Novel Building Blocks for Biomimetic Assemblies. Synthesis, Characterization, and Spectroscopic and Electrochemical Properties of New Bidentate Ligands Derived from Lysine and Cysteine and Their Complexes with Bis(2,2′-bipyridine)ruthenium(II)

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Synthetic amino acids suitable for the assembly of small, redox-active metallopeptides are described. N^{α}-((1,1-Dimethylethoxy)carbonyl)-N^{ϵ}-(2-pyridylmethyl)-L-lysine (**1**), N^{α}-acetyl-*S*-(2-pyridylmethyl)-L-cysteine (**2**), and N^{α}-acetyl-*S*-(2-(2-pyridyl)ethyl)-L-cysteine (**3**) have been synthesized by alkylation of the N^{α}-protected amino acids. Their $[Ru(bipy)_2]^{2+}$ complexes $[(bipy)_2Ru(BocLysCH_2py)]^{2+}$ (**4**), $[(bipy)_2Ru(AcCysCH_2py)]^{2+}$ (**5**), and $[(bipy)_2Ru(AcCys(CH_2)_2py)]^{2+}$ (**6**) have been prepared by reactions of the ligands with $[Ru(bipy)_2Cl_2]$. On the basis of ^{1}H-NMR spectroscopy, **4**−**6** can be described best as *trans*-tetrapyridine complexes with the lysine amino N atom and the cysteine S atom occupying one of the apical positions. It was shown by luminescence spectroscopy that **4** can serve as a possible photoredox-active module for the construction of photochemically active peptides. The redox properties of the complexes are described with the aid of the Lever parameters. It was demonstrated that the amino acid ligands in **5** and **6** can be viewed as methionine units. Particularly interesting is the unique redox chemistry of **4**. Upon metal oxidation, a two-electron ligand oxidation occurred, followed by fast hydrolytic cleavage of the lysine−methylpyridine N−C bond. The physical and chemical properties of the compounds are discussed in terms of future applications in biomimetic chemistry such as the activation of small molecules.

Introduction

A recent development in bioinorganic chemistry is the *de novo* synthesis of metalloproteins.[1] In this research area, functionalized amino acids with additional metal-binding sites are attractive building blocks for the construction of new synthetic peptides. They provide stable coordination sites and can be regarded as artificial "bioinorganic chips" [2] suitable for assembling small, functional metallopeptides,[3−5] and for the semisynthetic incorporation of transition metal complexes in natural proteins.[6]

A particularly interesting and well-developed field for the application of modular approaches is the synthesis of photoredox-active assemblies to convert solar into chemical energy. Polypyridylruthenium compounds are well suited for these purposes and have been extensively used for studies in this context.[7−17] Meyer et al. have reported a series of donor−acceptor complexes with a tris(2,2′-bipyridine)ruthenium chromophore covalently attached to a lysine side chain.[18−20] Incorporation of this ruthenium unit into small peptides has been described also.[21]

Electron transfer processes in proteins have also been studied with the aid of photoredox-active (bipyridine)ruthenium complexes covalently attached to the biomolecule. Site-specific functionalized lysine residues were used as tris(2,2′-bipyridine)-ruthenium-binding sites for the study of photoinduced electron transfer in cytochromes and cytochrome *c* oxidase.[22−27] In these

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(1) Kraatz, H.-B. *Angew. Chem.* **1994**, *106*, 2143−2144.
(2) Lippard, S. J. *Science* **1993**, *261*, 699−700.
(3) Imperiali, B.; Roy, R. S. *J. Am. Chem. Soc.* **1994**, *116*, 12083−12084.
(4) Imperiali, B.; Fisher, S. L. *J. Org. Chem.* **1992**, *57*, 757−759.
(5) Imperiali, B.; Fisher, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 8527−8528.
(6) Wuttke, D. S.; Gray, H. B.; Fisher, S. L.; Imperiali, B. *J. Am. Chem. Soc.* **1993**, *115*, 8455−8456.
(7) Zahavy, E.; Seiler, M.; Marx-Tibbon, S.; Joselevich, E.; Willner, I.; Dürr, H.; O'Connor, D.; Harriman, A. *Angew. Chem.* **1995**, *107*, 1112−1115.
(8) Strouse, G. F.; Schoonover, J. R.; Duesing, R.; Boyde, S.; Jones, W. E., Jr.; Meyer, T. J. *Inorg. Chem.* **1995**, *34*, 473−487.
(9) von Zelewsky, A.; Belser, P.; Hayoz, P.; Dux, R.; Hua, X.; Suckling, A.; Stoeckli-Evans, H. *Coord. Chem. Rev.* **1994**, *132*, 75−85.
(10) Opperman, K. A.; Mecklenburg, S. L.; Meyer, T. J. *Inorg. Chem.* **1994**, *33*, 5295−5301.
(11) Jones, W. E., Jr.; Bignozzi, C. A.; Chen, P.; Meyer, T. J. *Inorg. Chem.* **1993**, *32*, 1167−1178.
(12) Worl, L. A.; Strouse, G. F.; Younathan, J. N.; Baxter, S. M.; Meyer, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7571−7578.
(13) Strouse, G. F.; Worl, L. A.; Younathan, J. N.; Meyer, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 9101−9102.
(14) Boyde, S.; Strouse, G. F.; Jones, W. E., Jr.; Meyer, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 7448−7454.
(15) Olmsted, J., III; McClanahan, S. F.; Danielson, E.; Younathan, J. N.; Meyer, T. J. *J. Am. Chem. Soc.* **1987**, *109*, 3297−3301.
(16) Danielson, E.; Elliot, C. M.; Merkert, J. W.; Meyer, T. J. *J. Am. Chem. Soc.* **1987**, *109*, 2519−2520.
(17) Margerum, L. D.; Murray, R. W.; Meyer, T. J. *J. Phys. Chem.* **1986**, *90*, 728−730.
(18) Mecklenburg, S. L.; McCafferty, D. G.; Schoonover, J. R.; Peek, B. M.; Erickson, B. W.; Meyer, T. J. *Inorg. Chem.* **1994**, *33*, 2974−2983.
(19) Mecklenburg, S. L.; Peek, B. M.; Schoonover, J. R.; McCafferty, D. G.; Wall, C. G.; Erickson, B. W.; Meyer, T. J. *J. Am. Chem. Soc.* **1993**, *115*, 5479−5495.
(20) Mecklenburg, S. L.; Peek, B. M.; Erickson, B. W.; Meyer, T. J. *J. Am. Chem. Soc.* **1991**, *113*, 8540−8542.
(21) Peek, B. M.; Ross, G. T.; Edwards, S. W.; Meyer, G. J.; Meyer, T. J.; Erickson, B. W. *Int. J. Pept. Protein Res.* **1991**, *38*, 114−123.
(22) Liu, R.-Q.; Hahm, S.; Miller, M.; Durham, B.; Millett, F. *Biochemistry* **1995**, *34*, 973−983.
(23) Liu, R.-Q.; Miller, M. A.; Han, G. W.; Hahm, S.; Geren, L.; Hibdon, S.; Kraut, J.; Durham, B.; Millett, F. *Biochemistry* **1994**, *33*, 8678−8685.
(24) Heacock, D. H., II; Harris, M. R.; Durham, B.; Millett, F. *Inorg. Chim. Acta* **1994**, *226*, 129−135.
(25) Pan, L. P.; Hibdon, S.; Liu, R.-Q.; Durham, B.; Millett, F. *Biochemistry* **1993**, *32*, 8492−8498.
(26) Pan, L. P.; Durham, B.; Wolinska, J.; Millett, F. *Biochemistry* **1988**, *27*, 7180−7184.
(27) Durham, B.; Pan, L. P.; Long, J. E.; Millett, F. *Biochemistry* **1989**, *28*, 8659−8665.

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approaches, a bipyridine ligand was attached via an amide bond to the lysine side chain.

While lysine-derived ligands have been successfully utilized to bind polypyridylruthenium(II) complexes in photoredox-active assemblies, $[Ru(bipy)_2]^{2+}$ complexes of sulfur-containing amino acids have not been reported. Only one paper deals with (cysteine)oxoruthenium(VI) complexes as model compounds for isopenicillin synthetase.[28] In general, bis(bipyridine)ruthenium complexes containing additional sulfur ligands are rare. A few reports have been published on thiometalate,[29] thiolate,[30−32] and thioether[33−35] complexes of the $[Ru(bipy)_2]^{2+}$ fragment.

We are interested in developing strategies for tuning the reactivity of metal complexes in order to optimize their properties with respect to fundamental chemical reactions such as electron transfer and the activation of small molecules. Our goal is to construct polyfunctional assemblies from versatile modules well suited for different tasks in biomimetic processes like the photoreduction of CO_2 or the activation of oxygen. Small peptides should be ideal candidates for this purpose, since they permit the control of physical and chemical properties such as dielectric constants, charge, and hydrophobicity or the ability to form hydrogen bonds, as well as the distance between two reaction centers, over a wide range by variation of their amino acid sequence. These factors are essential for the highly specific function of metalloproteins,[2] and their controlled utilization is crucial for the development of efficient biomimetic coordination compounds. Moreover, peptide synthesis should provide a simple way to combine metal centers suitable for different tasks like substrate activation, photosensibilization, or electron transfer.

The synthesis of artificial metallopeptides depends strongly on the availability of amino acids suitable for stable binding of functional metal complex fragments. Since there are only a few examples of functionalized, metal-binding amino acids in the literature, it is important to develop methods for the synthesis of such ligands with a variety of different coordination sites.

Herein we wish to report the synthesis of various bidentate ligands based on the amino acids lysine and cysteine. The amino acid side chains were covalently linked to an alkylpyridine unit, yielding the N,N- and N,S-chelating ligands **1**−**3**. A 2-pyridylmethyl moiety was connected to the lysine side chain via an amine link. This is an important difference compared to the lysine bipyridine ligands described in the literature, where the amino acid is linked to the bidentate ligand via an amide bond.[18−20] The ϵ-amino group of the N^{α}-protected amino acid **1** is capable of direct metal coordination. The thiolate function of cysteine was covalently linked to a 2-pyridylmethyl (**2**) and 2-(2-pyridyl)ethyl (**3**) substituent, respectively. The ligands **2** and **3** can be viewed as chelating ligands containing a methionine-like thioether moiety . Methionine coordination plays an important role in tuning the redox properties of metalloproteins.[36] Thus, **2** and **3** should be useful for the assembly of small, redox-active peptides.

Bis(2,2′-bipyridine)ruthenium(II) complexes of the new ligands were prepared to serve as modules for the assembly of redox-active peptides. These systems allow an extensive discussion of the ligand electrochemical properties in the context of Lever's ligand electrochemical series.[37] Furthermore, the luminescence properties of $[Ru(bipy)_2(BocLysCH_2py)]^{2+}$, **4**, demonstrate the possibility of using this compound for the construction of photoredox-active assemblies. The wealth of data available for $[Ru(bipy)_2]^{2+}$ complexes enables us to present a detailed interpretation of our spectroscopic observations. This is of fundamental importance for future applications of the new ligands.

Experimental Section

Measurements. UV−vis spectra were recorded on a Shimadzu UV-2101PC scanning spectrophotometer. Molar extinction coefficients were obtained from absorbance measurements as a function of complex concentration. Proton NMR spectra were obtained on a 270 MHz JEOL JNM EX 270 spectrometer. TMS was used as an internal standard for measurements in acetone-d_6 and methanol-d_4. Chemical shifts in D_2O were measured relative to TMS. IR spectra were recorded on either a Nicolet 5SX or a Mattson Polaris FT IR spectrophotometer. Electrochemical measurements were performed on a Princeton Applied Research potentiostat/galvanostat, Model 263. All measurements at ambient temperature were recorded against the Ag/AgCl reference electrode using a glassy carbon working electrode. The potentials are uncorrected for junction potential effects. Roth Rotipuran acetonitrile was used for cyclic voltammetry without further purification. Solutions contained 0.1 M tetra-*n*-butylammonium hexafluorophosphate (TBAH) as supporting electrolyte. The best results were obtained at scan rates of 50 mV/s. $E_{1/2}$ values were calculated from half the difference between E_p values for the anodic and cathodic waves from the cyclic voltammograms. The ferrocene−ferrocenium couple was observed at +0.49 V (ΔE_p = 90 mV) in acetonitrile under the measurement conditions. Exhaustive oxidative electrolysis at constant potential and platinum gauge electrodes was performed in Roth Rotipuran acetonitrile. The solvent was used without further purification. Uncorrected luminescence spectra and luminescence quantum yields were obtained on a Perkin-Elmer LS 50B spectrophotometer. Solutions (1×10^{-4} M; $A_{459} \sim 1.1$) of the complexes in Roth Rotipuran acetonitrile were used. The solutions were deoxygenated by bubbling with high-purity argon for at least 10 min. Quantum yields were obtained relative to $[Ru(bipy)_3][PF_6]_2$, for which $\phi_{em} = 0.062$ in CH_3CN at 295 K. FD mass spectra were obtained using methanol solutions of the compounds on a Varian MAT 212 mass spectrometer. FAB mass spectra of the complexes were measured in a 3-nitrobenzyl alcohol matrix on a Finnigan MAT 90 mass spectrometer by Prof. F. Kreissl at the Technical University, Munich. C,H,N elemental analyses were performed on a Carlo Erba Model 1106 elemental analyzer, and C,H,N,S elemental analyses on a Carlo Erba Model 1108 elemental analyzer at the analytical service station of this department.

Materials. THF needed for the synthesis of **1** was dried over a Na/K alloy and freshly distilled before use. All other solvents used in synthetic work were reagent grade and were used without further purification. Deuterated solvents were purchased from Aldrich. NMR reagents were used without further purification, apart from acetone-d_6, which was purified by distillation under reduced pressure into a chilled flask before use. $[Ru(bipy)_2Cl_2]$ was prepared as described in the literature.[38] N^{α}-Boc-L-lysine was purchased from Bachem and used as received. Reagent grade solvents were obtained from Roth, and all other chemicals were purchased from Aldrich. Pyridine-2-carbaldehyde and 2-vinylpyridine were freshly distilled under vacuum before use. The other chemicals were used as received.

Ligands. Sodium Salt of N^{α}-((1,1-Dimethylethoxy)carbonyl)-N^{ϵ}-(2-pyridylmethyl)-L-lysine (NaBocLysNHCH$_2$py, **Na-1**). Pyridine-2-carbaldehyde (0.4 mL, 4.08 mmol) was added in one portion to a stirred suspension of N^{α}-Boc-L-lysine (1 g, 4.08 mmol) in 50 mL of dry THF. Stirring was continued overnight. The mixture was then

(28) Bigham, W. S.; Shapley, P. A. *Inorg. Chem.* **1991**, *30*, 4093−4095.
(29) Tanaka, K.; Morimoto, M.; Tanaka, T. *Inorg. Chim. Acta* **1981**, *56*, L61−L63.
(30) Johnson, M. D.; Nickerson, D. *Inorg. Chem.* **1992**, *31*, 3971−3974.
(31) Greaney, M. A.; Coyle, C. L.; Harmer, A. J.; Stiefel, E. I. *Inorg. Chem.* **1989**, *28*, 912−920.
(32) Root, M. J.; Deutsch, E. *Inorg. Chem.* **1984**, *23*, 622−624.
(33) Kroener, R.; Heeg, M. J.; Deutsch, E. *Inorg. Chem.* **1988**, *27*, 558−566.
(34) Root, M. J.; Sullivan, B. P.; Meyer, T. J.; Deutsch, E. *Inorg. Chem.* **1985**, *24*, 2731−2739.
(35) Root, M. J.; Deutsch, E. *Inorg. Chem.* **1985**, *24*, 1464−1471.
(36) Gray, H. B.; Ellis, W. R., Jr. In *Bioinorganic Chemistry*; Bertini, I., Gray, H. B., Lippard, S. J., Valentine, J. S., Eds.; University Science Books: Mill Valley, CA, 1994; pp 315−363.
(37) Lever, A. B. P. *Inorg. Chem.* **1990**, *29*, 1271−1285.
(38) Sullivan, B. P.; Salmon, D. J.; Meyer, T. J. *Inorg. Chem.* **1978**, *17*, 3334−3341.

Table 1. Proton NMR Chemical Shifts of the Free Ligands **1**−**3** and of the Amino Acid Ligands in **4**−**6** (δ, ppm)

functional group	**1** (D_2O)	**2** (D_2O)	**3** (D_2O)	**4** ($CD_3C(O)CD_3$)	**5** (CD_3OD)	**6** (CD_3OD)
O^{t}Bu	1.42 (s)			1.38 (s)		
C(O)Me		2.00 (s)	2.02 (s)		1.90; 1.98 (s)	1.91; 1.83 (s)
α-CH	3.88 (m)	4.33 (dd)	4.36 (dd)	3.75 (br)	3.59; 4.38 (m)	3.92; 4.38 (m)
β,γ,δ-CH_2	1.30−1.85 (m)	2.95 (ABX)	2.95 (ABX)	0.85−1.60 (m)	1.90;[a] 2.23;[b] 2.45[c]	1.38; 2.32 (m)
ϵ-CH_2	2.64 (t)			2.00[d]		
py CH_2	3.88 (s)	4.15 (s)		4.05; 4.80 (m, br)	4.44 (2d); 4.85[e]	
py C_2H_4			3.36; 3.04 (m)			2.91;[f] 3.40[g] (m)
py H3	7.45 (d)	7.99 (d)	7.95 (d)	7.20 (m, br)	7.06 (m, br)	7.13 (m, br)
py H4	7.86 (ddd)	8.47 (dd)	8.48 (dd)	7.78 (m)	7.58 (m)	7.69−7.88 (m)
py H5	7.38 (dd)	7.89 (dd)	7.89 (dd)	7.40 (m)	7.33 (m)	7.48 (m)
py H6	8.43 (d)	8.67 (d)	8.65 (d)	8.47 (m)	8.43 (m)	8.13−8.34 (m)

[a] Under OMe resonance, COSY and integral, 0.5H. [b] m, 0.5H. [c] m, 1H. [d] Under solvent resonance, two broad signals at 1.84 and 2.04 ppm in D_2O. [e] Under solvent resonance, two doublets at 4.67 and 5.07 ppm in D_2O. [f] 1H. [g] 3H

filtered to remove unreacted amino acid; 250 mg (25%) of the starting material was recovered. Most of the solvent was then removed under vacuum and the resulting light yellow oil diluted with methanol (50 mL). Solid $NaBH_4$ (150 mg, 4.08 mmol) was added to the stirred solution in small portions. After vigorous hydrogen evolution had stopped, the mixture was heated under reflux for 4 h. The solution was filtered and all solvent removed by rotary evaporation. The residue was the product (Na-**1**) in addition to 2-(hydroxymethyl)pyridine (NMR spectroscopy). Water (10 mL) was added to the light yellow, oily reaction product. The mixture was slowly heated to 130 °C in an oil bath to remove the solvent together with the contaminating (hydroxymethyl)pyridine. Spectroscopically pure NaBocLysCH$_2$py (yield: 900 mg, 2.5 mmol, 52%) was obtained as a light yellow, hygroscopic powder. The product was stored under dry nitrogen at room temperature. The analytical data indicated the presence of moisture.

Anal. Calcd for $C_{17}H_{26}N_3NaO_4 \cdot 1.5H_2O$: C, 52.84; H, 7.56; N, 10.87. Found: C, 52.97; H, 7.78; N, 10.24. ^{1}H-NMR (D_2O, internal standard TSP): see Table 1. Selected IR bands (KBr pellet, cm^{-1}): 3408 (br, H_2O), 3055 (br, w), 2999 (w), 2971 (m), 2922 (m), 2851 (w), 1694 (s, Boc), 1591 (s, CO_2^-), 1475 (m), 1452 (m), 1433 (m), 1406 (m), 1363 (m), 1168 (s), 1046 (m), 1023 (m), 756 (s).

***N*$^\alpha$-Acetyl-*S*-(2-pyridylmethyl)-L-cysteine (Ac-CysCH$_2$py, 2).** 2-Picolyl chloride hydrochloride (5.08 g, 31 mmol) was dissolved in water (5 mL) and slowly neutralized with NaOH (1.24 g, 31 mmol) in water (10 mL). A yellow oil separated from the aqueous solution. Solid *N*$^\alpha$-acetylcysteine (5.00 g, 31 mmol) was added in one portion to the stirred emulsion. An aqueous solution (10 mL) of NaOH (1.24 g, 31 mmol) was added dropwise to the reaction mixture over a period of 1 h. Stirring was continued for 2 d, during which the solution developed a light yellow color. All solvent was removed by rotary evaporation at 60 °C. Upon drying, the mixture turned bright red. Ethanol (100 mL) was added to the partially solid red product. Solid NaCl (2.5 g) precipitated and was removed by filtration. The red filtrate was evaporated to dryness and the residual red oil redissolved in a minimum amount of water. An orange precipitate was obtained overnight at + 4 °C. The solid was stirred with ethanol (5 mL) for $^1/_2$ h. The suspension was left at −20 °C for 1 week. Filtration afforded an orange solution and the product as a light orange solid (yield: 1 g, 3.9 mmol, 12.6%).

Anal. Calcd for $C_{11}H_{14}N_2O_3S$: C, 51.95; H, 5.55; N, 11.02; S, 12.61. Found: C, 51.75; H, 5.54; N, 10.74; S, 12.09. FD-MS: calcd for $[C_{11}H_{14}N_2O_3S]^+$, *m/z* = 254; found, *m/z* = 255.8. ^{1}H-NMR (D_2O, internal standard TSP): see Table 1. Selected IR bands (KBr pellet, cm^{-1}): 3288 (sh, s), 3063 (m), 3020 (w), 2978 (m), 2943 (w), 2922 (w), 2893 (w), 2830 (w), 1706 (s, N−Ac), 1644 (s, CO_2H), 1596 (s, aromatic rings, CO_2^-), 1547 (s), 1477 (w), 1431 (m), 786 (m), 696 (s), 683 (s).

***N*$^\alpha$-Acetyl-*S*-(2-(2-pyridyl)ethyl)-L-cysteine (AcCysC$_2$H$_4$py, 3).** *N*$^\alpha$-Acetylcysteine (5.00 g, 31 mmol) was dissolved in methanol (50 mL). 2-Vinylpyridine (3.3 mL, 31 mmol) was added dropwise to the stirred solution. The mixture was heated under reflux for 5 h. After cooling to room temperature and filtration, all solvent was removed by rotary evaporation. The remaining oil was stirred with ethanol (20 mL). A white precipitate resulted. The suspension was cooled to −20 ° C overnight, and the product collected by filtration. A second batch was obtained by removal of about two-thirds of the solvent, cooling to −20 °C for 24 h, and filtration. The combined product fractions were dried under vacuum to give AcCysC$_2$H$_4$py as a white solid (yield: 7.8 g, 29 mmol, 93%).

Table 2. Aromatic Proton Chemical Shifts of Complexes **4**,[a] **5**,[b] and **6**[b] (δ, ppm)

cmpd	position	py	b	b′	b″
4	H3	7.20	7.40	7.65	8.90
5	H3	7.06	7.48	7.70−7.90	8.74
6	H3	7.13	7.33	7.64	8.74
4	H4	7.78	8.05	8.20	8.33
5	H4	7.58	7.95−8.10	8.20	8.30
6	H4	7.69−7.88	8.13−8.34	8.00	8.13−8.34
4	H5	7.40	7.78	7.89	7.96
5	H5	7.33	7.70−7.90	7.70−7.90	7.70−7.90
6	H5	7.48	7.69−7.88	7.69−7.88	7.69−7.88
4	H6	8.47	8.76	8.85	9.55
5	H6	8.43	8.57	8.57	9.52
6	H6	8.13−8.34	8.74	8.59	9.34

[a] In acetone-d_6. [b] In methanol-d_4.

Anal. Calcd for $C_{12}H_{16}N_2O_3S$: C, 53.71; H, 6.01; N, 10.44; S, 11.95. Found: C, 53.61; H, 6.24; N, 10.33; S, 11.62. FD-MS: calcd for $[C_{12}H_{16}N_2O_3S]^+$, *m/z* = 268; found, *m/z* = 269.8. ^{1}H-NMR (D_2O, internal standard TSP): see Table 1. Selected IR bands (KBr pellet, cm^{-1}): 3337 (sh, s), 3063 (m), 3049 (m), 2950 (m), 2922 (m), 2844 (m), 2817 (m), 1710 (s, N−Ac), 1640 (s, CO_2H), 1597 (s, aromatic rings, CO_2^-), 1562 (m), 1527 (m), 1478 (m), 1443 (m), 1434 (m), 773 (s), 698 (m).

Metal Complexes. (Sodium *N*$^\alpha$-((1,1-dimethylethoxy)carbonyl)-*N*$^\epsilon$-(2-pyridylmethyl)-L-lysinate)bis(2,2′-bipyridine)ruthenium(II) Bis(hexafluorophosphate) ([Ru(bipy)$_2$(NaBocLysNHCH$_2$py)][PF$_6$]$_2$, Na-4). Solid $[Ru(bipy)_2Cl_2]$ (270 mg, 0.56 mmol) was added to a stirred solution of **1** (200 mg, 0.56 mmol) in methanol (100 mL). The mixture was heated under reflux overnight, yielding an orange solution. After removal of all solvent by rotary evaporation, water (5 mL) was added. The product was obtained as a red-orange precipitate upon addition of NH_4PF_6 (1.00 g, 6.13 mmol) in water (1 mL). The compound was filtered off, washed several times with small amounts of water, and dried overnight in a desiccator over P_2O_5 (yield: 330 mg, 0.31 mmol, 55%).

In some cases, a dark-red gum was obtained after addition of the NH_4PF_6 solution. When this occurred, the solvent was decanted and the product was dried in a desiccator over P_2O_5 and powdered in a mortar. Water (5 mL) was added and the suspension stirred overnight. After this treatment, the product was isolated as described above.

Anal. Calcd for $C_{37}H_{42}F_{12}N_7NaO_4P_2Ru$: C, 41.82; H, 3.95; N, 9.23. Found: C, 41.09; H, 3.94; N, 8.99. FAB-MS: calcd for $[C_{37}H_{42}F_6N_7O_4PRu]^+$ (**4**-PF_6^+), *m/z* = 895; found, *m/z* = 895.4; calcd for $[C_{36}H_{42}N_7O_4Ru]^+$ (**4**$^+$), *m/z* = 749; found, *m/z* = 749.6; calcd for $[C_{32}H_{33}N_7O_2Ru]^+$ (**4** Boc$^+$), *m/z* = 648; found, *m/z* = 649.7. ^{1}H-NMR ($(CD_3)_2CO$, internal standard TMS): see Tables 1 and 2. Significant IR bands (KBr pellet, cm^{-1}): 3424 (br, m), 3364 (m), 3285(m), 3202 (m), 3121 (m), 2967 (m), 2872 (m), 1701 (s, Boc), 1605 (s, CO_2^-), 1466 (m), 1447 (m), 1425 (m), 1398 (m), 841 (vs, PF_6^-), 746 (s), 731 (m), 557 (s, Ru−N).

(*N*$^\alpha$-((1,1-Dimethylethoxy)carbonyl)-*N*$^\epsilon$-(2-pyridylmethyl)-L-lysine)-bis(2,2′-bipyridine)ruthenium(II) Bis(hexafluorophosphate) ([Ru(bipy)$_2$(BocLysCH$_2$py)][PF$_6$]$_2$, 4). The reaction of $[Ru(bipy)_2Cl_2]$ (75

mg, 0.15 mmol) and **1** (56 mg, 0.15 mmol) in methanol (50 mL) was carried out as described above. After addition of the NH_4PF_6 solution (100 mg, 0.61 mmol in 1 mL of H_2O), the product was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic fractions were dried over Na_2SO_4. The solvent was removed by rotary evaporation and the resulting red-orange, oily solid treated with hexane (5 mL). Filtration and drying under vacuum yielded the product as a red-orange powder (yield: 40 mg, 0.05 mmol, 33%).

Anal. Calcd for $C_{37}H_{43}F_{12}N_7O_4P_2Ru$: C, 42.70; H, 4.16; N, 9.42. Found: C, 41.83; H, 4.07; N, 8.92. No differences between the Na salt and the free acid were observed in the NMR spectrum of the compounds. Significant IR bands (KBr pellet, cm^{-1}): 3422 (br, m), 3119 (w), 3084 (w), 2957 (m), 2922 (m), 2858 (m), 1703 (s, CO_2H and Boc), 1598 (w, aromatic rings), 1499 (m), 1456 (m), 1436 (m), 1421 (m), 835 (vs, PF_6^-), 753 (s), 724 (m), 550 (s, Ru−N).

(N^{α}-Acetyl-*S*-(2-pyridylmethyl)-L-cysteine)bis(2,2′-bipyridine)ruthenium(II) Bis(hexafluorophosphate) ([Ru(bipy)$_2$(AcCysCH$_2$py)][PF$_6$]$_2$, 5). Solid $[Ru(bipy)_2Cl_2]$ (1.00 g, 2.07 mmol) was added in one portion to a stirred solution of **2** in methanol (200 mL). Stirring was continued and the mixture heated under reflux overnight. An orange solution resulted, which was rotary-evaporated to dryness. The orange residue was redissolved in water (15 mL) and the solution filtered to remove insoluble material. NH_4PF_6 (2.00 g, 12.26 mmol) was added. A voluminous yellow-orange precipitate resulted. The solid was collected by filtration and washed several times with small amounts of water. A second fraction was obtained after cooling the mother liquor to 4 °C overnight followed by filtration and washing with water. The combined, yellow-orange solids were dried in a desiccator over P_2O_5. The product (1.46 g, 1.52 mmol, 76%) contained small amounts of NH_4PF_6 but was spectroscopically pure. In order to obtain the analytically pure title compound, the following procedure was adopted. A small amount of the solid was dissolved in hot water, cooled, and left at 4 °C for 1 week, during which pure $[Ru(bipy)_2(AcCysCH_2py)][PF_6]_2$ precipitated. The orange powder was collected by filtration and dried in a desiccator over P_2O_5.

Anal. Calcd for $C_{31}H_{30}F_{12}N_6O_3P_2Ru$: C, 38.88; H, 3.16; N, 8.77; S, 3.35. Found (before recrystallization from H_2O): C, 37.93; H, 2.89; N, 8.28. Found (after recrystallization from H_2O): C, 39.14; H, 3.24; N, 8.89; S, 3.16. FAB-MS: calcd for $[C_{31}H_{30}N_6O_3RuS]^+$ (**5**$^+$), *m/z* = 668; found, *m/z* = 666.6; calcd for $[C_{26}H_{24}N_5RuS]^+$ ((bipy)$_2$Ru(SCH$_2$py)$^+$), *m/z* = 539; found, *m/z* = 537.7. ^{1}H-NMR (CD_3OD, internal standard TMS): see Tables 1 and 2. Selected IR bands (KBr pellet, cm^{-1}): 3408 (br, m), 3112 (m), 3076 (m), 2922 (m), 2851 (m), 1731 (s, N−Ac), 1664 (s, CO_2H), 1601 (m, aromatic rings), 1525 (m), 1463 (m), 1443 (m), 1420 (m), 1237 (m), 1160 (m), 839 (vs, PF_6^-), 759 (vs), 730 (s), 555 (s, N−Ru).

(N^{α}-Acetyl-*S*-(2-(2-pyridyl)ethyl)-L-cysteine)bis(2,2′-bipyridine)ruthenium(II) Bis(hexafluorophosphate) ([Ru(bipy)$_2$(AcCysC$_2$H$_4$py)][PF$_6$]$_2$, 6). **3** (540 mg, 2.07 mmol) was dissolved in methanol (250 mL). Solid $[Ru(bipy)_2Cl_2]$ (1.00 g, 2.07 mmol) was added in one portion to the stirred solution. Stirring was continued and the mixture heated under reflux overnight. An orange solution resulted. After removal of all solvent by rotary evaporation, water (10 mL) and solid NH_4PF_6 (2.00 g, 12.26 mmol) were added. The product precipitated as a red-orange solid, which was collected by filtration, washed several times with small amounts of water, and dried in a desiccator over P_2O_5 (yield: 1.38 g, 1.42 mmol, 71%).

Anal. Calcd for $C_{32}H_{32}F_{12}N_6O_3P_2RuS$: C, 39.55; H, 3.32; N, 8.65; S, 3.30. Found: C, 39.59; H, 3.43; N, 8.59; S, 3.34. FAB-MS: calcd for $[C_{32}H_{32}N_6O_3RuS]^+$ (**6**$^+$), *m/z* = 682; found, *m/z* = 680.6; calcd for $[C_{27}H_{26}N_5RuS]^+$ ((bipy)$_2$Ru(SCH$_2$CH$_2$py)$^+$), *m/z* = 551; found, *m/z* = 551.7. ^{1}H-NMR (CD_3OD, internal standard TMS): see Tables 1 and 2. Selected IR bands (KBr pellet, cm^{-1}): 3408 (m), 3105 (m), 3070 (m), 2916 (m), 2844 (m), 1727 (s, N−Ac), 1664 (s, CO_2H), 1600 (m, aromatic rings), 1525 (m), 1464 (m), 1443 (m), 1421 (m), 1241 (m), 1160 (m), 840 (vs, PF_6^-), 761 (vs), 728 (s), 556 (s, N−Ru)

(N^{α}-((1,1-Dimethylethoxy)carbonyl)-L-lysine)(pyridine-2-carbaldehyde)bis(2,2′-bipyridine)ruthenium(II) Bis(hexafluorophosphate) ([Ru(bipy)$_2$(BocLys)(pyC(O)H)][PF$_6$]$_2$, 8). BocLys (260 mg, 1.04 mmol) was dissolved in p.a. methanol (250 mL). Pyridine-2-carbaldehyde (0.1 mL, 1.04 mmol) was added in one portion to the stirred solution. After 15 min, $[Ru(bipy)_2Cl_2]$ (500 mg, 1.04 mmol) was added. Stirring was continued for another 5 h at ambient temperature. The mixture was then heated under reflux overnight, resulting in the formation of an orange solution. All solvent was removed by rotary evaporation. A red-orange residue was obtained, which was redissolved in 5 mL of H_2O. Addition of NH_4PF_6 (1.00 g) resulted in the formation of a brown-orange precipitate. Filtration and drying of the solid under vacuum yielded 800 mg (0.77 mmol, 74%) of the title compound **8**. The obtained crude product was pure by NMR spectroscopy but contained small amounts of NH_4PF_6. In order to obtain analytically pure **8**, a small sample of the crude compound was recrystallised from water (overnight, at +4 °C). The red-orange solid was collected by filtration and dried in a desiccator over P_2O_5.

Anal. Calcd for $C_{37}H_{42}F_{12}N_7O_5P_2Ru$: C, 42.05; H, 4.10; N, 9.28. Found: C, 41.58; H, 3.89; N, 9.32. ^{1}H-NMR ($CD_3C(O)CD_3$, solvent as internal standard, ppm): 0.9−1.6 (br, 6H, $^{\beta,\gamma,\delta}CH_2$); 1.38 (s, 9H, ^{t}Bu); 3.79 (br, 2H, $^{\epsilon}CH_2$); 3.91 (br, 1H, $^{\alpha}$CH); 5.90 (br, 1H, NH−Boc); 7.55 (m, 3H, 2 × b3, py3); 7.71 (m, 2H, b′3, py5); 7.88 (m, 2H, 2 × b5); 8.05 (m, 2H, 2 × b4); 8.11−8.36 (m, 5H, b′5, b′4, b″4, b″5, py4); 8.40 (m, 1H, b″3); 8.57 (m, 1H, py6); 8.76 (m, 3H, 2 × b6, b′6); 8.85 (m, 1H, b″6); 9.33 (s, 1H, C(O)H). Selected IR bands (KBr pellet, cm^{-1}): 3414 (br, m), 3104 (m), 3083 (m), 2971 (m), 2921 (m), 2858 (m), 1704 (s, Boc, C═O, CO_2H), 1602 (w, aromatic rings), 1464 (m), 1445 (m), 1420 (m), 840 (vs, PF_6^-), 763 (vs), 731 (m), 557 (s, N−Ru).

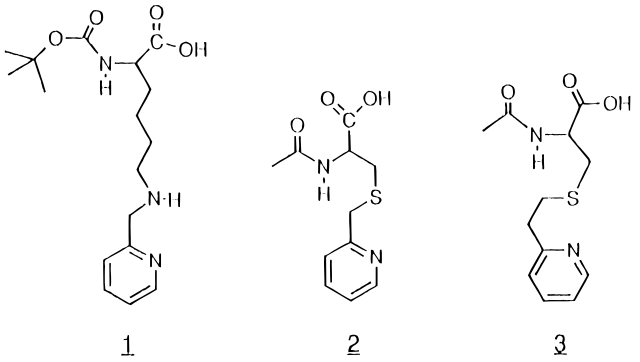
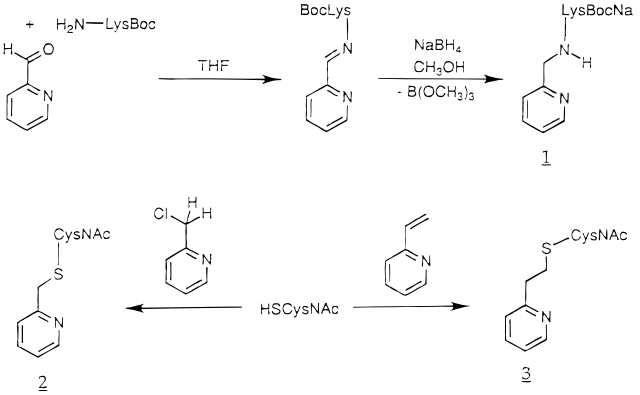


Figure 1. Structures of the ligands.

Scheme 1. Synthesis of Ligands **1**−**3**.



Results and Discussion

Synthesis of the Compounds. Ligands. Three different methods were employed to synthesize amino acid derivatives suitable for bidentate metal binding. The N^{α}-protected amino acids lysine and cysteine were linked to alkylpyridines via their amino and thiol side chains, respectively, to obtain N−N- and N−S-chelating ligands. The structures of the new ligands **1**−**3** are shown in Figure 1.

NaBocLysCH$_2$py (Na-**1**) was prepared via Schiff base condensation of N^{α}-Boc-L-lysine with pyridine-2-carbaldehyde followed by reduction of the intermediate imine with $NaBH_4$ (Scheme 1). Dry THF was used as a solvent for the initial condensation. This has the advantage that unreacted N^{α}-Boc-L-lysine can be recovered almost quantitatively by filtration because of its low solubility. The Schiff base formed in the

first reaction step was not isolated. Attempts to isolate the pure compound failed, due to its instability. The reduction with $NaBH_4$ was carried out in methanol. Several hours of reflux were necessary to destroy excess reductant. The crude product after removal of all solvent contained 2-(hydroxymethyl)pyridine as the sole major contaminant. This compound is the reduction product of excess 2-pyridinecarbaldehyde and was identified by its characteristic ^{1}H-NMR spectrum, which exhibits a singlet at 4.72 ppm for the methylene protons.[39] The alcohol was removed by distillation using water as a carrier. **1** was isolated as its sodium salt and characterized by ^{1}H-NMR and IR spectroscopy. Moderate yields of ca. 50% were obtained. However, the facile synthesis and the possibility of recovering most of the valuable unreacted amino acid make **1** a very attractive candidate for the preparation of large molecular assemblies. The ligand was spectroscopically pure, but no satisfactory C,H,N analysis could be obtained. The reason for this is that the product is very hygroscopic and always contained variable amounts of water. NaBocLysCH_2py (Na-**1**) is soluble in water and alcohols.

An unsuccessful attempt was made to synthesize **1** starting from 2-picolyl chloride and N^{α}-Boc-L-lysine. This reaction is the standard route to aminopolypyridine compounds.[40] In the course of our work, this method was used to prepare CysCH_2-py (**2**). The compound was obtained in low yields of only about 13% after reaction of N^{α}-acetylcysteine with 2-picolyl chloride in basic, aqueous solution (Scheme 1). Large losses occurred during purification. This was due to the small difference in solubility between the starting material and the product, causing difficulties in recrystallization of the product. **2** was characterized by its NMR and IR spectra in addition to C,H,N,S analysis and FD mass spectrometry. The compound was spectroscopically and analytically pure, despite its light orange color. It is soluble in water and alcohols.

The low yield and the difficult purification procedure limit the use of **2** for large-scale synthesis. Another cysteine derivatization method was therefore applied to synthesize a pyridine−thioether chelating ligand. The reaction of vinylpyridines with cysteine thiol groups in peptides and proteins has been employed to link pharmaceutically active metal complexes to monoclonal antibodies.[41] We reacted 2-vinylpyridine with N^{α}-acetylcysteine in methanol solution to produce the bidentate ligand N^{α}-CysCH_2CH_2py (**3**) in almost quantitative yields (Scheme 1). The product, which is soluble in water and alcohols, was characterized by proton NMR and IR spectroscopy, as well as FD-MS and C,H,N,S elemental analysis.

Complexes. Bis(2,2′-bipyridine)ruthenium(II) complexes of the novel amino acid ligands were synthesized by utilizing [Ru(bipy)$_2$Cl$_2$] as the source of the metal fragment.[42] The synthesis followed a slightly modified procedure described by Meyer et al. for the preparation of tris(2,2′-bipyridine)ruthenium(II) derivatives covalently attached to lysine.[19] [Ru(bipy)$_2$Cl$_2$] was reacted overnight with the respective ligand in boiling methanol. After removal of the solvent, a small amount of water was added and complexes **4**−**6** (Figure 2) precipitated with an excess of NH_4PF_6. The complexes were obtained as their orange hexafluorophosphate salts and were characterized by IR and NMR spectroscopy, C,H,N and C,H,N,S elemental analysis, UV−vis spectroscopy, and cyclic voltammetry. Luminescence spectra

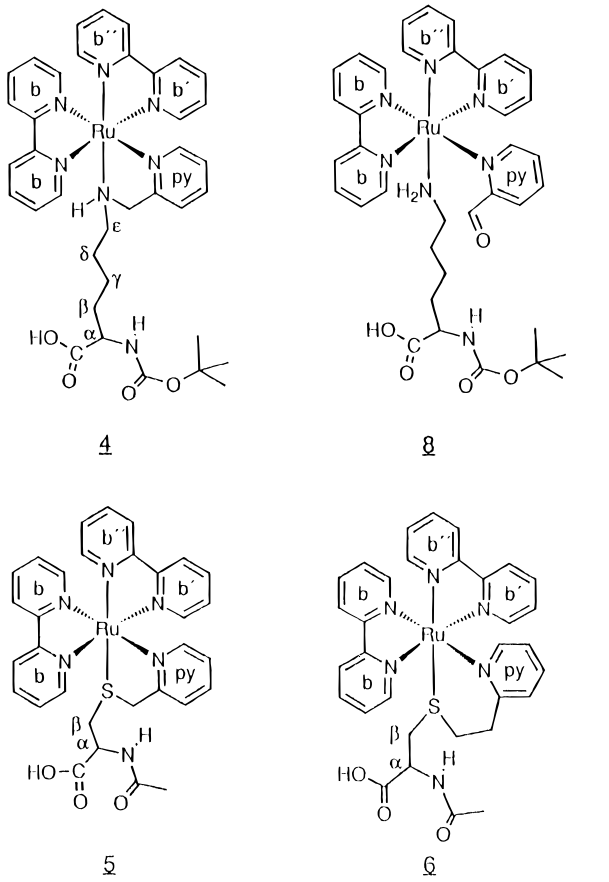


Figure 2. Structures and NMR labeling scheme for **4**−**6** and **8**.

of the N^{ϵ}-(pyridylmethyl)lysine complex **4** were recorded in acetonitrile. The emission quantum yield of the complex was determined (vide infra).

The lysine derivative **4** was isolated from aqueous solution as the double salt Na[Ru(bipy)$_2$(BocLysCH_2py)][PF_6]$_2$ (Na-**4**), containing the N^{ϵ}-(pyridylmethyl)lysine ligand as its carboxylate anion. The stoichiometry was evident from C,H,N analysis. Furthermore, the IR spectrum of the complex showed a carboxylate band at 1605 cm^{-1}, which is typical for carboxylate salts.[43] The amide band of the protected α-amino group was observed at 1701 cm^{-1}. If the product was not isolated by filtration of the NH_4PF_6 precipitate but extracted with CH_2Cl_2, the free acid [Ru(bipy)$_2$(BocLysCH_2py)][PF_6]$_2$ (**4**) was obtained. A shift of the carboxylate band in the IR spectrum to 1709 cm^{-1}, typical for free carboxylic acids,[43] was observed. The free acid was also obtained by cation exchange chromatography on Sephadex SP-C25 resin, using 0.1 M aqueous NaCl as eluent. Yields of ca. 50 % for the sodium salt and 33% for the free acid were obtained.

Higher yields of more than 70% were obtained for the synthesis of [Ru(bipy)$_2$(AcCysCH_2py)][PF_6]$_2$ (**5**). The crude complex contained small amounts of NH_4PF_6. Analytically pure samples were obtained by redissolution of the compound in hot water and precipitation at +4 °C. Large losses occur with this procedure, due to the relatively high solubility of the compound in water in the absence of excess NH_4PF_6. However the crude product was pure by both NMR and UV−vis spectroscopy, as well as cyclic voltammetry, and should be suitable for synthetic purposes.

The *S*-(pyridylethyl)cysteine complex **6** was obtained as an analytically pure compound after precipitation from the reaction

(39) Pouchert, C. J. *The Aldrich Library of NMR Spectra*, 2nd ed.; Aldrich Chemical Co., Inc.: Milwaukee, WI, 1983; Vol. 2, p 632.
(40) Anderegg, G.; Wenk, F. *Helv. Chim. Acta* **1967**, *50*, 2330−2332.
(41) Parker, D. *Chem. Soc. Rev.* **1990**, *19*, 271−291.
(42) Schröder, M.; Stephenson, T. A. In *Comprehensive Coordination Chemistry*, 4th ed.; Wilkinson, G., Gillard, R. D., McCleverty, J. A., Eds.; Pergamon Press: Oxford, New York, Beijing, Frankfurt, Sao Paulo, Sydney, Tokyo, Toronto, 1987; Vol. 4; pp 325−357.
(43) Nakamoto, K. *Infrared and Raman Spectra of Inorganic and Coordination Compounds*, 4th ed.; John Wiley & Sons: New York, Chichester, Brisbane, Toronto, Singapore, 1986; pp 231−239.

mixture with excess NH_4PF_6. Good yields of about 70% were observed.

All three complexes are highly soluble in methanol and acetonitrile and are moderately soluble in CH_2Cl_2. Their solubility in water is relatively low. The more hydrophobic character of **4** becomes evident in its slightly higher solubility in methylene chloride and its slightly lower solubility in water, as compared to those of **5** and **6**.

^{1}H-NMR Spectra. Ligands. Proton NMR spectroscopy has proved to be the most valuable tool for structural characterization of the compounds discussed in this paper. The labeling scheme is given in Figure 2. For comparative reasons the chemical shifts of the free and coordinated ligands are summarized in Table 1.

In the spectrum of NaBocLysCH_2py (Na-**1**), the most significant signal is a singlet at 3.88 ppm. This chemical shift is typical for 2-(aminomethyl)pyridine derivatives[44] and corresponds to the 2-pyridylmethyl protons in **1**. The triplet found for the lysine ϵ-CH_2 protons (2.64 ppm) of the ligand is shifted by 0.26 ppm to higher field compared to the signal for the free amino acid.[45] This shift clearly indicates substitution at the ϵ-amino group. As expected, the resonances of the α-CH and the α-amino protecting group were unaffected by substitution. The data are thus consistent with the structure of **1**.

Similar observations were made for the corresponding resonances of **2** and **3**. Sulfur substitution is evident from the shifts of the aromatic protons as well as the bridging alkyl groups. A low-field shift was observed for all pyridine protons of **2** and **3** compared to those for **1**. This effect must be assigned to the attached thioether sulfur atom, even though it is not clear why no difference was observed for the chemical shifts of these signals for the methylene-bridged ligand **2** and the ethylene-bridged ligand **3**.

In **3**, one CH_2 group of the ethylene bridge is attached to the pyridine ring and one is attached to the cysteine sulfur atom. A multiplet at 3.36 ppm was assigned to the py−CH_2 group. The multiplet for the S−CH_2 group was found at 3.04 ppm, overlapping with the left half of the typical ABX system characteristic for the diastereotopic β-CH_2 cysteine protons. For comparison, the spectrum of 2-picoline shows a singlet at 2.55 ppm[44] and the methionine S−CH_3 group is observed at 2.1 ppm.[45] The two CH_2 groups therefore experience a low-field shift caused by both the pyridine ring and the sulfur atom. This shift is even larger for the methylene bridge in **2**, as would be expected. The ABX systems observed for the cysteine CH_2 protons are centered at 2.94 ppm for both thioether ligands **2** and **3**. This value is close to the corresponding resonances given in the literature[45] for cysteine (3.0 ppm) and methionine (2.7 ppm). Thus, in contrast to the ϵ-CH_2 protons in **1**, the amino acid protons in **2** and **3** are almost unaffected by substitution at the heteroatom.

Complexes. The aliphatic parts of the spectra are much easier to interpret than the complex aromatic parts. We will therefore discuss the former first. Unless otherwise mentioned, the discussion of the thioether complexes **5** and **6** refers to spectra obtained from methanol-d_4 solutions, whereas the spectrum of **4** was measured in acetone-d_6. The chemical shifts are summarized in Table 1.

The most obvious feature in the spectrum of the cysteine derivatives is the presence of two sets of signals for the C(O)-Me and α-CH groups, due to the presence of two diastereomers, Λ*S*(Δ*R*) and Λ*R*(Δ*S*). This is common for thioether complexes[46] because of the relatively high inversion barrier around the sulfur atom. The relative intensities indicate that both diastereomers are formed in a 1:1 ratio. Note the chemical shifts of the α-CH groups, which should not be affected by direct metal coordination. For complex **6** the signals were found at 3.92 and 4.38 ppm. The latter resonance appears almost unshifted compared to that of the free ligand (4.36 ppm), whereas a significant high-field shift is observed for the former. This effect is even more pronounced in the spectrum of **5**, where chemical shifts of 3.59 and 4.38 ppm are observed. A likely explanation is that the α-CH group of one diastereomer experiences a strong ring current effect, which depends on the geometry of the compound and is stronger for the five-member chelate in **5** than for the six-member chelate in **6**.

The splitting of the methylene bridge signal in the spectrum of **5** is significant, as the two methylene protons become diastereotopic upon coordination of the pyridine−thioether moiety. In acetone-d_6 four doublets were observed, due to the presence of two diastereomers. The differences in shift between the two isomers are small. One pair of doublets is centered at 5.06 ppm, and another is centered at 4.67 ppm. Thus, one of the protons experiences a significant low-field shift of almost 1 ppm upon coordination, whereas the other signal is shifted about 0.4 ppm to lower field strength compared to that of the free ligand (4.15 ppm). It is a little surprising that the ethylene protons in **6** remain almost unshifted. Two sets of multiplets were observed at 3.40 (3H) and 2.91 ppm (1H), respectively. Coupling of the two signal groups was confirmed by a ^{1}H-COSY experiment.

The signals observed for the methylene bridge in the N^{ϵ}-(pyridylmethyl)lysine complex **4** follow the same trend as those for **5**. Two sets of doublets were found, centered at 4.05 and 4.80 ppm, respectively. **4** also apparently exists in two diastereomeric forms, but the shift differences between the isomers are less pronounced than in the two thioether complexes. The formation of Λ*S*(Δ*R*) and Λ*R*(Δ*S*) diastereoisomers was also reported for the 2-(1-aminoethyl)pyridine complex [Ru(bipy)$_2$(MeAMPy)]$^{2+}$.[47] The ϵ-CH_2 protons of the lysine side chain in **4** become diastereotopic upon coordination. Two broad, unresolved signals at 1.84 and 2.04 ppm were observed in the spectrum of **4** in methanol-d_4. Integration shows that each of the signals belongs to one proton. A ^{1}H-COSY NMR spectrum confirmed coupling between these signals, thus supporting the assignment of the signals to two diastereotopic protons. The observed high-field shift for the coordinated ligand compared to **1** (2.64 ppm) parallels the behavior of the corresponding CH_2 groups in **5** and **6**. The diastereoisomers were not resolved, since the signals were very broad. It is possible that geometric inversion occurs at the amine center, since the barrier is usually considerably lower than for thioether sulfur atoms. This could account for the line broadening in the spectrum of **4**. No effect was observed on the chemical shifts of the Boc and the α-CH group, consistent with coordination of **1** only via the (aminomethyl)pyridine moiety.

Assignment of the signals observed in the aromatic region of the spectra was difficult. Table 2 contains the chemical shifts and the assignments. It should be noted at this point that the chemical shift ranges for the different proton resonances of the three complexes were very similar. It is therefore not necessary to discuss each complex separately.

As is shown in Figure 2, four different types of pyridine ligands are expected: two equivalent pyridine rings of the

(44) Günther, H. *NMR-Spektroskopie*, 2nd ed.; Georg Thieme Verlag: Stuttgart, New York, 1983; pp 317−323.
(45) Abraham, R. J.; Fisher, J.; Loftus, P. *Introduction to NMR Spectroscopy*, 2nd ed.; John Wiley & Sons: Chichester, New York, Brisbane, Toronto, Singapore, 1993; pp 219−228.
(46) Abel, E. W.; Bush, R. P.; Hopton, F. J.; Jenkins, C. R. *J. Chem. Soc., Chem. Commun.* **1966**, 58.
(47) Keene, F. R.; Ridd, M. J.; Snow, M. R. *J. Am. Chem. Soc.* **1983**, *105*, 7075−7081.

Table 3. Electronic Spectral Data for the Amino Acid Complexes **4**−**6** in CH_3CN

	λ, nm (ϵ, M^{-1} cm^{-1})					
cmpd	dπ−π*				π−π*	
4		472 (8800)	426 (sh)	340 (10 000)	290 (>50 000)	245 (25 000)
5	480 (sh)	425 (8600)	400 (sh)	284 (>50 000)	251 (sh)	243 (23 000)
6	480 (sh)	425 (8800)	386 (sh)	284 (>50 000)	251 (sh)	243 (24 000)

bipyridine ligand in the equatorial position (b2−b6), one pyridine ring of the other bipyridine ligand occupying an equatorial position (b′2−b′6), the axial pyridine ring of the second bipyridine ligand (b″2−b″6), and the pyridine ring of the amino acid ligand, occupying the fourth equatorial position (py2−py5). The signals of the axial pyridine ligand (positions b″2−b″6) should be significantly different from the other resonances, since they experience the trans effect of the thioether and the amino ligand, respectively.

On this basis, the signal at highest field was assigned to Hb″6. If one compares methanol-d_4 spectra of the three complexes, the Hb″6 signal of **4** appears at highest field (9.00 ppm), compared to the same signal in the spectra of **5** (9.34 ppm) and **6** (9.42 ppm). This is in agreement with the expectation that the thioether S atom should cause a larger trans effect compared with the amine N atom. Unfortunately, the methanol-d_4 spectrum of **4** was poorly resolved in the aromatic region. The acetone-d_6 spectrum of **4** is therefore the basis for this discussion. ^{1}H-COSY experiments performed on methanol-d_4 solutions of **5** and **6** helped to identify the cross-coupling proton signals for Hb″2−Hb″5. Comparison of the spectra allowed the assignment of the corresponding Hb″ signals of **4**. A characteristic doublett is found for the b″3 protons in a range 8.74−8.65 ppm. The order of the b″ protons with increasing field strength is Hb″6 > Hb″3 > Hb″4 > Hb″5. The same order and comparable chemical shifts were reported for the proton resonances of the equatorial bipyridine ligands in the ^{1}H-NMR spectra of *trans*-$[Ru(bipy)_2(4\text{-}Etpy)(ISNE)][PF_6]_2$ (ISNE = ethyl isonicotinate)[48] and *trans*-$[Ru(bipy)_2(CH_3CN)_2][PF_6]_2$.[49] This is somewhat surprising, since the order observed for the equatorial pyridine protons in **4**−**6** was H6 > H4 > H5 > H3 for each ring, as reported for *trans*-tetrapyridine complexes of ruthenium(II).[50] The chemical shift ranges also suggest that the electronic properties of **4**−**6** can be compared to those of *trans*-tetrapyridine complexes.

Absorption and Luminescence Spectra. Complexes **4**−**6** exhibit UV−visible spectra consisting of MLCT- and interligand $\pi \rightarrow \pi^*$ bands, typical for bipyridine−ruthenium(II) complexes.[31,34,51] Table 3 summarizes the results. Extinction coefficients were obtained from solutions with concentrations of 1×10^{-4} to 5×10^{-5} M in CH_3CN. In this range, the values were constant. At lower concentrations, the spectra were obscured by significant tailing of high-energy bands. Figure 3 shows the absorption spectra of **4** (Figure 3a) and **5** (Figure 3c). The spectrum of **6** is virtually identical to that obtained for compound **5**.

The band assignments were made as reported for amino−bipyridine[51] and thioether−bipyridine−ruthenium(II)[31,34] complexes. A band at 472 nm with a shoulder at 426 nm, assigned to a d$\pi \rightarrow \pi^*$ MLCT transition, was observed in the spectrum of the *N*-(pyridylmethyl)-lysine complex **4**. In the spectra of the thioether−pyridine complexes **5** and **6**, this band is shifted to 425 nm. This is consistent with the observation of other

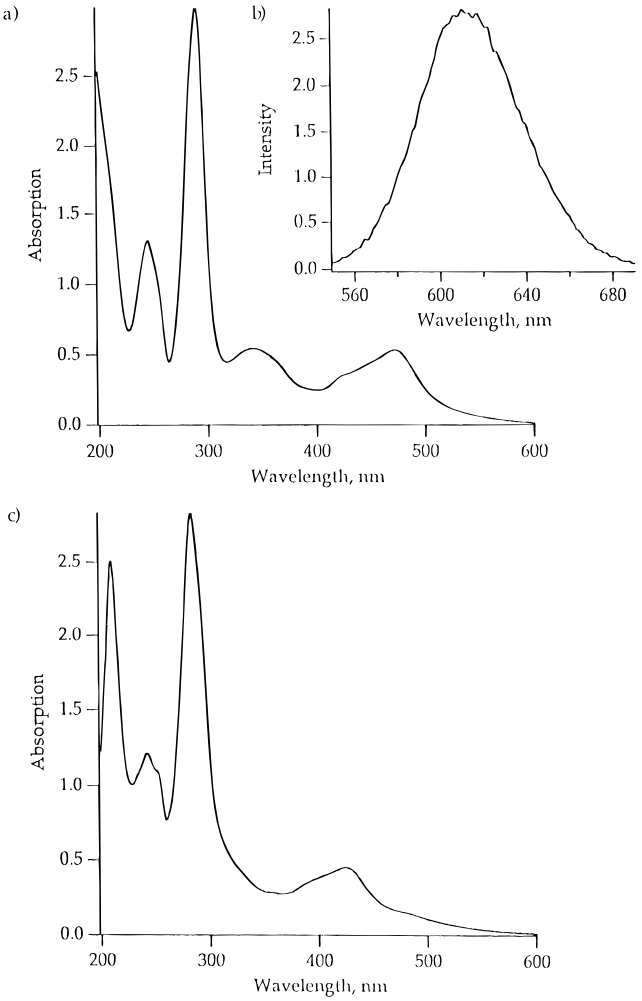


Figure 3. UV−vis spectra of **4** (a) and **5** (c), together with the luminescence spectrum of **4**.

authors that the energies of the MLCT transitions of ruthenium complexes are linearly correlated with their metal oxidation potentials.[31,52,53] For **5** and **6** metal oxidation occurs at +1.34 and +1.30 V vs the Ag/AgCl electrode (see electrochemical results), respectively. Oxidation of Ru(II) in **4** takes place at a lower potential of 0.96 V. The redox potentials are related to the energy required to excite photochemically an electron from a metal dπ into a ligand π^* orbital.

In the spectrum of **4** a second band at 340 nm can be assigned to a d$\pi \rightarrow \pi^*$ transition. This is due to two different types of bipyridine acceptor orbitals, one symmetric (χ) and one antisymmetric (ψ) with respect to the C_2 axis of the ligand,[54−57] giving rise to two d$\pi \rightarrow \pi^*$ transitions. Other authors have assigned the lower energy band around 450 nm to the d$\pi \rightarrow$

(48) Coe, B. J. *Inorg. Chem.* **1993**, *32*, 4012−4020.
(49) Walsh, J. L.; Durham, B. *Inorg. Chem.* **1982**, *21*, 329−332.
(50) Coe, B. J.; Meyer, T. J.; White, P. S. *Inorg. Chem.* **1995**, *34*, 593−602.
(51) Brown, G. M.; Weaver, T. R.; Keene, F. R.; Meyer, T. J. *Inorg. Chem.* **1976**, *15*, 190−196.
(52) Ghosh, P.; Chakravorty, A. *Inorg. Chem.* **1984**, *23*, 2242.
(53) Curtis, J. C.; Sullivan, B. P.; Meyer, T. J. *Inorg. Chem.* **1983**, *22*, 224.
(54) Ceulemans, A.; Vanquickenborne, L. G. *J. Am. Chem. Soc.* **1981**, *103*, 2238−2241.
(55) Mayoh, B.; Day, P. *Theor. Chim. Acta* **1978**, 259−275.
(56) Hipps, K. W.; Crosby, G. A. *J. Am. Chem. Soc.* **1975**, *97*, 7042−7048.
(57) Orgel, L. E. *J. Chem. Soc.* **1961**, 3683−3686.

$\pi^*(\psi)$ and the higher energy band around 350 nm to the $d\pi \rightarrow \pi^*(\chi)$ charge transfer.[34] The most pronounced difference between the spectra of **4** and the thioether complexes **5** and **6** is the lack of the higher energy $d\pi \rightarrow \pi^*(\chi)$ band in the latter. This spectroscopic behavior has been observed earlier for [Ru(bipy)$_2$] complexes with chelating bis(thioether) ligands[34] and for (methyl 8-quinolinyl thioether-N,S)bis(2,2′-bipyridine)ruthenium(II) salts.[32] The spectra of these compounds did not show a $d\pi \rightarrow \pi^*(\chi)$ band in the UV region. In contrast to this, the $d\pi \rightarrow \pi^*(\chi)$ transition was observed for amino−thioether complexes with R-S(CH_2CH_2)NH_2 chelating ligands.[34]

Luminescence spectra of the N^{ϵ}-(pyridylmethyl)-lysine complex **4** were recorded in CH_3CN solution (Figure 3b). At an excitation wavelength of 459 nm, the compound exhibits a relatively weak emission at 612 nm. The quantum yield was determined by comparison with a 10^{-4} M acetonitrile solution of [Ru(bipy)$_3$][PF_6]$_2$ ($\phi_{em,r} = 0.062$[58]). The excitation wavelength was chosen such that the standard and sample absorptions were equal. The emission quantum yield for complex **4** ($\phi_{em,s}$) was calculated as reported by Meyer et al.:[59]

$$\phi_{em,s} = \phi_{em,r}(A_r/A_s)(I_s/I_r)(n_s/n_r)^2 \quad (1)$$

where A_s, A_r are the absorption values of sample and reference, I_s, I_r are the emission intensities of sample and reference, and n_s, n_r are the refractive indices of sample and reference. Since A_r and A_s are equal and the refractive indices were assumed to be similar, eq 1 can be simplified to eq 2.

$$\phi_{em,s} = \phi_{em,r}(I_s/I_r) \quad (2)$$

The calculated quantum yield of 0.01 is relatively low compared to the value reported for the analogous bipyridine carboxamido-substituted lysine complex reported by Meyer et al. ($\phi_{em} = 0.077$[19]). A reason for this may be the subsequent two-electron oxidation of the coordinated (aminomethyl)pyridine moiety, which may lead to an efficient reductive quenching mechanism. Electrochemical ligand oxidation was observed in the cyclic voltammogram of **4**. However the quantum yield for the N^{ϵ}-(pyridylmethyl)lysine complex is 10 times larger than that for [Ru^{II}(bipy)$_2$Cl(4,4′-bipy)]$^+$ ($\phi_{em} < 10^{-3}$),[60] which has been successfully used for studies on intramolecular electron transfer in mixed-valence dimers. Thus, **4** should be well suited for the investigation of photoinduced redox processes in large molecular assemblies.

Electrochemistry. The cyclic voltammogram of [Ru(bipy)$_2$(BocLysCH$_2$py)] (**4**) is shown in Figure 4b. Three oxidation waves were observed at 0.96, 1.26, and 1.41 V, respectively. These signals can be unequivocally assigned to $Ru^{II/III}$ couples. Only one reduction wave occurred at a potential of 1.33 V. The signal at 0.96 V was assigned to the initial oxidation of Ru^{II} to Ru^{III} in complex **4**. This oxidation was followed by rapid ligand oxidation, resulting in the formation of an imine (N=C) double bond. The oxidation wave at 1.26 V was assigned to the $Ru^{II/III}$ couple in **7** (Scheme 2). Similar two-electron ligand oxidations were reported for [Ru(bipy)$_2$(AMPy)] (AMPy = 2-(aminomethyl)pyridine)[47,51,61] and [Ru(bipy)$_2$]$^{2+}$ complexes with RSCH$_2$CH$_2$NH$_2$ chelating ligands.[34] In contrast to the formation of [Ru(bipy)$_2$(AMPy)]$^{2+}$, where the corresponding imine complex is stable and can be isolated after exhaustive electrolysis of the parent compound, formation of the imine complex **7** upon

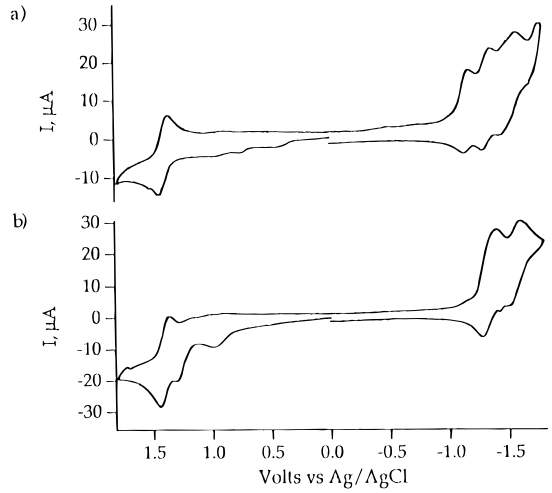
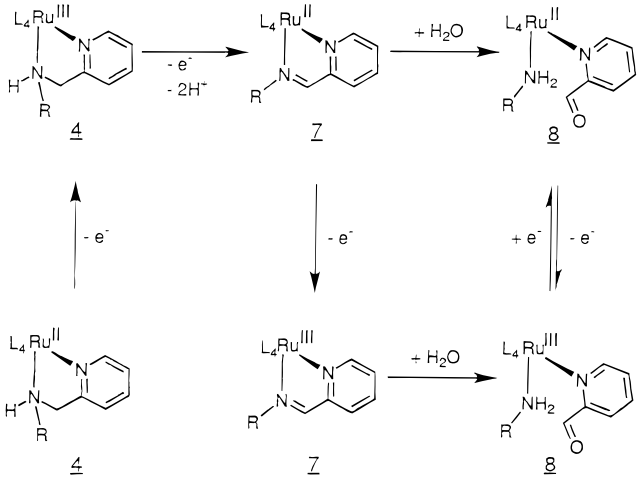


Figure 4. Cyclic voltammograms of **8** (a) and **4** (b) in CH_3CN containing 0.1 M TBAH at scan rates of 50 mV/s, respectively.

Scheme 2. Reactions following Initial Oxidation of **4** As Observed by Cyclic Voltammetry



oxidation of **4** is followed by rapid hydrolytic cleavage of the C=N bond. Thus, a third, quasi-reversible redox reaction is observed at $E_{1/2} = 1.37$ V ($\Delta E_p = 80$ mV). The product giving rise to this feature was identified as the 2-pyridinecarbaldehyde complex [Ru(bipy)$_2$(2-pyC(O)H)(BocLysOH)] (**8**). This complex was the only product obtained after exhaustive electrolysis of **4** at a potential of 1.20 V. It has a very characteristic ^{1}H-NMR spectrum with a singlet at 9.33 ppm for the aldehyde proton. **8** was also synthesized by the reaction of [Ru(bipy)$_2$Cl$_2$] with pyridine-2-carbaldehyde and N^{α}-Boc-L-lysine. The cyclic voltammogram of the product is shown in Figure 4a. It resembles the high-potential part of the voltammogram obtained for **4**. The measured half-wave potential for this product was 1.40 V ($\Delta E_p = 90$ mV) in CH_3CN, 30 mV higher than that of the redox couple observed for **4**. This small difference may be due to electrode processes leading to the formation of **8** in the latter experiment. The NMR spectra of the bulk electrolysis product and the ligand substitution product were identical.

All observed redox reactions following the initial oxidation of **4** at +0.96 V are shown in Scheme 2. Table 4 contains the measured redox potentials of **4** and **8**, together with the values for the thioether complexes **5** and **6**.

Theoretical values for the observed $Ru^{II/III}$ redox couples were calculated according to the literature.[37] The tabulated Lever parameters for pyridine (0.25 V), butylamine (0.13 V), and bipyridine (0.26 V) were used to obtain a theoretical value of +1.22 V vs NHE for the initial oxidation of **4**. When the

(58) Godefroi, E. F.; Little, E. L. *J. Org. Chem.* **1956**, *21*, 1163−1168.
(59) Chen, P.; Duesing, R.; Graff, D. K.; Meyer, T. J. *J. Phys. Chem.* **1991**, *95*, 5850−5858.
(60) Curtis, J. C.; Bernstein, J. S.; Meyer, T. J. *Inorg. Chem.* **1985**, *24*, 385−397.
(61) Ridd, M. J.; Keene, F. R. *J. Am. Chem. Soc.* **1981**, *103*, 5733−5740.

Table 4. Calculated[a,37] and Observed Electrochemical Parameters of **4**−**6** and **8** As Measured by Cyclic Voltammetry[b]

	metal oxidation		ligand reduction
cmpd	obsd $E_{1/2}$, V (ΔE_p, V)	calcd $E_{1/2}$, V	$E_{1/2}$, V (ΔE_p)
4	0.96[c] 1.16,[d] 1.37 (80)[e]	1.00,[c] 1.18,[d] 1.12[e]	−1.35 (100), −1.59 (100)
8	1.40 (90)	1.12	−1.16 (50), −1.33 (70), −1.51 (140)
5	1.50 (90)	1.30	−1.28 (110), −1.48 (90)
6	1.47 (80)	1.30	−1.29 (140), −1.51 (100)

[a] Corrected for the Ag/AgCl reference electrode: $E_{1/2,Ag/AgCl} = E_{1/2,NHE} - 0.222$ V. [b] Conditions: 0.1 M TBAH in CH_3CN, glassy carbon electrode, vs Ag/AgCl, scan rate 50 mV/s. [c] **4**, irreversible oxidation. [d] **7**, irreversible oxidation. [e] **8**.

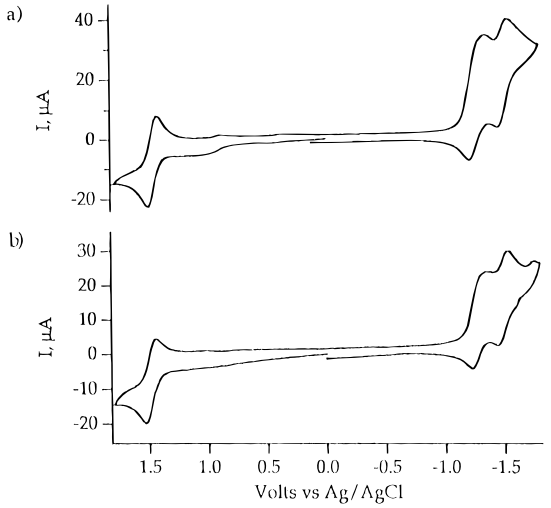


Figure 5. Cyclic voltammograms of **6** (a) and **5** (b) in CH_3CN containing 0.1 TBAH at scan rates of 50 mV/s, respectively.

potential of +0.222 V for the Ag/AgCl reference electrode used in the experiments is taken into consideration, the calculated and observed values (+1.18 V vs NHE) are in good agreement.

For the imine complex **7**, the tabulated increment for pyridine was used to describe the electronic properties of the imine N donor. The calculated value is 1.40 V vs NHE, which is also in good agreement with the experimental result (1.48 V vs NHE). For the oxidation of **8**, a theoretical value of 1.34 V vs NHE was calculated using the increments reported for butylamine and pyridine-4-carbaldehyde (+0.31 V). This is 250 mV less than the observed half-wave potential of 1.59 V vs NHE. It is likely that the electrochemical properties of pyridine-2-carbaldehyde are not accurately described by the increment tabulated for its isomer.

At negative potentials, two reversible couples at half-wave potentials of −1.35 V (ΔE_p = 100 mV) and −1.59 V (ΔE_p = 100 mV) were observed attributable to reductions of the bipyridine ligands. In the cyclic voltammogram of **8**, three reversible waves occurred at −1.15 V (ΔE_p = 50 mV), −1.33 V (ΔE_p = 70 mV), and −1.51 V (ΔE_p = 140 mV). Apparently only the reduction of **4** is observed in the former case. This is reasonable, since enough time passes for diffusion of **4** from the bulk to replace **8** at the electrode surface.

The two pyridine−thioether complexes **5** and **6** have much simpler cyclic voltammograms at positive potentials (Figure 5). Only one reversible couple was found in each at +1.50 V (ΔE_p = 90 mV) (**5**) and +1.47 V (ΔE_p = 80 mV) (**6**), respectively, attributable to the $Ru^{II/III}$ transition. Two reversible ligand reductions were observed in each voltammogram (Table 4).

The half-wave potentials for the $Ru^{II/III}$ couples are typical for thioether coordination to a $[Ru(bipy)_2]^{2+}$ fragment.[33,34] Calculation of the theoretical oxidation potential using the tabulated value for diethyl sulfide (+0.35 V)[37] results in +1.52 V vs NHE for the thioether complexes. The experimental values, corrected for NHE, are +1.72 V for **5** and +1.69 V for **6**. These values are somewhat higher than expected. However, it must be noted that the redox potentials are significantly solvent dependent. In CH_2Cl_2, irreversible couples were observed at +1.56 V (ΔE_p = 200 mV) for **5** and +1.52 V (ΔE_p = 240 mV) for **6**. These numbers are in very good agreement with the calculated value.

The higher metal oxidation potentials of the pyridine−thioether complexes **5** ($E_{1/2}$ = 1.50 V vs Ag/AgCl) and **6** ($E_{1/2}$ = 1.47 vs Ag/AgCl) compared to that of **4** ($E_{1/2}$ = 0.96 V vs Ag/AgCl) reflect the stabilization of the +2 oxidation state by the soft thioether ligand. This is consistent with the energy difference observed for the MLCT absorption bands at 472 nm (**4**) and 425 nm (**5** and **6**), respectively. These values are a measure of the photochemical oxidation potentials of the complexes.

Conclusions

Derivatization of L-lysine and L-cysteine has proved to be a facile route for the synthesis of new metal-coordinating amino acids. The ligands **1**−**3** have been prepared in good yields by standard procedures from readily available starting materials. They are well suited for the synthesis of redox-active transition metal complexes. In the $[Ru(bipy)_2]^{2+}$ complexes **5** and **6** the thioether ligands **2** and **3** behave as a coordinated methionine, as is evident from NMR and electrochemical studies. This is important for possible applications, since methionine coordination is known to play an important role in fine-tuning the reactivity of metal complexes in metalloproteins such as class I cytochromes *c* and blue copper proteins.[36]

The spectroscopic and electrochemical properties of $[Ru(bipy)_2(BocLysCH_2py)]$ (**4**) are particularly interesting. The luminescence data suggest that the complex could be used as a building block for the construction of photochemically active redox peptides. However the inherent instability of the coordinated ligand **1** with respect to metal oxidation imposes a serious limitation on its use. Current work in our laboratory focuses on the synthesis of derivatives of **1**, which are protected from ligand oxidation by substitution of the ϵ-amino proton and whereby it should be possible to prevent the oxidative decomposition of the ligand. In addition, first results show that it is possible to introduce the ruthenium(II) complexes described into small peptides. We are also investigating possibilities of utilizing the photoelectrochemical potential of **4** for the reduction of CO_2 by Cu and Ni complexes covalently attached to **[**$Ru(bipy)_2(BocLysCH_2py)]^{2+}$ via peptide bonds. The applications of the new series of ligands and their metal complexes as building blocks for biomimetic assemblies offer many exciting challenges for future work.

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