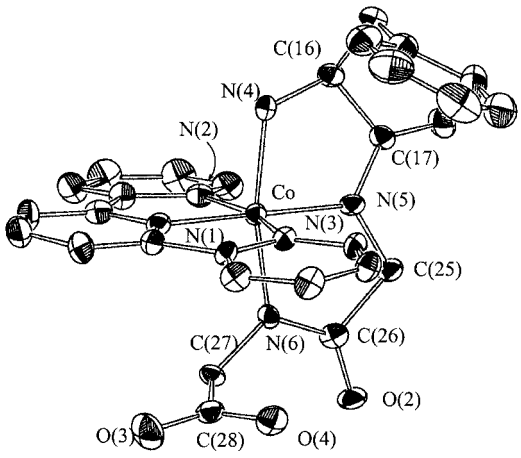


Figure 2. Molecular structure of the tripeptide compound, [Co(fgg)(terpy)] (**6c**); hydrogen atoms are omitted for clarity; selected bond lengths (Å) and angles (°): Co−N(1) 1.850(8), Co−N(2) 1.974(8), Co−N(3) 1.934(9), Co−N(4) 1.961(9), Co−N(5) 1.887(8), Co−N(6) 1.942(9); N(4)−Co−N(6) 166.5(3), N(4)−Co−N(5) 83.5(4), N(1)−Co−N(5) 180.0(4), N(2)−Co−N(3) 164.9(3)

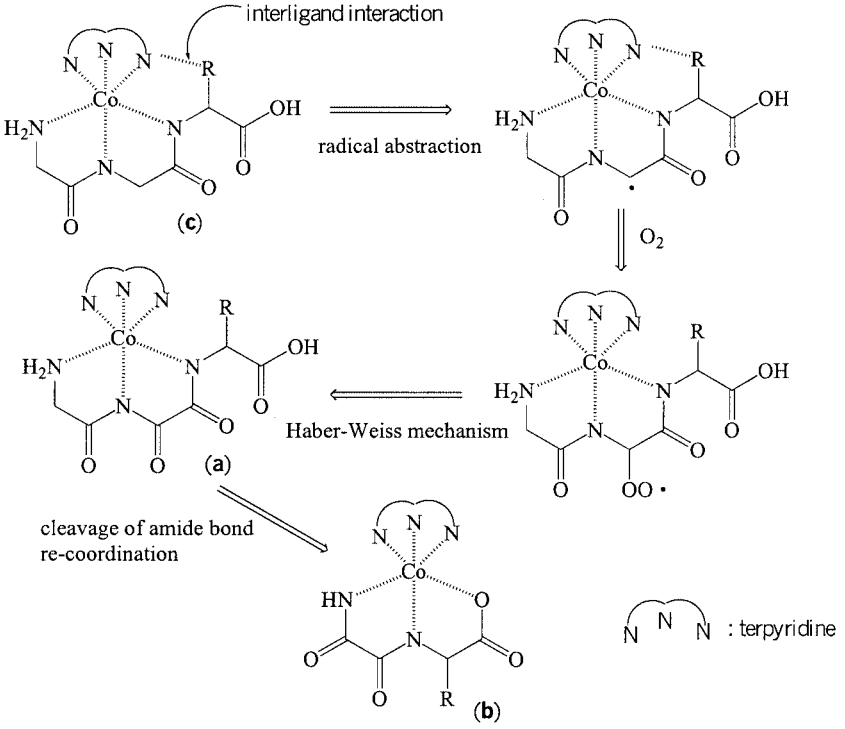
Oxidative Degradation Pathway of the Peptide Bond

In this reaction, **1c** is considered as the starting compound for **1a** and **1b**, because the yield of **1c** decreases after a long reaction time. HPLC analysis of the reaction mixture also revealed that it is the primary product of the complex formation with Co-terpy and GGL. Similar time-dependent product distributions found by HPLC were observed in the reaction with BGL (**2**) and GGF (**3**). The reaction pathway from **1c** to **1b** is obviously different from the cobalt(III)-promoted hydrolysis, which generally gives both amine and carboxylic compounds.[11,13,14] The G′L ligand in **1b** is gen-

erated by the loss of N-terminal glycine and oxygenation of the α-position of the N-2 glycine residue of the starting GGL. The structure of complex **1a**, a plausible intermediate for **1b**, is suggested by the positive ion ESI mass spectrum: The prominent peaks at m/z = 549.2 and 571.0 indicate the formation of a tripeptide complex containing glycyl(2-oxoglycyl)leucine (GG′L), which is consistent with the NMR spectroscopic data (no signal of N-2 protons in Table 1). Such an unprecedented cleavage reaction takes place only in tripeptides (**1**−**4**) with an alkyl side-chain at the C-terminal amino-acid residue, and not in the C-terminal glycine (**5** and **6**) and N-2 β-alanyl compounds (**7**). These results indicate that the oxidative degradation of the tripeptide ligand mediated by the ternary cobalt(III) terpy complex occurs sequence-specifically.

Although the detailed mechanism for this cleavage reaction is not yet clear, the downfield shift of the α-protons of the N-2 glycine moiety in **1c** relative to the metal-free GGL (δ = 4.01 and 4.03 ppm), might be essential for the reaction. Since the GGL ligand in **1c** strongly coordinates to the metal center in an N-terminal N-N-N manner, a nucleophile in aqueous solution (e. g. hydroxide ion) prefers to attack an electro-deficient state at the N-2 moiety. The α-proton of the glycine moiety is known to be easily abstracted to give a glycyl radical, whose stability is explained by the captodative effect.[15] In the oxidative transformation of the dipeptide ligand previously reported, the downfield shift of the α-proton attached to the N-2 residue of the dipeptide is important for the abstraction of the proton.[7] The radical intermediate generated at this position is attacked by dioxygen to give a peroxy radical, which decomposes by the Haber−Weiss mechanism to give the α-carbonyl compound **1a** because the transition metal-terpy system acts as a redox center for the electron-transfer reaction (Scheme 3).[8] Such an oxidative transformation of a methylene moiety adjacent to an amide group has also been reported in the case of iron(III) and cobalt(III) complexes with an *N*-(picolyl)picolinamide ligand under aerobic alkaline conditions, although the reaction mechanism is also unclear.[16] In aqueous conditions the amide complex **1a** might be hydrolyzed to give **1b**. Under anaerobic conditions, however, the transformation product **1b** was not detected in the HPLC analysis.

The terpy ligand is known to demonstrate very attractive features in electron-transfer, photochemical, and related reactions[8] and activate the *trans*-positioned ligand through the central metal,[17,18] which is attributed to the vacant low-lying π* orbitals that attract electron density from the metal.[19] Moreover, the assistance of terpy for hydrolysis of diribonucleoside monophosphate diesters has been demonstrated with a manganese(II) complex.[20] The interligand interaction caused by terpy is also known to regulate the α-hydroxylation of dipeptides.[7] From these results, we consider that the terpy ligand in this ternary cobalt(III) complex plays an important role in the oxidative transformation of the tripeptide. For sequence specificity, the interligand interaction between the C-terminal side chain and terpy in **1c** is important to abstract the α-proton or to stabilize the radical intermediate that gives **1a** under aerobic conditions. In the ternary complex **1c**, the CH-π interaction between the peptide and terpy ligands, as shown from the upfield shifts



Scheme 3. Plausible oxidation pathway of the cleavage reaction

of γ-H (δ = 0.82 ppm) and the δ-H's (δ = 0.23 and 0.58 ppm) of the leucine moiety, seems to fix the C-terminal side chain of GGL on the terpy ring. On the other hand, in the ternary complexes **5c** or **6c**, where the C-terminal residues are glycine, such upfield shifts are not observed. Consequently, the corresponding oxidative-degradation compounds were not generated in the cases of **5** and **6**. It is clear that the interligand interaction caused by the bulkiness of the C-terminal side-chain controls the sequence specificity of this reaction. The reason why the cleavage reaction does not take place in GBL (**7**), which contains a C-terminal bulky side-chain might be explained by the difficulty of abstraction of the protons attached on the N-2 β-alanine residue.

Conclusion

A new type of oxidative transformation of peptide compounds is carried out nonenzymatically in the presence of transition metal complexes containing a terpy ligand. The sequence-specific cleavage of peptides consisting of C-terminal aliphatic amino acids occurs because of the interligand interactions. Previously, the regioselective hydrolysis of peptides containing histidine or methionine residues has been reported with palladium(II) complexes,[21] in which coordination of the functional group of the peptide side chain to the palladium center was the key step for generating the selectivity. As compared with the previous reactions, our finding that the bulkiness of the aliphatic side chain — a nonfunctional group of the amino-acid residue — controls the specificity is the first report of the oxidative degradation of a peptide due to intramolecular noncovalent interactions with a ternary cobalt(III) complex.

Experimental Section

General: Reagents used for synthesis were of the highest grade available and were employed without further purification. The starting cobalt(III) complex, [Co(CO_3)(OH)(terpy)], was prepared according to the reported method.[22] All solvents for spectroscopic measurements were purified by distillation before use. Electronic absorption spectra were recorded on a JASCO UVIDEC-660 spectrometer. ^{1}H NMR spectra were measured on a Varian VXR-300S or JEOL Lambda-500 spectrometer with TMS as an internal standard. Crystal-structure analyses were performed with an Enraf−Nonius CAD4-EXPRESS four-circle diffractometer. Single crystals of the complexes suitable for the X-ray diffraction measurement were mounted on a glass capillary. The diffraction data were collected with graphite-monochromated Mo-K_α radiation with the ω-2θ scan technique at room temperature. Crystal data and experimental details are listed in Table 2, in which weighted refinement values (Rw) are obtained as follows: $Rw = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$. At the appropriate time of the reaction with GGL, the yields of [Co(gg′l)(terpy)] (**1a**), [Co(g′l)(terpy)] (**1b**), and [Co(ggl)(terpy)] (**1c**) were determined by HPLC analysis (column, ODS CrestPak C18s. eluent, MeOH/water gradient method (5:95 → 35:65). UV-detector, wavelength = 513 nm). The ratio of these complexes varied during the reaction.

Complexation and Characterization of Ternary Cobalt(III) Complexes: Under aerobic conditions, the reaction of [Co(CO_3)(OH)(terpy)] (0.37 g, 2 mmol) and an equimolar amount of tripeptide [GGL (**1**), BGL (**2**), GGF (**3**), GGA (**4**), GGG (**5**), FGG (**6**), or GBL (**7**)] was carried out at pH 8.5 and 40 °C in an aqueous solution (50 mL). After 10 h, separation of the reaction mixture on a SP Sephadex C-25 column gave three separation patterns. In the cases of **1**−**3** as the first group separation pattern, two fraction bands (**a** and **b**) containing a neutral complex were eluted with water, one (**c**) containing a positively charged complex was eluted with 0.1 M NaCl solution, and one (**d**) was eluted with 0.2 M solution. In the case of **4** as the second group, one fraction band (**a** + **b**) was eluted with water, in which obvious separation of **4a** and **4b**

Table 2. Crystal data for the complexes **1b** and **6c**

Complex	{[Co(g′l)(terpy)]}$_2$·3.5H_2O (**1b**)	[Co(fgg)(terpy)]·2H_2O (**6c**)
Formula	$Co_2C_{46}H_{51}N_{10}O_{11.5}$	$CoC_{28}H_{29}N_6O_6$
Fw	1045.84	604.51
Crystal system	triclinic	triclinic
Space group	*P*1	*P*1
a (Å)	11.336(6)	8.884(1)
b (Å)	14.668(6)	11.694(2)
c (Å)	8.304(4)	7.594(2)
α (°)	96.50(3)	96.75(2)
β (°)	100.06(4)	105.75(2)
γ (°)	96.92(4)	72.55(1)
V (Å^3)	1336(1)	723.8(3)
Z	1	1
$\rho_{calcd.}$ (g cm^{-3})	1.299	1.387
μ (cm^{-1})	6.85	6.44
R_1 [a]	0.083	0.067
*R*w[b]	0.275	0.190
λ. Å	0.71070	0.71070
No. of reflections used [$I > 2\sigma(I)$]	3805	2500
No. of variables	631	371

[a] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [b] $Rw = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$; $w = 4F_o^2/\sigma^2(F_o)^2$.

from the column was not accomplished, and two bands, containing (**4c**) and (**4d**), were eluted with 0.1 M NaCl, and 0.2 M NaCl solution, respectively. In the case of the reaction with **5**−**7**, no fractional band corresponding to **a** or **b** was eluted with water; one band (**c**) was eluted with 0.1 M NaCl solution and another (**d**) with 0.2 M NaCl solution. These column patterns for the fractional bands are typical for the sequence of tripeptides employed here. In all cases, the complex contained in the last band (**d**) was identified as $[Co(terpy)_2]^{3+}$.[9] In the case of GGL (**1**), the amounts of **1b** increased with increasing reaction time. The structure of **1b** was confirmed by elemental analysis as well as by X-ray single crystal and ^1H NMR analysis. Elemental analysis of **1b**: $[Co(g'l)(terpy)]\cdot 4H_2O$; $C_{23}H_{30}CoN_5O_8$ (563.45): calcd. C 49.03, H 5.37, N 12.43; found C 49.23, H 5.30, N 12.13.

After 24 h, the isolated yield of **1b** was over 70% based on the starting cobalt complex, while the total yields of **1a** and **1c** were under 10%. Reverse-phase HPLC analyses of the reaction mixture indicated that the primary product of the complex formation with Co-terpy and GGL at the initial stage of the reaction was **1c**, which was oxidized to **1a** under aerobic conditions. Under anaerobic conditions, however, **1a** was not detected in the HPLC analyses. Similar time-dependent product distributions were observed in the reaction with BGL (**2**) and GGF (**3**). In the case of GGG (**5**), FGG (**6**), and GBL (**7**), the positively charged complexes, **5c** (75%), **6c** (65%), and **7c** (60%), eluted with 0.1 M NaCl solution, were the main products, respectively; neutral products, corresponding to **5a**, **5b**, **6a**, **6b**, **7a**, and **7b**, were not detected even after 24 h. NMR measurement of all complexes isolated from the eluting solution was carried out in D_2O solution. These data are listed in Table 1. The X-ray analyses of the single crystals of **1b** and **6c** were performed according to the previous methods.[7] Crystal data are summarised in Table 2. During the crystallization of **6c** at room temperature, the positively charged complex eluted from the column changed to a neutral one (presumably, carbonate ions generated from carbon dioxide in the atmosphere might act as a reagent for charge neutralization), presumably because a neutral compound crystallizes more easily than a positive one.

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