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Ruthenium naphthalene complexes with a carboxy-substituted cyclopentadienyl ligand

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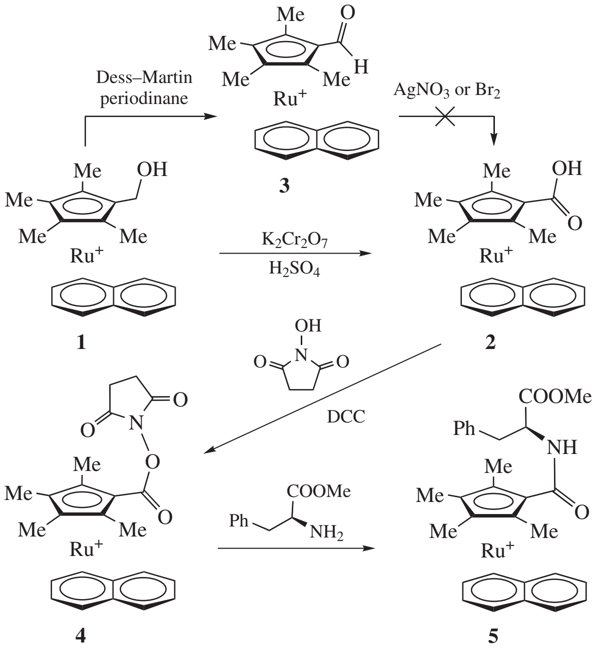
The oxidation of the ruthenium naphthalene complex $[(C_5Me_4CH_2OH)Ru(C_{10}H_8)]^+$ gave the carboxylic acid $[(C_5Me_4COOH)Ru(C_{10}H_8)]^+$ which was further converted into the phenylalanine amide $\{[C_5Me_4CONHCH(CH_2Ph)COOMe]Ru(C_{10}H_8)\}^+$; the structures of both acid and amide were determined by X-ray diffraction analysis.

Ruthenium arene complexes are potential anticancer agents.[1] Attention is focused on the half-sandwich complexes (arene)$RuLCl_2$ and $[(arene)RuL_2Cl]^+$ (L = 2-electron ligand), which exhibit promising cytotoxic and antimetastatic activities.[2] However, Loughrey *et al.* recently found that the sandwich naphthalene complex $[(C_5Me_5)Ru(C_{10}H_8)]^+$ can also inhibit the growth of 11 cancer cell lines including those resistant to cisplatin.[3] Later, we synthesized amino acid esters of similar hydroxy-substituted complex $[(C_5Me_4CH_2OH)Ru(C_{10}H_8)]^+$ **1** (Scheme 1), which also possess cytotoxic activity.[4] Here, we report the preparation of carboxylic acid derivatives from compound **1**, which are promising not only for anticancer studies but also for the preparation of ruthenium complexes with various ligands *via* replacement of naphthalene.[5] In particular, they can be useful for the synthesis of organometallic enzyme inhibitors.[6]

Complex **1** can be easily obtained by a published procedure[4,7] in two steps from $RuCl_3 \cdot xH_2O$. However, we found that its further oxidation to carboxylic acid $[(C_5Me_4COOH)Ru(C_{10}H_8)]^+$ **2** requires carefully selected conditions. The conventional oxidation[8] of **1** by $KMnO_4$ in alkaline or neutral media is very slow, while the naphthalene ligand decomposes in acidic media. Oxidation of **1** by Dess–Martin periodinane cleanly gives aldehyde $[(C_5Me_4CHO)Ru(C_{10}H_8)]^+$ **3** in 80% yield,[†] which, however, could not be converted into acid **2** using $AgNO_3$ or bromine. This can be attributed to the electron acceptor effect of the cationic ruthenium center and the steric effect of methyl groups. Finally, we found that **1** reacts with $K_2Cr_2O_7$ in the presence of H_2SO_4 to afford product **2** in 79% yield.[‡]



Scheme 1

The direct reaction of carboxylic acid **2** with L-phenylalanine methyl ester in the presence of dicyclohexylcarbodiimide (DCC) proceeds unexpectedly slowly (conversion is less than 50% in a week), presumably because of the steric hindrance. In order to facilitate the process, we prepared *N*-hydroxysuccinimide ester **4** (83%), which was then treated with L-phenylalanine methyl ester to provide the target amide $\{[C_5Me_4CONHCH(CH_2Ph)COOMe]Ru(C_{10}H_8)\}^+$ **5** in 78% yield.[§]

[†] [**3**]BF_4: a solution of [**1**]BF_4[4] (46 mg, 0.1 mmol) and Dess–Martin periodinane (64 mg, 0.15 mmol) in CH_2Cl_2 (3 ml) and water (0.1 ml) was stirred for 12 h. The mixture was then eluted with CH_2Cl_2–acetone (1:1) through a short silica gel column (4×0.5 cm). A yellow fraction was collected and evaporated to dryness, and the residue was reprecipitated from CH_2Cl_2 by Et_2O to give pure [**3**]BF_4 (37 mg, 80%). ^1H NMR (400 MHz, acetone-d_6) δ: 10.06 (s, 1H, CHO), 7.89–7.80 (m, 4H, $C_{10}H_8$), 7.07 (m, 2H, $C_{10}H_8$), 6.48 (m, 2H, $C_{10}H_8$), 1.93 (s, 6H, C_5Me_4), 1.88 (s, 6H, C_5Me_4). ^{13}C NMR (100 MHz, acetone-d_6) δ: 190.59 (1C, CHO), 132.11 ($C_{10}H_8$ uncoord.), 127.90 ($C_{10}H_8$ uncoord.), 97.84, 97.57, 94.85, 89.65, 86.39, 82.95, 8.63 ($C_5\mathit{Me}_4$), 8.50 ($C_5\mathit{Me}_4$). Found (%): C, 50.65; H, 4.68. Calc. for $C_{20}H_{21}BF_4ORu \cdot 0.5H_2O$ (%): C, 50.43; H, 4.52.

[‡] [**2**]BF_4: a solution of [**1**]BF_4 (450 mg, 0.97 mmol) in 30 ml of Me_2CO was added dropwise to a solution of $K_2Cr_2O_7$ (852 mg, 2.9 mmol) in H_2O (20 ml) and H_2SO_4 (4 ml), and the mixture was stirred overnight. Then, isopropanol (1 ml) was added to quench the oxidant. Aqueous HBF_4 (1 ml, 48%) was added, and acetone was extracted with Et_2O (2×15 ml). The remaining aqueous solution was extracted with $MeNO_2$ (3×15 ml); the extract was dried with Na_2SO_4 and evaporated to dryness. The product was reprecipitated from $MeNO_2$–CH_2Cl_2 by Et_2O, yielding [**2**]BF_4 (365 mg, 79%) as a yellow powder. ^1H NMR (400 MHz, acetone-d_6) δ: 7.86–7.72 (m, 4H, $C_{10}H_8$), 6.88 (m, 2H, $C_{10}H_8$), 6.35 (m, 2H, $C_{10}H_8$), 1.90 (s, 6H, C_5Me_4), 1.82 (s, 6H, C_5Me_4). ^{13}C NMR (100 MHz, acetone-d_6) δ: 166.98 (1C, COOH), 131.93 ($C_{10}H_8$ uncoord.), 127.69 ($C_{10}H_8$ uncoord.), 97.59, 96.65, 95.26, 89.52, 86.65, 9.85 (2C, $C_5\mathit{Me}_4$), 8.73 (2C, $C_5\mathit{Me}_4$). Found (%): C, 48.21; H, 4.32. Calc. for $C_{20}H_{21}BF_4O_2Ru \cdot H_2O$ (%): C, 48.11; H, 4.64.

[§] [**4**]BF_4: a solution of [**2**]BF_4 (46 mg, 0.1 mmol), DCC (21 mg, 0.1 mmol), with *N*-hydroxysuccinimide (64 mg, 0.15 mmol) in CH_2Cl_2 (4 ml) and $MeNO_2$ (1 ml) was stirred overnight. The resulting mixture was eluted with CH_2Cl_2–acetone (2 : 1) through a short silica gel column (4×0.5 cm). An orange fraction was collected and evaporated to dryness, and the residue was reprecipitated from CH_2Cl_2 by Et_2O to give [**4**]BF_4 (48 mg, 83%) as an orange-brown powder. ^1H NMR (400 MHz, acetone-d_6) δ: 7.91–7.81 (m, 4H, $C_{10}H_8$), 7.08 (m, 2H, $C_{10}H_8$), 6.52 (m, 2H, $C_{10}H_8$), 3.05 (s, 4H, CH_2CH_2), 1.90 (s, 6H, C_5Me_4), 1.88 (s, 6H, C_5Me_4). ^{13}C NMR

Cations **2**–**5** were isolated as air-stable BF_4^- salts. They were characterized by ^1H and ^{13}C NMR spectroscopy and elemental analysis. Four distinct signals of the methyl groups of a cyclopentadienyl ligand appear in the ^1H NMR spectrum of **5** due to the chirality of the amino acid substituent. The structures of the carboxylic acid [**2**]BF_4 and amide [**5**]BF_4 were established by X-ray diffraction (Figures 1 and 2).[¶] The distances from metal to ligand planes Ru···C_5 (1.804 and 1.795 Å) and Ru···C_6 (1.726 and 1.724 Å) are almost identical in both complexes, being very close to those in the parent cation $[Cp^*Ru(C_{10}H_8)]^+$ (1.803 and 1.723 Å, respectively).[3] In accordance with a general tendency, the ruthenium atoms in cations **2** and **5** are shifted from the bridgehead carbon atoms of the naphthalene ligand so that the Ru–C(bridge) distances (av. 2.271 Å) are notably longer than other Ru–C($C_{10}H_8$) bonds (av. 2.217 Å).

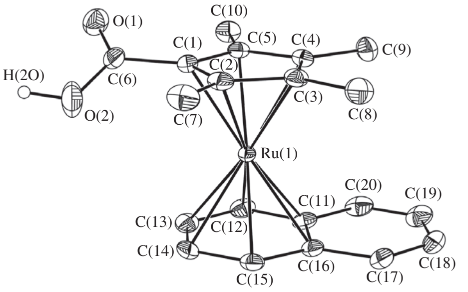


Figure 1 Structure of cation **2** with ellipsoids at a 50% probability level. All hydrogen atoms except of OH are omitted for clarity. Selected interatomic distances (Å): Ru(1)–C(1) 2.152(2), Ru(1)–C(2) 2.172(2), Ru(1)–C(3) 2.183(2), Ru(1)–C(4) 2.198(2), Ru(1)–C(5) 2.195(2), Ru(1)–C(11) 2.269(2), Ru(1)–C(12) 2.216(2), Ru(1)–C(13) 2.225(2), Ru(1)–C(14) 2.229(2), Ru(1)–C(15) 2.224(2), Ru(1)–C(16) 2.271(2), Ru···C_5 1.804, Ru···C_6 1.726.

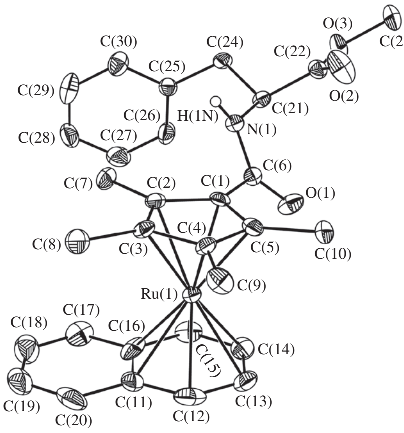


Figure 2 Structure of cation **5** with ellipsoids at a 50% probability level. All hydrogen atoms except of NH are omitted for clarity. Selected interatomic distances (Å): Ru(1)–C(1) 2.164(5), Ru(1)–C(2) 2.172(5), Ru(1)–C(3) 2.183(5), Ru(1)–C(4) 2.179(5), Ru(1)–C(5) 2.151(5), Ru(1)–C(11) 2.274(6), Ru(1)–C(12) 2.211(6), Ru(1)–C(13) 2.217(6), Ru(1)–C(14) 2.204(6), Ru(1)–C(15) 2.210(6), Ru(1)–C(16) 2.270(5), Ru···C_5 1.795, Ru···C_6 1.724.

Thus, we developed a simple method for the synthesis of the carboxylic acid derivatives of ruthenium naphthalene complexes. They can be used for the preparation of ruthenium complexes with other ligands *via* naphthalene replacement and for anticancer studies.

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(100 MHz, acetone-d_6) δ: 169.87 (C, CO), 132.50 ($C_{10}H_8$ uncoord.), 127.79 ($C_{10}H_8$ uncoord.), 98.15, 97.80, 95.23, 90.47, 87.29, 25.59 (CH_2CH_2), 9.74 (C_5Me_4), 8.91 (C_5Me_4). Found (%): C, 50.11; H, 4.02. Calc. for $C_{24}H_{24}BF_4NO_4Ru$ (%): C, 49.84; H, 4.18.

[**5**]BF_4: a solution of [**4**]BF_4 (93 mg, 0.16 mmol) and methyl ester of L-phenylalanine (100 mg, 0.56 mmol) in CH_2Cl_2 (5 ml) was heated at 55 °C for 24 h. The resulting mixture was eluted with CH_2Cl_2–acetone (10 : 1) through a silica gel column (10×0.5 cm). The orange fraction was collected and evaporated to dryness, and the residue was reprecipitated twice from CH_2Cl_2 by Et_2O to give [**5**]BF_4 (80 mg, 78%) as an orange-brown foamy powder. ^1H NMR (400 MHz, acetone-d_6) δ: 7.81 (m, 2H, $C_{10}H_8$), 7.71 (m, 2H, $C_{10}H_8$), 7.56 (bd, 1H, NH, *J* 8 Hz) 7.39–7.28 (m, 5H, Ph), 6.84 (m, 2H, $C_{10}H_8$), 6.27 (m, 2H, $C_{10}H_8$), 4.93 (ddd, 1H, CH, *J* 10, 8 and 5 Hz), 3.80 (s, 3H, COOMe), 3.35 (dd, 1H, CH_2, *J* 14 and 4 Hz), 3.08 (d, 1H, CH_2, *J* 14 and 10 Hz), 1.74 (s, 3H, C_5Me_4), 1.66 (s, 3H, C_5Me_4), 1.65 (s, 3H, C_5Me_4), 1.56 (s, 3H, C_5Me_4). ^{13}C NMR (100 MHz, acetone-d_6) δ: 171.45 (CO), 137.17 (Ph), 131.62 (Ph), 129.25 ($C_{10}H_8$ uncoord.), 128.48 ($C_{10}H_8$ uncoord.), 127.95 (Ph), 126.84 (Ph), 97.68, 94.45, 93.30, 89.53, 86.70, 54.00 (CH), 51.82 (COO*Me*), 36.83 (CH_2), 9.12 (C_5Me_4), 8.29 (C_5Me_4). Found (%): C, 54.46; H, 4.81. Calc. for $C_{30}H_{32}BF_4NO_3Ru\cdot H_2O$ (%): C, 54.56; H, 5.19.

[¶] *Crystallographic data*. Crystals of [**2**]BF_4 ($C_{20}H_{21}BF_4O_2Ru$, $M = 481.25$) are monoclinic, space group $P2_1/c$, at 100 K: $a = 12.2172(5)$, $b = 12.2172(5)$ and $c = 14.5434(6)$ Å, $\beta = 100.3840(10)°$, $V = 1899.27(14)$ Å^3, $Z = 4$ ($Z' = 1$), $d_{calc} = 1.683$ g cm^{-3}, μ(MoKα) = 8.76 cm^{-1}, F(000) = 968.

Crystals of [**5**]BF_4 ($C_{30}H_{32}BF_4NO_3Ru$, $M = 642.45$) are monoclinic, space group $P2_1$, at 120 K: $a = 11.2703(5)$, $b = 15.3631(7)$ and c = = 16.8590(7) Å, $\beta = 108.4230(10)°$, $V = 2769.5(2)$ Å^3, $Z = 4$ ($Z' = 2$), $d_{calc} = 1.543$ g cm^{-3}, μ(MoKα) = 6.26 cm^{-1}, $F(000) = 1312$.

Intensities of 15135 and 31552 reflections for [**2**]BF_4 and [**5**]BF_4, respectively, were measured with Bruker APEX2 DUO and APEX2 CCD diffractometers [λ(MoKα) = 0.71072 Å, ω-scans, $2\theta < 58°$]; 5039 and 14651 independent reflections [$R_{int} = 0.0204$ and 0.0536] were used in a further refinement for [**2**]BF_4 and [**5**]BF_4, respectively. The structures were solved by a direct method 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 were located from the Fourier density synthesis. The H(C) atom positions were calculated. All hydrogen atoms were refined in the isotropic approximation within a riding model. For [**2**]BF_4, the refinement converged to $wR_2 = 0.0888$ and GOF = 1.029 for all the independent reflections [$R_1 = 0.0302$ was calculated against F for 4642 observed reflections with $I > 2\sigma(I)$]. For [**5**]BF_4, the refinement converged to $wR_2 = 0.1372$ and GOF = 1.016 for all the independent reflections [$R_1 = 0.0581$ was calculated against F for 10839 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.

CCDC 985572 and 985573 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk. For details, see ‘Notice to Authors’, *Mendeleev Commun.*, Issue 1, 2014.