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ARTICLE

Bis-cyclometalated Rhodium and Iridium Chloride Complexes Yield Different Products Upon Reaction With 9,10-Diaminophenanthrene

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Abstract. The reaction of 9.10-diaminophenanthrene with [{Rh(μ-Cl)(ptpy)$_2$}$_2$] yields – quite unexpected – the new cyclometalated complex salts [Rh(ptpy)$_2$(9,10-diiminophenanthrene)]PF$_6$ (**1**), whereas with the corresponding dinuclear iridium compound the "usual" [Ir(ptpy)$_2$(9,10-diaminophenanthrene)]PF$_6$ (**2**) is obtained. The molecular structure of compound **1** was confirmed by single-crystal X-ray diffraction. **1** crystallized in the monoclinic space group $P2_1/n$ as a dichloromethane solvate. Both compounds display significant cytotoxicity against human cancer cell lines with the IC_{50} values in the low micromolar range.

Introduction

Bis-cyclometalated Ir^{III} complexes play an important role in the development of modern optoelectronic technologies (e.g. organic light-emitting diodes – OLEDs and light-emitting electrochemical cells – LEECs), biological labels, and chemical sensors.[1–3] Recently also many studies were devoted towards therapy of cancers due to the high cytotoxic activities of many of these compounds.[4] Our group's long-time interest in cyclometalated M^{III} complexes (M = Rh, Ir), triggered also a study of the cytotoxic properties of heteroleptic cationic [M(N^C)$_2$(N^N)]$^+$ complexes with ancillary ligands N^N of the substituted bipyridine or phenanthroline type.[5] 9,10-Diaminophenanthrene ("pham") and its oxidation product 9,10-diiminophenanthrene ("phim") appear structurally related to the phenanthroline ligands already studied by us, which is important in view of the known anti-cancer activity of the "metallointercalators" based on Rh^{III} complexes with this and closely related diimino ligands.[6]

In this communication we describe the synthesis, characterization, and the evaluation of the biological properties of two new cyclometalated complex salts [M(C^N)$_2$(L)]PF$_6$ (M = Rh, L = 9,10-diiminophenanthrene; M = Ir, L = 9,10-diaminophenanthrene).

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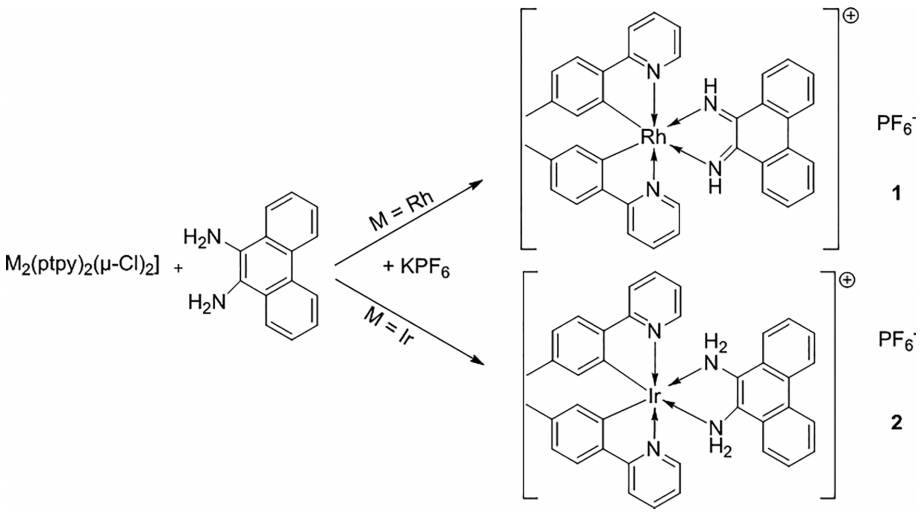
Results and Discussion

The preparation of the cationic mononuclear title complexes started by cleavage of the dimeric precursor compounds [{M(μ-Cl)(ptpy)$_2$}$_2$] (M = Rh, Ir; ptpy = 2-*para*-tolyl-pyridinato) by the chelating 9,10-diaminophenanthrene ligand in a refluxing mixture of dichloromethane / methanol. The thus formed chloride salts [M(C^N)$_2$(L)]Cl yielded after metathesis with KPF$_6$ the corresponding hexafluorophosphate salts which were obtained as red-brown powders (Scheme 1). The new complexes were characterized by elemental analysis, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, infrared and UV/Vis spectroscopy. Moreover, for **1** a single-crystal X-ray diffraction study was undertaken.

The ^{1}NMR spectrum of the rhodium compound **1** in CD_2Cl_2 is characterized by the presence of a low-field singlet at δ = 11.19 ppm, which is absent in the spectrum of the iridium complex **2**. This signal is reminiscent of the = NH proton signals of the above-mentioned "phim" complexes.[6] Examination of the mass spectra of both compounds shows that the molecular peak in **1** corresponds to the formula [Rh(ptpy)$_2$(phim)]$^+$ complex, while in **2** a formula [Ir(ptpy)$_2$(pham)]$^+$ can be derived. Thus it can be concluded that a primarily formed rhodium complex of "pham" had been oxidized by air to the final compound **1**. This result is fully analogous to the earlier observation that the reaction of [Rh(phpy)$_2$Cl]$_2$ with "pham" leads to isolation of [Rh(phpy)$_2$(phim)]$^+$ salts.[6b] This "non-innocent" redox behavior of the "pham"/"phim" system has also been observed with Rh^I and Ru^{II} complexes.[7,8]

The UV/Vis-absorption spectrum of the rhodium complex **1** was recorded in dichloromethane. The spectrum of **1** showed bands at 245, 256, 268, 289, and 305 nm, respectively, which could be assigned to spin-allowed (IL) ($\pi \rightarrow \pi^*$)(ptpy) transitions. The band at 368 and 433 nm corresponds to a ^{1}MLCT [d_π(Rh) $\rightarrow \pi^*$(ptpy)] transition. The UV/Vis-absorption spectrum of the iridium complex **2** was also recorded in dichloromethane. The spectrum of **2** showed bands at 258 and 310 nm, respectively, which could be assigned to spin-allowed (IL)



Scheme 1. Synthesis of **1** and **2**.

($\pi \rightarrow \pi^*$) (ptpy) transitions. The band at 393, 468 and 504 nm corresponds to a ^{1}MLCT [d_π(Ir) $\rightarrow \pi^*$(ptpy)] transition.

We were able to obtain red- brown single crystals of compound **1** suitable for X-ray diffraction. **1** crystallizes in the monoclinic space group $P2_1/n$ as a bis-dichloromethane solvate. A selected view of the cation of **1** is shown in Figure 1. Table 1 lists selected bond lengths and angles in comparison with two other rhodium-"phim" complexes. **1** exhibits two cyclometalated 2-(p-tolyl)pyridinato ligands in the usual trans N,N configuration and one 9,10-diiminophenanthrene ligand in pseudooctahedral coordination.

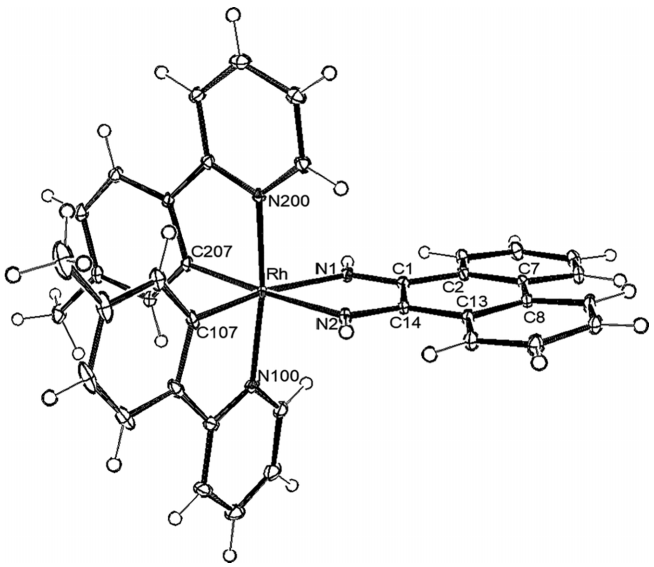


Figure 1. Molecular structure of the cation of **1** in the crystal (ORTEP drawing and atom labeling scheme with 30 % probability level).

The Rh–N and Rh–C bond parameters within the cyclometallating chelate rings have the usually observed values. The long C1–C14 bond together with the short C1–N1 and C14–N2 bonds clearly proof the diiminophenanthrene nature of the ancillary ligand. Somewhat surprising is the relatively large asymmetry in the bonding of the two imino nitrogen atoms to the central rhodium atom, which differ by 0.053(2) Å, whereas in the closely related bis(phenylpyridinato) complex this difference is only 0.031(2) Å and in the bis(ethylenediamine) complex this difference is even smaller [0.011(15) Å].

Table 1. Important bond lengths /Å and angles /° in **1** and two related compounds.

	1	[Rh(phpy)$_2$(phi)]Cl [6b]	[Rh(en)$_2$(phi)]Br$_3$ [9]
Rh–N$_{phim}$	2.168(2), 2.115(2)	2.153(2), 2.122(2)	1.996(15), 2.007(14)
Rh–N(N^C)	2.047(1), 2.038(2)	2.033(2), 2.043(2)	–
Rh–C(N^C)	2.010(2), 1.985(2)	2.003(2), 1.996(3)	–
C=NH	1.292(2), 1.290(2)	1.300(3), 1.281(3)	1.29(2), 1.28(2)
C1–C14	1.498(2)	1.487(3)	1.45(2)
(NRhC)(N^C)	80.99(6), 81.22(7)	80.66(9), 80.79(9)	–
(NRhN)$_{phim}$	73.40(6)	73.92(8)	77.1(6)

Organometallic Ir^{III} and Rh^{III} compounds containing bis-aryl ligands attracted considerable attention as potential candidates for the rational design of novel metal-based anti-cancer drugs. In recent years, we examined different series of 2-(*p*-tolyl)pyridine-containing Ir and Rh complexes for their in vitro cytotoxicity and demonstrated the modulating effects of selected ancillary bidentate aromatic ligands.[5] To continue our efforts in establishing detailed structure-activity relationships for this promising compound class, complexes **1** and **2** were subjected to an MTT assay probing the in vitro antiproliferative activity on the representative two human cancer cell lines HT-29 (colorectal adenocarcinoma) and MCF-7 (breast adenocarcinoma) (see Table 2).

Both complexes show a high activity against both tested cell lines reaching IC_{50} values of 0.6 μM (**1**) and 1.4 μM (**2**) against HT-29 as well as 0.7 μM (**1**) and 0.9 μM (**2**) against MCF-7 respectively. In direct comparison to cisplatin, the activity of the complexes is significantly increased (factor 10 on

Table 2. IC_{50} values in μM of **1** and **2** for the antiproliferative effects in MCF-7 and HT-29 cells.

	IC_{50} /μM	
	HT-29	MCF-7
1	0.6 ± 0.1	0.7 ± 0.2
2	1.4 ± 0.2	0.9 ± 0.2
Cisplatin	9.9 ± 0.5	23.0 ± 0.6

HT-29 and approximately factor 20 against MCF-7). Thus, the presented complexes are comparable to the most active complexes tested in our recent works. It is evident that the substitution neither of the metal cation nor the oxidation state of the bidentate imine/amine ligand seems to negatively affect the overall activity, which might be explained by a similar mode of action that is not disturbed by the introduced structural changes. In view of the results of *Barton* et al., who showed specific interactions of related Rh^{III} complexes with DNA, especially DNA base-pair mismatches,[10] it can be assumed that one influencing factor for the mode of action of **1** and **2** is the ability to intercalate into DNA. The overall efficiency is further controlled by the cellular uptake, which crucially depends on the solubility and lipophilicity of the complexes. Further studies concerning these factors are envisioned for the most active complexes published by our group in recent years.

Conclusions

The synthesis and characterization of the new bis-cyclometalated cationic complex salts $[Rh(ptpy)_2(9.10\text{-diiminophenanthrene})]PF_6$ (**1**) and $[Ir(ptpy)_2(9.10\text{-diaminophenanthrene})]PF_6$ (**2**) were reported and their biological activities were investigated. The compounds exhibit cytotoxic effects towards two cell lines (HT29 and MCF-7). For **1** and **2** high activities were observed, providing IC_{50} values in the low micromolar range and an approximately tenfold increase in activity compared to cisplatin. Furthermore, the crystal and molecular structure of the new compound **1** was confirmed by X-ray crystal structure determination.

Experimental Section

General: All manipulations were performed under an atmosphere of dry nitrogen using conventional Schlenk techniques. 9,10-Diaminophenanthrene was purchased from Alfa Aesar and used as received. $[\{M(\mu\text{-Cl})(C^{\wedge}N)_2\}_2]$ (*M* = Rh, Ir) were prepared by adequately modified literature methods.[3a,3b] NMR spectra were usually recorded in CD_2Cl_2 using a Jeol Eclipse 400 instrument operating at 400 MHz (^1H) and 100 MHz (^{13}C) respectively. Chemical shifts are given in ppm, referenced to the solvent signals at δ = 5.30 (^1H) or 53.8 ppm (^{13}C). Mass spectra were measured using a JeolMstation JMS 700 spectrometer. IR spectra were recorded as KBr pellets on a Bruker IFS 66v/S spectrometer. UV/Vis spectra were obtained on a Cary 50 Bio UV/Vis spectrophotometer. Elemental analyses (C, H, N) were performed by the Microanalytical Laboratory of the Department of Chemistry, LMU Munich, using a Heraeus Elementar Vario EL instrument.

Biological Activities: Dulbecco's Modified Eagle's Medium (DMEM), containing 10 % fetal calf serum, 1 % penicillin and streptomycin, was used as growth medium. MCF-7 and HT-29 cells were detached from the wells with trypsin and EDTA, harvested by centrifugation and resuspended again in the cell culture medium. The assays were carried out on 96 well plates with 6000 (3000) cells per well for MCF-7 (HT-29, respectively). After 24 h of incubation at 37 °C and 10 % CO_2, the cells were treated with the compounds **1** and **2** (with DMSO concentrations of 0.5 %) with a final volume of 200 μL per well. For a negative control, one series of cells was left untreated. The cells were incubated for 48 h followed by adding 50 μL MTT (2.5 mg·mL^{-1}). After an incubation time of 2 h, the medium was removed and 200 μL DMSO were added. The formazan crystals were dissolved and the absorption was measured at 550 nm, using a reference wavelength of 620 nm. Each test was repeated in quadruplicates in two independent experiments for each cell line. IC50 values for cisplatin were determined under identical conditions.

Synthesis of 1 and 2: To a solution of $[\{M(\mu\text{-Cl})(ptpy)_2\}_2]$ (*M* = Rh, Ir) (0.15 mmol) in 25 mL of a mixture of CH_2Cl_2/MeOH (3:1) the ligand 9,10-diaminophenanthrene (0.3 mmol) was added and the mixture refluxed with stirring for 2 h. After cooling to room temperature KPF_6 (0.5 mmol) was added and stirred for 20 min. The solvent was removed to dryness in vacuo and the residue dissolved in dichloromethane and chromatographed on alumina with CH_2Cl_2/acetone (9:1) as the eluent. The resulting solution was evaporated to dryness, the residue was redissolved in 5 mL of dichloromethane, and the product was precipitated by slow diffusion of methanol and *n*-hexane.

$[Rh(ptpy)_2(9,10\text{-diiminophenanthrene})]PF_6$ (1): Yield: 80 mg (33.7 %). $C_{38}H_{30}N_4F_6PRh$: calcd. C, 57.73; H, 3,83; N, 7.07 %; found: C, 57.82; H, 4.21; N, 6.97 %. **MS** (FAB+): *m*/*z* = 645.7 $[M]^+$ complex cation. **^1H NMR**: δ = 11.19 (2 H, NH), 8.27 (d, 8 Hz, 2 H, H6), 8.06 (d, 7 Hz, 2 H, H3), 8.02–7.78 (m, 8 H, H4+H_{phim}), 7.67 (d, 8 Hz, 2 H, H8), 7.60 (t, 8 Hz, 2 H, H_{phim}), 7.13 (m, 2 H, H5), 6.94(d, 6 Hz, 2 H, H9), 6.06 (s, 2 H, H11), 2.11 (s, 6 H, CH3). **^1H NMR** (400 MHz, CD_3OD): δ = 8.36 (d, 8 Hz, 2 H, H6), 8.30 (dd, *J* = 8/1.2 Hz, 2 H, H_{phim}), 8.11–8.08 (m, 4 H, H3+H4), 7.98 (ddd, *J* = 8/7/1.6 Hz, 2 H, H_{phim}), 7.79 (ddd, *J* = 8/7/1.3 Hz, 2 H, H_{phim}), 7.75 (d, *J* = 8 Hz, 2 H, H8), 7.56 (ddd, *J* = 8/7/1.0 Hz, 2 H, H_{phim}), 7.20 (ddd, *J* = 7/6/1.5 Hz, 2 H, H5), 6.89 (ddd, *J* = 8/1.7/0.7 Hz, 2 H, H9), 6.06 (s, 2 H, H11), 2.05 (s, 6 H, CH_3). **$^{13}C\{^1H\}$ NMR**: δ = 168.9 (C=NH), 166.0 (d, JRh-C = 28.5 Hz, C12), 165.8 (C2), 150.7 (C6), 141.5/ 141.1 (C7+C10), 138.9 (C4), 136.0 (C_{phim}), 133.8 (C11), 130.6 (C_{phim}), 126.5 (C8), 126.0 (C_{phim}), 125.7 (C9), 125.3/124.9 (C_{phim}), 123.6 (C5), 120.2 (C3), 22.2 (CH_3). **IR** (KBr) $\tilde{\nu}$ = 3343 w,br, 3300 w,br, 3035 w, br, 2915 w,br, 2863 w,br, 1603 s, 1588 s, 1563 m, 1481 s, 1462 s, 1451 s, 1428 m, 1387 s, 1315 m, 1270 w, 1241 w, 1209 w, 1163 m, 1138 w, 1064 w, 1033 w, 957 w, 841 vs, br, 773 m, 755 w, 714 w, 677 w, 617 w, 557 s, 525 m, 513 w, 469 w, 429 w cm^{-1}. **UV/Vis** (0.025 mM, CH_2Cl_2): λ (nm) = 245 (60.000), 256 (58.280), 268 (59.400), 289 (37.840), 305 (21.960), 368 (12.960), 433 (12.900).

$[Ir(ptpy)_2(9,10\text{-diaminophenanthrene})]PF_6$ (2): Yield: 90 mg (34 %). $C_{38}H_{32}N_4F_6PIr$: calcd. C, 51.75; H, 3.66; N, 6.35 %; found: C, 51.44; H, 3.73; N, 6.16 %. **MS** (FAB+): *m*/*z* = 735.8 $[M + H]^+$. **^1H NMR**: δ = 8.32 (d, 8 Hz, 2 H, H6), 8.25–8.10 (m, 2 H, NH_2?) 7.92 (d, *J* = 8 Hz, 2 H, H3), 7.88 (d, *J* = 6 Hz, 2 H, H_{phim}), 7.81 (ddd, *J* = 8/7/1.5 Hz, 2 H, H4), 7.69 (d, *J* = 8 Hz, 2 H, H8), 7.63 (t, *J* = 7.5 Hz, 2 H, H_{phim}), 7.06 (m, 2 H, H5), 6.87 (ddd, *J* = 8/1.7/0.6 Hz, 2 H, H9), 6.02 (s, 2 H, H11) 2.12 (s, 6 H, CH_3). **$^{13}C\{1H\}$ NMR**: δ = 170.7 (CNH?), 168.4 (C2), 152.0 (C6?), 149.5 (C12?), 141.6/ 141.5 (C7+C10), 138.9 (C4), 136.1/ 133.9 (C_{phi}m) 132.9 (C11), 130.1 (2Cphim), 126.3 (C8), 125.6/125.4/125.1 (C9+3Cphim), 123.7 (C5), 120.0 (C3), 22.1 (CH3). **IR** (KBr) $\tilde{\nu}$ = 3343 w,br, 3305 w,br, 3037 w,br, 2918 w,br, 2862 w,br, 1603 s, 1590 s, 1563 m, 1479 s, 1463 s,

1452 s, 1428 w, 1398 s, 1318 m, 1269 w, 1242 w, 1222 w, 1163 m, 1137 w, 1066 w, 1036 w, 957 w, 846 vs,br, 770 m, 757 w, 717 w, 679 w, 615 w, 557 s, 528 m, 514 w, 452 w, 426 w cm^{-1}. **UV/Vis** (0.025 mM, CH_2Cl_2) λ (nm) = 258 (75.200), 310 (27.200), 393 (10.560), 468 (17.920), 504 (15.129).

Crystal Structure Determination and Refinement: A suitable crystal for X-ray diffraction of **1** was obtained from dichloromethane/MeOH/n-hexane solution. The crystal was selected by means of a polarization microscope, mounted on the tip of a glass fiber, and investigated at 100 K with a Bruker D8 venture TXS diffractometer using Mo-K_α radiation (λ = 0.71073 Å). The structures were solved by SHELXT[11] and refined by full-matrix least-squares calculations on F^2 (SHELXL-2014/7).[12] Anisotropic displacement parameters were refined for all non-hydrogen atoms. Details of the crystal data, data collection, structure solution, and refinement parameters of compound **1** are summarized in Table 3.

Table 3. Experimental data for the crystal structure determination of **1**.

	[Rh(ptpy)$_2$(9,10-diiminophenanthrene)]PF_6 (**1**)
Empirical formula	$C_{40}H_{34}Cl_4F_6N_4PRh$
Formula weight	960.39
Temperature /K	100(2)
Crystal system	monoclinic
Space group	$P2_1/n$
Unit cell dimensions	
a /Å	14.6641(4)
b /Å	16.9956(5)
c /Å	15.6241(4)
β /°	101.0760(10)
Volume /Å^3	3821.39(18)
Z	4
ρ calcd. /g·cm^{-3}	1.669
μ (Mo-K_α) /mm^{-1}	0.835
F(000)	1936
Crystal size /mm^3	0.1 × 0.08 × 0.03
Θ-range	2.784 to 30.522°.
Index ranges	$-20 \le h \le 20$, $-24 \le k \le 24$, $-22 \le l <= 22$
Reflections collected	70682
Independent reflections	11653 [*R*(int) = 0.0373]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7461 and 0.7137
Data / parameters	11653 / 515
Goodness-of-fit on F^2	1.012
Final *R* indices [$I > 2\sigma(I)$]	R_1 = 0.0295, wR_2 = 0.0732
R indices (all data)	R_1 = 0.0367, wR_2 = 0.0777
Largest diff. peak and hole /e·Å^{-3}	1.478 and –1.188

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB21EZ, UK. Copies of the data can be obtained free of charge on quoting the depository number CCDC-1938428 (**1**) (Fax: +44-1223-336-033; E-Mail: deposit@ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk)

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Keywords: Iridium; Rhodium; Cyclometalated complexes; Organometallic anti-cancer drugs; Bioorganometallic Chemistry

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