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Simple Synthesis of Ruthenium π Complexes of Aromatic Amino Acids and Small Peptides

Dmitry S. Perekalin,[a] Eduard E. Karslyan,[a] Pavel V. Petrovskii,[a] Yulia V. Nelyubina,[a] Konstantin A. Lyssenko,[a] Alexey S. Kononikhin,[b] Eugene N. Nikolaev,[b] and Alexander R. Kudinov*[a]

Abstract: The interaction of $[Ru(\eta^6\text{-}C_{10}H_8)(Cp)]^+$ ($Cp = C_5H_5$) with aromatic amino acids (L-phenylalanine, L-tyrosine, L-tryptophane, D-phenylglycine, and L-*threo*-3-phenylserine) under visible-light irradiation gives the corresponding $[Ru(\eta^6\text{-amino acid})(Cp)]^+$ complexes in near-quantitative yield. The reaction proceeds in air at room temperature in water and tolerates the presence of non-aromatic amino acids (except those which are sulfur containing), monosaccharides, and nucleotides. The complex $[Ru(\eta^6\text{-}C_{10}H_8)(Cp)]^+$ was also used for selective labeling of Tyr and Phe residues of small peptides, namely, angiotensin I and II derivatives.

Keywords: amino acids · bioorganometallic chemistry · compound labeling · ruthenium · sandwich complexes

Introduction

Selective labeling of peptides by organometallic compounds attracts considerable attention as a valuable method to analyze and modify their structure and functions.[1] For these applications it is desirable to accomplish labeling under near-physiological conditions, that is, in the presence of oxygen, water, and contaminant biosubstances. The resulting species must also withstand typical reactions of peptide chemistry, such as protection, deprotection, coupling, and cleavage from support.

The $[Ru(C_5R_5)]^+$ fragments proved to be useful for peptide labeling because of their high tendency to coordinate aromatic rings of amino acids giving stable $[Ru(\eta^6\text{-arene})(C_5R_5)]^+$ derivatives.[2,3] Besides labeling applications, the activation of Ru-coordinated arenes towards nucleophilic substitution allows effective construction of biologically active biphenyl ether peptides.[4] The preparation of $[Ru(\eta^6\text{-arene})(C_5R_5)]^+$ complexes is usually achieved by heating $[Ru(C_5R_5)(MeCN)_3]^+$ solvates with a desired arene.[5] However, in the case of biomolecules, π-complexation can be complicated by metal coordination at amino, imidazole, and thioether functional groups, which therefore must be protected.[2c,6] To overcome this limitation Grotjahn et al. have synthesized the chelate ruthenium complex $[Ru(\eta^5,\eta^1\text{-}C_5H_4(CH_2)_3NH_2)(MeCN)_2]^+$, which metalates unprotected phenylalanine and small peptides.[7] More recently, Fairchild and Holman showed that $[Ru(C_5Me_5)(MeCN)_3]^+$ (generated from $[\{RuCl(C_5Me_5)\}_4]$ and MeCN) reacts with free aromatic amino acids, giving the corresponding π complexes.[8] Both methods require an inert atmosphere, which makes them somewhat inconvenient for common biochemical practice. Herein, we describe an alternative simple approach for the synthesis of the ruthenium π complexes of aromatic amino acids and small peptides that tolerate the presence of air, water, various functional groups, and contaminant biosubstances.

Results and Discussion

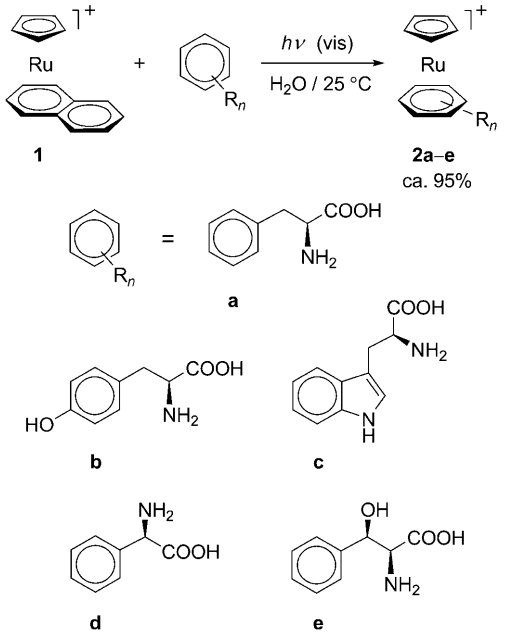
Recently we have shown that the naphthalene ligand in the Kündig complex $[Ru(\eta^6\text{-}C_{10}H_8)(Cp)]^+$ (**1**; $Cp = C_5H_5$)[9,10] is easily replaced by other arenes under visible-light irradia-

[a] Dr. D. S. Perekalin, E. E. Karslyan, Dr. P. V. Petrovskii, Dr. Y. V. Nelyubina, Prof. K. A. Lyssenko, Prof. A. R. Kudinov
A. N. Nesmeyanov Institute of Organoelement Compounds
Russian Academy of Sciences, 119991 Moscow (Russian Federation)
Fax: (+7) 499135-50-85
E-mail: arkudinov@ineos.ac.ru

[b] Dr. A. S. Kononikhin, Prof. E. N. Nikolaev
Emanuel Institute of Biochemical Physics
Russian Academy of Sciences, 119334 Moscow (Russian Federation)

Supporting information (NMR spectra for metalation of phenylalanine and angiotensin peptides) for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201000520.

tion with the formation of $[Ru(\eta^6\text{-arene})(Cp)]^+$ cations.[11] Applying this method to aromatic amino acids, we found that the tetrafluoroborate **1**·BF_4 reacts with one equivalent of L-phenylalanine, L-tyrosine, L-tryptophane, D-phenylglycine, and L-*threo*-3-phenylserine to give the corresponding π complexes **2a–e** in almost quantitative yield (Scheme 1). Importantly, this reaction proceeds in air at room temperature



Scheme 1. Synthesis of the ruthenium complexes **2a–e**.

in water solution.[12] The workup is simple evaporation of the reaction mixture, which removes both water and naphthalene.

Cations **2a–e** were isolated as water-soluble salts with the BF_4^- anion and characterized by ^1H NMR spectroscopy and elemental analysis. Upon π coordination, ^1H NMR signals of aromatic protons of amino acids are high-field shifted by around 1 ppm, allowing convenient monitoring of the reaction (see Figure S1 in the Supporting Information). All of the compounds obtained are indefinitely stable in air, except for **2c**·BF_4, which notably decomposes within several weeks.[13]

The structure of the N-protonated form of **2b** (as the [**2b**–H][SiF_6] salt)[14] was determined by X-ray diffraction (Figure 1). The Ru···Cp (1.812 Å) distance in cation [**2b**–H]$^{2+}$ is close to that in the starting naphthalene complex **1** (1.811 Å).[15] The coordinated arene ring is folded along the C7–C9 line by 4.0° due to conjugation with the OH substituent. Accordingly, the Ru1–C8 distance (2.269 Å) is about 0.08 Å longer that other Ru–C_{arene} bonds (av. 2.192 Å). A similar effect was observed in the dicationic ruthenium complex with a tyrosine ligand $[Ru(\eta^6\text{-Tyr})(1\text{-}i\text{Pr-4-Me}C_6H_4)]^{2+}$.[3b] In the crystal, cations [**2b**–H]$^{2+}$ are packed in columns through intermolecular Cp···C_6 stacking interactions with the shortest C1···C7 distance of 3.152 Å and 1.6° angle between the Cp and C_6 planes.

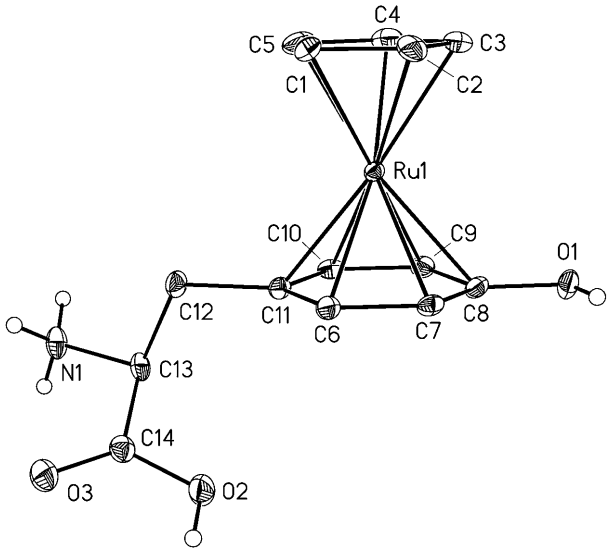


Figure 1. The structure of cation [**2b**–H]$^{2+}$ with ellipsoids at the 50% probability level. All hydrogen atoms, except those of NH_2 and OH groups, are omitted for clarity. Selected interatomic distances [Å]: Ru1–C1 2.193(2), Ru1–C2 2.189(3), Ru1–C3 2.179(3), Ru1–C4 2.164(3), Ru1–C5 2.1778(15), Ru1–C6 2.198(2), Ru1–C7 2.208(2), Ru1–C8 2.269(2), Ru1–C9 2.213(3), Ru1–C10 2.200(3), Ru1–C11 2.202(2), O1–C8 1.333(3).

For peptide labeling not only mild conditions but also a selectivity of metal coordination is an important issue. We found that reaction of **1** with phenylalanine cleanly gives the desired π complex **2a** in the presence of most natural amino acids (alanine, arginine, aspartic acid, glutamic acid, glutamine, glycine, histidine, isoleucine, lysine, leucine, proline, serine, threonine, valine), some monosaccharides (glucose, galactose), and nucleotides (sodium adenosine triphosphate). However, in the presence of sulfur-containing amino acids (1 equiv of methionine, cysteine, or cistine) this reac-

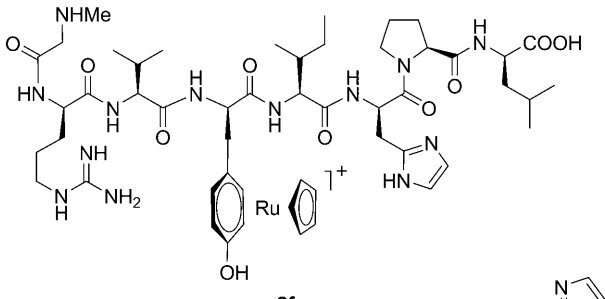
Abstract in Russian:

Взаимодействие $[CpRu(\eta^6\text{-}C_{10}H_8)]^+$ с ароматическими аминокислотами (L-фенилаланин, L-тирозин, L-триптофан, D-фенилглицин, L-*трео*-3-фенилсерин) при облучении видимым светом дает соответствующие комплексы $[CpRu(\eta^6\text{-аминокислота})]^+$ с практически количественным выходом. Реакция протекает на воздухе при комнатной температуре в водном растворе и не затрагивает неароматические аминокислоты (за исключением серосодержащих), моносахариды и нуклеотиды. Комплекс $[CpRu(\eta^6\text{-}C_{10}H_8)]^+$ был также использован для селективного введения метки в тирозиновые и фенилаланиновые фрагменты малых пептидов – производных ангиотензина.

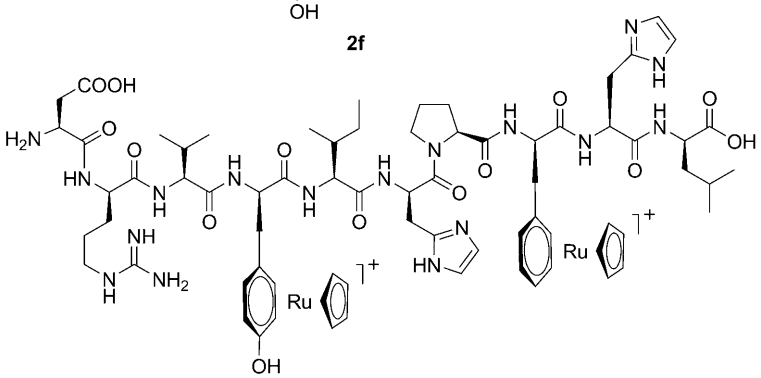
tion yields only around 30% of **2a**, presumably because of the concurrent coordination of ruthenium at the sulfur atom.[2c,16] Interestingly, such S coordination is not observed for *N*-acetyl methionine.

The irradiation of **1** with a 1:1:1 mixture of phenylalanine, tyrosine, and tryptophane leads to the preferred formation of the tryptophane complex **2c** (80%) versus **2a** (10%) and **2b** (10%), probably due to electron donation of the heterocyclic nitrogen atom. Complex **2c** is formed as roughly an equimolar mixture of both possible diastereomers.

Inspired by successful π complexation of free aromatic amino acids, we have attempted to use our method for the metalation of peptides. The irradiation of angiotensin II derivative (Sar-Arg-Val-Tyr-Ile-His-Pro-Leu) with **1** (4 equiv) in D_2O resulted in near-quantitative formation of complex **2f** as indicated by ^{1}H NMR spectroscopy and ESI mass spectra. The analogous reaction with angiotensin I (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu) allowed metalation of both aromatic rings to give **2g**. At the same time, the reaction of **1** (20 equiv) with a larger peptide, lysozyme (129 amino acids), gave no reproducible π complexation, according to the ESI mass spectrometry results. Presumably, in this case the reaction is hindered because all hydrophobic aromatic residues of lysozyme are hidden inside the peptide globule. In this respect, it is interesting to note that lysine residues located on the surface of lysozyme have been successfully labeled recently by a ruthenocenyl pyrillium salt.[17]



2f



2g

Conclusion

A simple approach to ruthenium π complexes of aromatic amino acids and small peptides was developed. The synthesis was carried out in water at room temperature in the presence of oxygen and concomitant biological substances (non-aromatic amino acids, sugars, and nucleotides). High selectivity of π coordination and the stability of the resulting complexes allow further application of this method for peptide labeling.

Experimental Section

General: All reactions were carried out in distilled water in air. The starting ruthenium complex $[Ru(\eta^6\text{-}C_{10}H_8)(Cp)][BF_4]$ was prepared as described in the literature.[9] Angiotensin II derivative (Sar-Arg-Val-Tyr-Ile-His-Pro-Leu) and angiotensin I (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu) were obtained from Sigma–Aldrich and used as received. Visible-light irradiation was performed by a high-pressure mercury vapor lamp with a phosphor coated bulb (e.g., Philips HPL-N 400W). The irradiation can be also performed with a household 100 W incandescent lamp, although the reaction time must be extended to 36 h. The ^{1}H NMR spectra were recorded with a Bruker Avance-400 spectrometer. The mass spectra were recorded on a commercial 7-Tesla Finnigan linear quadrupole ion trap-Fourier transform (LTQ FT) mass spectrometer (Thermo Electron Corp., Bremen, Germany) equipped with an Ion Max electrospray ion source. The following conditions were used for electrospray: flow rate = 1 ul min^{-1}, positive ion mode, needle voltage = 3.4 kV; no sheath and auxiliary gas flow, tube lens voltage = 130 V; heated capillary temperature = 250 °C. Full-scan MS spectra (m/z 200 to 2000) were acquired in the FT-ICR with a resolution $R = 100000$ at m/z 400.

General procedure for synthesis of [2a–e][BF$_4$]: A mixture of $[Ru(\eta^6\text{-}C_{10}H_8)(Cp)][BF_4]$ (38.1 mg, 0.1 mmol) and aromatic amino acid (0.1 mmol) was dissolved in H_2O (5 mL)[18] and irradiated for 8 h. The solution changed from yellow to colorless and white precipitate of the naphthalene appeared. The resulting mixture was evaporated at 40 °C and the residue was triturated with Et_2O to give compounds [**2a–e**][BF_4] as off-white solids, which were pure according to ^{1}H NMR spectroscopy (ca. 95% yield). Compounds [**2a–c**][BF_4] obtained this way were analytically pure (although can contain solvate water), whereas [**2d–e**][BF_4] were further crystallized by vapor diffusion of Et_2O into a solution of the products in MeOH/MeCN (ca. 85% yield).

The reaction also worked well in phosphate buffer solution with pH 7.0 and ionic strength 0.1. In case excess of $[Ru(\eta^6\text{-}C_{10}H_8)(Cp)][BF_4]$ was used, it was extracted from water with CH_2Cl_2. Occasionally, the reaction mixture turns pale orange after irradiation, presumably due to formation of $[Ru(Cp)(H_2O)_3]^+$ or similar solvate species. To remove such impurities, the product can be heated in toluene for 10 min, filtered, and then washed with EtOH/CH_2Cl_2 (1:1).[19] On the other hand, the reactions with a slight excess of aromatic amino acid (ca. 5%) were usually cleaner. After irradiation, the remaining amino acid was removed by filtration of the water solution of the product (**2b**·BF_4, **2d**·BF_4) or by washing the solid sample with EtOH/CH_2Cl_2 (1:1) ([**2a**,**c–d**][BF_4]).

Cations **2a**–**e** can be also precipitated from water as salts with the BPh_4^- anion. These salts can be easily purified by reprecipitation from solutions in acetone by Et_2O.

Compound ***2a*·BF_4**: ^{1}H NMR (400 MHz, D_2O, 25 °C): $\delta = 2.96$ (t, $J = 6.8$, 2H; CH_2), 3.88 (d, $J = 6.8$, 1H; CH), 5.34 (s, 5H; Cp), 6.05–6.20 ppm (m, 5H; C_6H_5); elemental analysis calcd (%) for $C_{14}H_{16}BF_4NO_2Ru \cdot 2H_2O$: C 37.02, H, 4.44; found: C 37.13, H 4.08.

Compound ***2b*·BF_4**: ^{1}H NMR (400 MHz, D_2O, 25 °C): $\delta = 2.83$ (t, $J = 7.2$, 2H; CH_2), 4.10 (d, $J = 7.2$, 1H; CH), 5.11 (s, 5H; Cp), 5.85–5.95 ppm (m, 4H; C_6H_4); elemental analysis calcd (%) for $C_{14}H_{16}BF_4NO_3Ru$: C 38.73, H, 3.71; found: C 38.81, H 3.69.

Compound ***2c*·BF_4** *(mixture of two diastereomers)*: ^{1}H NMR (400 MHz, D_2O, 25 °C): $\delta = 3.15$–3.35 (m, 2H; CH_2), 3.90–3.95 (m, 1H; CH), 4.83 (s, 5H; Cp), 4.85 (s, 5H; Cp), 5.65–5.80 (m, 2H; C_6H_4), 6.72–6.86 (group of doublets, 2H; C_6H_4), 7.49 (s, 1H, CH), 7.51 ppm (s, 1H, CH); elemental analysis calcd (%) for $C_{16}H_{17}BF_4N_2O_2Ru \cdot H_2O$: C, 40.44; H, 4.03; found: C, 40.03; H, 4.18.

Compound ***2d*·BF_4**: ^{1}H NMR (400 MHz, D_2O, 25 °C): $\delta = 4.49$ (s, 1H, CH), 5.31 (s, 5H, Cp), 6.15 (m, 3H, C_6H_5), 6.26 ppm (m, 2H, C_6H_5); elemental analysis calcd (%) for $C_{13}H_{14}BF_4NO_2Ru$: C 38.64, H 3.49; found: C 38.45, H 3.71.

Compound ***2e*·BF_4**: ^{1}H NMR (400 MHz, D_2O, 25 °C): $\delta = 3.75$ (d, $J = 5.2$, 1H; CH), 4.81 (d, $J = 5.2$, 1H; CH), 5.31 (s, 5H; Cp), 6.07 (s, 2H; C_6H_5), 6.15 (m, 2H; C_6H_5), 6.291 ppm (d, $J = 6.0$, 1H; C_6H_5); elemental analysis calcd (%) for $C_{14}H_{16}BF_4NO_3Ru$: C 38.73, H 3.71; found: C 39.06, H 3.82.

Metalation of angiotensin peptides: A mixture of [Ru(η^6-$C_{10}H_8$)(Cp)]-[BF_4] (1.5 mg, 0.004 mmol) and Sar-Arg-Val-Tyr-Ile-His-Pro-Leu or Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu (1.0 mg, 0.001 mmol) was dissolved in D_2O (0.7 mL). A ^{1}H NMR spectrum and a ESI mass spectrum were measured from this solution. The mixture was then irradiated in an NMR tube for 8 h and the measurements were repeated. ESIMS for **2f**: *m*/*z*: 1134.50 [M^+] ($C_{51}H_{78}N_{13}O_{10}Ru$), 567.76 [$M^{2+}$]. Full NMR spectra are given in the Supporting information.

X-ray analysis: Crystals of [**2b**–H]·SiF_6·$2H_2O$ ($C_{14}H_{21}F_6NO_5RuSi$, $M = 526.48$) are monoclinic, space group $P2_1$, at 100 K: $a = 6.8868(4)$, $b = 9.8711(5)$, $c = 13.2049(7)$ Å; $\beta = 96.160(1)°$; $V = 892.49(8)$ Å^3; $Z = 2$ ($Z' = 1$); $\rho_{calcd} = 1.959$ g cm^{-3}; $\mu(Mo_{K\alpha}) = 1.034$ cm^{-1}; $F(000) = 528$. Intensities of 5806 reflections were measured with a Bruker SMART APEX2 CCD diffractometer ($\lambda(Mo_{K\alpha}) = 0.71072$ Å, ω scans, $2\theta < 58°$) and 4467 independent reflections ($R_{int} = 0.0151$) were used in further refinements. The structure was solved by direct methods and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. The hydrogen atoms of NH and OH groups and those of water molecules were located in difference Fourier synthesis. The positions of CH hydrogen atoms were calculated. All hydrogen atoms were refined in isotropic approximation by a riding model. The refinement converged to $wR2 = 0.0454$ and GOF = 1.001 for all independent reflections ($R1 = 0.0179$ was calculated against F for 4434 observed reflections with $I > 2\sigma(I)$). All calculations were performed by using SHELXTL PLUS 5.0.[20] CCDC-748972 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[13] We did not observe any significant decomposition of **2b**·BF_4 in contrast to the reported instability of the related [Ru(η^6-*N*-Ac,O-Et-tyrosine)(Cp)][PF_6]; see ref. [2b].

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