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Cytotoxic Activities of Half-sandwich *M*(III) Complexes (*M* = Rh, Ir) Bearing Chloro-substituted Bidentate-coordinated Phenanthroline or Terpyridine Ligands

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The synthesis and characterization of four compounds [*M*(η^5-C_5Me_5)(N^N)Cl]PF_6 [N^N = 4,7-dichloro-1,10-phenanthroline with *M*=Rh, **1**, and *M* = Ir, **2**, and N^N = 4'-(4-chlorophenyl)-2,2':6',2''-terpyridine in the κ^2N,N'-coordination mode with *M*=Rh, **3**, and *M*=Ir, **4**] are described. All compounds were characterized by spectroscopic means and their molecular structures in the crystal were confirmed by single-crystal X-ray diffraction studies. The cytotoxicity of all compounds was evaluated by MTT assay against the three cancer cell lines HeLa (cervical carcinoma), HT-29 (colon adenocarcinoma) and MCF-7 (human breast adenocarcinoma). The complexes **3** and **4** display promising activity with IC_{50} values of 1 μM. The rhodium(III) complex **1** also shows highly improved cytotoxicity compared to cisplatin against the cancer cell lines HT-29 and MCF-7. In contrast to this, the iridium(III) complex **2** is even less active against the HeLa cell line than cisplatin.

Introduction

In searching for less toxic and more potent alternatives to the well-established anticancer drug cisplatin, organometallic complexes of other transition metals have been widely studied as promising anticancer agents in the last years.[1] When considering organometallic transition metal compounds, Ru(arene) complexes are certainly most intensively investigated, see a very recent overview.[1i] Within the group of the other platinum metals, half-sandwich type of complexes containing the central atoms rhodium(III) and iridium(III) respectively, have also received significant attention in this field, *e.g.*[2–7] It is also interesting to note that totally new modes of action and cell death mechanisms are being considered in conjuction with transition metal complexes, *e.g.* ferroptosis and induction of the immune system.[7b,c] During the last years we investigated the biological activities of octahedral bis-cyclometalated *M*(III) complexes (*M*=Rh, Ir) containing modified phenanthroline and related bipyridine ligands in light of their use as promising anticancer agents.[8] Now we focus our efforts in this field additionally on several half-sandwich complexes [Ir(η^5-C_5Me_5)(N^N)Cl]$^+$ (N^N = bidentate N-donor ligand).[9] In this paper, we report the synthesis, the characterization as well as studies of the cancer cell cytotoxicity of some new compounds representing the latter type of complex. The compounds contain modified neutral N^N chelating ligands stemming from 1,10-phenanthroline and terpyridine in the κ^2N,N'-coordination mode respectively. During these investigations, the molecular structures of all new compounds in the crystal were determined by X-ray single-crystal diffraction.

Results and Discussion

The synthesis of the compounds was realized by cleavage of the precursor complexes [{*M*(η^5-C_5Me_5)(μ-Cl)Cl}$_2$] (*M* = Rh, Ir) with the corresponding bidentate chelating ligands by stirring the components for one hour in methanol at room temperature. The intermediately formed chloride salts were transformed by metathesis into their hexafluoridophosphate compounds **1** – **4** using KPF_6 (see Eq. 1 and Scheme 1 respectively).

$$[\{M(\eta^5\text{-}C_5Me_5)(\mu\text{-}Cl)Cl\}_2] + 2\,N\hat{}N + 2\,KPF_6 \rightarrow 2\,[M(\eta^5\text{-}C_5Me_5)(N\hat{}N)Cl]PF_6 + 2\,KCl \quad \mathbf{1}-\mathbf{4} \qquad (1)$$

(N^N = 4,7-dichloro-1,10-phenanthroline; *M*=Rh, **1**; *M* = Ir, **2**). (N^N = 4'-(4-chlorophenyl)-2,2':6',2''-terpyridine-κ^2N,N'; *M*=Rh, **3**; *M* = Ir, **4**).

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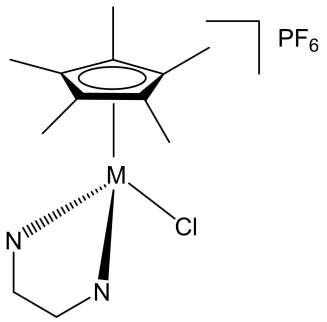

N^N = 4,7-dichloro-1,10-phenanthroline:
M = Rh (**1**), M = Ir (**2**);
N^N = 4´-(4-chlorophenyl)-2,2´:6´,2´´-terpyridine (κ^2N,N´-terpy): M = Rh (**3**), M = Ir (**4**)

Scheme 1. Graphical overview of compounds **1**–**4**.

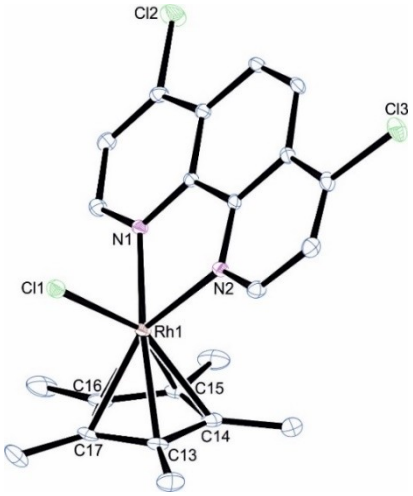

Figure 1. The molecular structure of the cation of compound **1** in the crystal (ORTEP drawing and atom labeling scheme with 25% probability level). Selected bond lengths/Å: Rh1–N1, 2.1241(17); Rh1–N2, 2.1165(17); Rh1–Cl, 2.3845(6).

During this procedure, all compounds were obtained in yields from 49 to 66% and characterized by elemental analysis, ^{1}H and ^{13}C{^{1}H} NMR spectroscopy, mass spectrometry and additionally, the molecular structures of all compounds in the solid state were determined by single-crystal X-ray diffraction studies. The ^{1}H and ^{13}C{^{1}H} NMR spectra of the new compounds supported the assumed molecular constitution (see Experimental Section). Exemplarily, the data will be illustrated on one selected compound in the following. The proton NMR spectrum of compound **1** (400 MHz, acetone-d_6) exhibited a singlet at 1.86 ppm indicating the protons of the five chemically equivalent methyl groups of the pentamethylcyclopentadienyl ligand. The aromatic protons of the 4,7-dichloro-substituted phenanthroline ligand resonated at 9.49 (d, 2H), 8.62 (s, 2H), 8.42 (d, 2H) exhibiting the expected couplings. The ^{13}C{^{1}H} NMR spectrum of **1** (100 MHz, acetone-d_6) showed a singlet at 8.2 ppm indicating the carbon atoms of the methyl groups of the pentamethyl-cyclopentadienyl ligand. The aromatic carbon atoms of the latter resonated as doublet at 97.7 ppm (J_{RhC} = 7.6 Hz). Finally, six singlets between 125.0 and 152.9 ppm corresponding to the aromatic carbon atoms of the substituted phenanthroline ligand were obtained. The observed data are well comparable to those of the reported ones for [Rh(η^5-C_5Me_5)(phen)Cl]ClO_4 and [Rh(η^5-C_5Me_5)(phen)Cl]OTf, respectively (phen = 1,10-phenanthroline).[10,11]

Molecular Structure of Compounds 1–4

Single-crystals of compounds **1**–**4** were grown by the layering method at room temperature from dichloromethane/methanol/*iso*-hexane mixtures. The solids were investigated by X-ray diffraction studies, and the results of the molecular structures in the crystal of the complex cations in compound **1**, **2**, and **4** are depicted in Figures 1–3. All the complexes exhibit the expected half-sandwich pseudo-octahedral three-legged "piano-stool" arrangement. In each case the metal atoms are bound to one η^5-C_5Me_5 group, one chlorido ligand, and the bidentate N^N ligand.

Compound **1** crystallized in the orthorhombic space group *P*bca with eight equivalent molecules in the unit cell. A selected ORTEP view of the molecular cation of **1** is depicted in Figure 1, selected bond lengths are given in the caption. The average distance between the rhodium atom and the carbon atoms of the η^5-C_5Me_5 ring in **1** is 2.16 Å. These bond lengths are comparable to those of η^5-C_5Me_5 rhodium complexes exhibiting a closely related coordination sphere.[12] The Rh–Cl distance of **1** is in very good accordance with the corresponding bond length in [Rh(η^5-C_5Me_5)(phen)Cl]$^+$ [2.386(1) Å], and also the Rh–N distances of the latter species with 2.128(3) and 2.109(3) Å,[10] agree very well with the corresponding ones in the cationic complex of **1**.

Compound **2** crystallized in the orthorhombic space group *P*bca with eight molecules in the unit cell. An ORTEP view of the molecular cation of **2** is shown in Figure 2, selected bond lengths are given in the caption.

The average distance between the iridium atom and the carbon atoms of the η^5-C_5Me_5 ring in **2** was determined with 2.17 Å. These bond lengths are comparable to those in the iridium complex [Ir(η^5-C_5Me_5)(bpy)Cl]$^+$ (2.16 Å), and even the Ir–N distances of the latter species with 2.076(8) and 2.090(9) Å as well as the Ir–Cl bond length with 2.404(2) Å[10] are well comparable with the corresponding bonding parameters in compound **2**.

Furthermore, during our investigations we obtained single-crystals of compound **3** and confirmed its molecular structure in the solid. However, the crystal structure of this compound has already published in the literature,[13] exhibiting the same space group, cell parameters and bonding characteristics as found during our X-ray study on compound **3**. Thus, we have

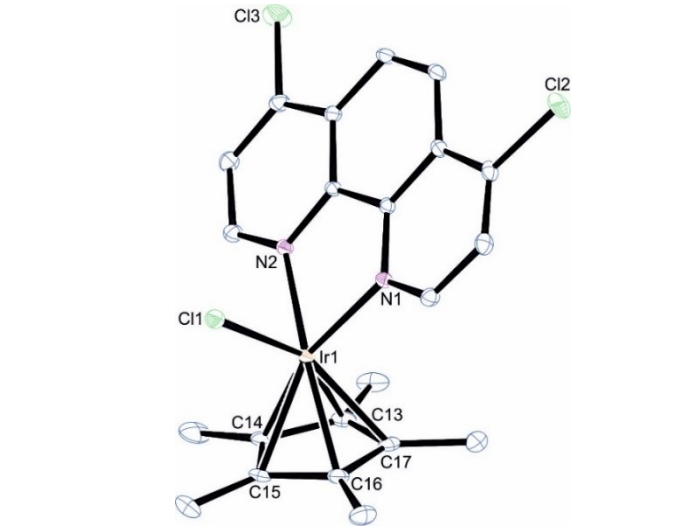

Figure 2. The molecular structure of the cation of compound **2** in the crystal (ORTEP drawing and atom labeling scheme with 25% probability level). Selected bond lengths/Å: Ir1–N1, 2.108(2); Ir1–N2, 2.108(2); Ir1–Cl, 2.3893(7).

deposited our results on these data for more support of the assumed structure of compound **3** only with the Supporting Information of this paper.

Compound **4** crystallized in the monoclinic space group $P2_1/n$ with four molecules in the unit cell. An ORTEP view of the molecular cation of **4** is depicted in Figure 3, selected bond lengths are given in the caption. The molecular structure of compound **4** exhibits a pseudo-octahedral piano-stool geometry around the iridium center and is best comparable with that of the closely related one of compound **3** as described in the literature.[13] Thus, for the latter hexafluoridophosphate salt the following bond distances were reported: Rh–N1, 2.1082(2) and Rh–N2, 2.192(2) and Rh–Cl, 2.4028(5) Å. Very similar data were found during our X-ray crystal study of compound **3** (see SI of this paper).

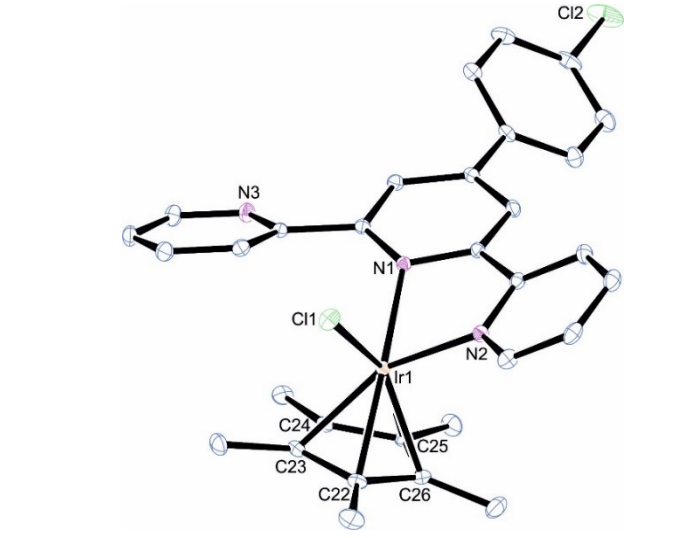

Figure 3. The molecular structure of the cation of compound **4** in the crystal (ORTEP drawing and atom labeling scheme with 25% probability level). Selected bond lengths/Å: Ir1–N1, 2.1658(15); Ir1–N2, 2.0668(15); Ir1–Cl1, 2.4137(5).

Another similarly constituted complex was also described in $[Rh(\eta^5\text{-}C_5Me_5)(Ph\text{-}terpy)Cl]BF_4$ containing the 4'-phenyl-2,2':6',2''terpyridine ligand (Ph-terpy) in the κ^2N,N'-coordination mode.[14] For the latter the bonding parameters Rh–N1, 2.086(3), Rh–N2, 2.197(3), and Rh–Cl, 2.398(1) Å were determined which correspond well with those found of compound **3**. That means, in all the complexes the two M–N distances are unequal in their lengths. This has been observed even in other complexes exhibiting the bidentate terpy in the κ^2N,N'-coordination mode.[15–17] The presence of the uncoordinated pyridine ring in the terpy system causes some steric interactions resulting in one significantly longer M–N bond in these complexes. In this light, complexes containing bidentate terpy ligands in the κ^2N,N' -coordination fashion have been reviewed very recently.[18]

Biological Activity of Compounds 1–4

Iridium(III) and rhodium(III) half-sandwich complexes were reported with anticancer properties.[1–7] In this work, we investigated the influence of the metal center and the coordinating ligand of iridium(III) and rhodium(III) half-sandwich centers on the antiproliferative properties. Of note, compounds **3** and **4** exist as racemic mixtures with chirality at the metal center, but no effort was made in this case to resolve the enantiomers. Thus, compounds **1**–**4** were tested against three different cell lines, namely HeLa (cervical cancer), HT-29 (colon cancer), and MCF-7 (human breast cancer). The determination of the cytotoxicity was done by the colorimetric MTT assay. The obtained IC_{50} values are shown in Table 1.

All compounds showed antiproliferative activity against all cell lines, with the iridium(III) complex **2** being the least active one. It has an order of magnitude lower activity against HeLa cells than cisplatin and only 50 μM activity against HT-29 and MCF-7. The corresponding rhodium complex **1** has a similar IC_{50} as cisplatin against HeLa (14.6 μM), while its cytotoxicity against HT-29 and MCF-7 is 6.2 and 4.5 μM, respectively, which is an order of magnitude lower than cisplatin. The enhanced

Table 1. IC_{50} values in μM of **1**–**4** for the antiproliferative activity towards HeLa, HT-29, and MCF-7 cells. MTT assay with 48 h incubation time, total concentration of DMSO was 0.5% in all samples including Cisplatin control. Values are given as mean of three independent experiments with standard deviation.

compound	HeLa	HT-29	MCF-7
Cisplatin	14.0 ± 4.8	82.4 ± 7.5	44.0 ± 6.4
1	14.6 ± 3.8	6.2 ± 2.2	4.5 ± 0.7
2	128.8 ± 9.0	47.3 ± 8.8	58.6 ± 7.7
3	5.6 ± 0.9	0.8 ± 0.7	1.1 ± 0.2
4	11.4 ± 1.6	0.7 ± 1.3	0.6 ± 0.6

antiproliferative activity against HT-29 and MCF-7 may indicate a different mode of action compared to cisplatin. The difference of the activity between the Ph-terpy coordinated complexes **3** and **4** is marginal. Both complexes show about 1 μM activity against the HT-29 and MCF-7 cell lines. The activity against HeLa cells is for the corresponding iridium complex **4** twice as high as for the rhodium complex **3** but with 11.4 μM in the range of cisplatin and complex **1**. These results indicate that the activity of rhodium complexes is better than that of the corresponding iridium ones.

Nonetheless, in this work the choice of the ligand mostly tunes the cytotoxicity. For example, terpy metal complexes are well known to be efficient DNA intercalators by π…π stacking of the ligand with the DNA bases.[19] The smaller phen ligand is on the edge of groove binding and intercalation.[20] If we assume that DNA binding is in operation also for the metal complexes with the ligands described therein, then the different size of the metal ions (Rh *vs.* Ir) may actually tilt the binding mode between groove binding and intercalation. This shift might help to explain the significant differences in light of the activities between compounds **1** and **2**, when at the same time very little difference in activity was observed between compounds **3** and **4**. Of course, entirely other modes of action are feasible as well, as recently established for organometallic compounds and indicated by many observations cited in the introduction of this paper.

Conclusions

The synthesis and characterization of four organometallic compounds exhibiting piano-stool shaped structures have been described. Single-crystal X-ray diffraction studies confirmed the presence of half-sandwich structures in the compounds [M(η^5-C_5Me_5)(N^N)Cl]PF_6 (M=Rh, Ir; N^N=4,7-dichloro-1,10-phenanthroline, **1** and **2**; N^N=4'-(4-chlorophenyl)-2,2':6',2''-terpyridine-κ^{2}N,N, **3** and **4**). The antiproliferative properties of all compounds were investigated against three cancer cell lines (HeLa, MT-29, MCF-7). Both Ph-terpy containing complexes (**3** and **4**) show promising activity with IC_{50} values around 1 μM. The phen complexes (**1**, **2**) differ strongly in activity from each other. While the rhodium(III) complex **1** has activity still under 10 μM against HT-29 and MCF-7, the iridium(III) complex **2** is less active by a factor of 5 against both cell lines and even an order of magnitude less active for HeLa. Presumably, both the metal ion and the ligand tune the activity in these cases.

Experimental Section

General: All manipulations were performed under an atmosphere of dry nitrogen using conventional Schlenk techniques. Solvents were dried with standard procedures and stored under nitrogen. The ligands 4,7-dichloro-1,10-phenanthroline and 4'-(4-chlorophenyl)-2,2':6',2''-terpyridine were purchased from Aldrich and used as received. The starting complex [{Ir(η^5-C_5Me_5)(μ-Cl)Cl}$_2$] was prepared following the literature method.[21] [{Rh(η^5-C_5Me_5)(μ-Cl)Cl}$_2$] was obtained using an improved preparation route described recently.[22] NMR spectra were recorded in CD_2Cl_2 and acetone-d_6 respectively using a Jeol Eclipse 400 instrument operating at 400 MHz (^{1}H) and 100 MHz (^{13}C) respectively. Chemical shifts are given in ppm, referenced to the solvent signals of dichloromethane at δ=5.36 (^{1}H) and 53.5 ppm (^{13}C). Mass spectra were measured using a JeolMstation JMS 700 instrument. 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

The cells – HeLa, MCF-7, and HT-29 – were grown in Dulbecco's Modified Eagle's Medium (DMEM), which contained 10% fetal calf serum, 1% penicillin and streptomycin. For plating, the cancer cells were detached with trypsin and EDTA, followed by harvesting by centrifugation and resuspension in the cell culture medium. For the colorimetric assay, 96 well plates (6000 cells per well) were prepared for each cell line and incubated at 37 °C and 10% CO_2 for 24 hours. Afterwards, the cells were treated with compounds **1**–**4** besides cisplatin as a control. The final volume in each well was 200 μL with a concentration of 0.5% DMSO. After 48 h incubation with the compounds, 50 μL 2.5 mg/mL MTT solution was added, further incubated for 2 h, and the medium was removed finally. The addition of 200 μL DMSO dissolved the formazan crystals, and the absorption was measured at 550 nm and with 620 nm the as reference wavelength. The experiment was carried out in triplicates for three independent tests.

Synthesis of compounds 1–4: To a suspension of [{*M*(η^5-C_5Me_5)(μ-Cl)Cl}$_2$] (0.15 mmol; *M*=Rh or Ir) in 25 mL of MeOH the corresponding phenanthroline or terpyridine ligand (0.3 mmol) respectively, was added and the mixture stirred for 1 h resulting in a clear yellow solution. Then KPF_6 (0.4 mmol) was added and the mixture stirred for additional 30 min. At this point the products were precipitated as yellows powders which were separated by filtration, washed twice with methanol and dried in vacuo affording an analytically pure product.

[Rh(η^5-C_5Me_5)(4,7-Cl_2-phen)Cl]PF_6 (1): Yield: 124 mg (61.9%). *Anal.* $C_{22}H_{21}Cl_3F_6N_2PRh$ (667.65): calcd. C, 39.58; H, 3.17; N, 4.20. Found: C, 39.30; H, 3.39; N, 3.96%. **MS** (FAB$^+$): *m/z*=522.9 [M$^+$] complex cation. **^{1}H NMR** (400 MHz, acetone-d_6): δ=9.49 (d, *J*=5.4 Hz, 2H), 8.62 (s, 2H), 8.42 (d, *J*=5.8 Hz, 2H), 1.86 (s, 15H). **^{13}C{^{1}H} NMR** (100 MHz, acetone-d_6): δ=152.9, 146.0, 145.7, 129.0, 127.7, 125.0, 97.7 (d, J_{RhC}=7.6 Hz, Cp*-*C*CH$_3$), 8.2 (Cp*-CH$_3$).

[Ir(η^5-C_5Me_5)(4,7-Cl_2-phen)Cl]PF_6 (2): Yield: 150 mg (66.1%). *Anal.* $C_{22}H_{21}Cl3F_6IrN_2P$ (756.96): calcd. C, 34.91; H, 2.80; N, 3.70. Found: C, 34.60; H, 2.82; N, 3.42%. **MS** (FAB$^+$): *m/z*=611.0 [M$^+$] complex cation. **^{1}H NMR** (400 MHz, acetone-d_6): δ=9.49 (d, *J*=6.0 Hz, 2H), 8.64 (s, 2H), 8.42 (d, *J*=5.6 Hz, 2H), 1.83 (s, 15H). **^{13}C{^{1}H} NMR** (100 MHz, acetone-d_6): δ=152.6, 147.6, 145.7, 129.6, 128.1, 125.3, 90.0 (Cp*-*C*CH$_3$), 7.9 (Cp*-*C*H$_3$).

[Rh(η^5-C_5Me_5)(κ^2*N,N'*-terpy-C_6H_4-Cl-*p*)Cl]PF_6 (3): Yield: 123 mg (53.8%). *Anal.* $C_{31}H_{29}Cl_2F_6N_3PRh$ (762.37): calcd. C, 48.84; H, 3.83; N, 5.51. Found: C, 48.66; H, 3.73; N, 5.64%. **MS** (FAB$^+$): *m/z*=617.0 [M$^+$] complex cation. **^{1}H NMR** (400 MHz, CD_2Cl_2): δ=8.79 (m, 2H), 8.72 (m, 2H), 8.59 (s, 2H), 8.09 (dt, *J*=1.6 Hz, 7.8 Hz, 2H), 7.90 (m, 2H), 7.67 (t, *J*=1.4 Hz, 2H), 7.58 (m, 2H), 1.14 (s, 15H). **^{13}C{^{1}H} NMR** (100 MHz, CD_2Cl_2): δ=160.3, 155.3, 151.3, 151.2, 151.1, 139.2, 139.1, 137.6, 133.5, 129.9 (3 C), 128.9 (3 C), 127.0, 125.9, 125.8, 123.8, 97.4 (d, J_{RhC}=8.6 Hz, Cp*-*C*CH$_3$), 8.4 (Cp*-*C*H$_3$).

[Ir(η^5-C_5Me_5)(κ^2*N,N'*-terpy-C_6H_4-Cl-*p*)Cl]PF_6 (4): Yield: 110 mg (48.8%). *Anal.* $C_{31}H_{29}Cl_2F_6IrN_3P$ (851.68): calcd. C, 43.72; H, 3.43; N, 4.93. Found: C, 43.74; H, 3.24; N, 4.91%. **MS** (FAB$^+$): *m/z*=706.7 [M$^+$

Table 2. Crystal data and structure refinement details of compounds **1**, **2**, and **4**.

Compound	**1**	**2**	**4**
Empirical formula	$C_{22}H_{31}Cl_3F_6N_2PRh$	$C_{22}H_{31}Cl_3F_6IrN_2P$	$C_{31}H_{29}Cl_2F_6IrN_3P$
M/g·mol^{-1}	667.64	756.93	851.64
Temperature/K	173(2)	173(2)	173(2)
Crystal system	orthorhombic	orthorhombic	monoclinic
Space group	*P*bca	*P*bca	$P2_1/n$
a /Å	13.4499(4)	13.3914(4)	12.3532(4)
b/Å	12.3984(3)	12.3478(4)	8.9872(3)
c/Å	29.2366(9)	29.4630(9)	27.6441(9)
α/°	90	90	90
ß/°	90	90	100.7260(10)
γ/°	90	90	90
V/Å^3	4875.4(2)	4871.8(3)	3015.45(17)
Z	8	8	4
$\rho_{calcd.}$/g⊥cm^3	1.819	2.064	1.876
μ/mm^{-1}	1.157	5.938	4.723
θ range for data collection/°	3.029–27.482	3.056–28.282	2.998–27.485
Reflections observed	5051	5535	6581
Reflections in refinement	5587	6049	6908
S	1.095	1.174	1.081
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0276$, w$R_2 = 0.0587$	$R_1 = 0.0211$, w$R_2 = 0.0449$	$R_1 = 0.0154$, w$R_2 = 0.0343$
$\Delta\varrho_{fin}$ (max/min)/e Å^{-3}	0.476/−0.463	0.004/−0.928	0.425/−0.565

] complex cation. **^{1}H NMR** (400 MHz, CD_2Cl_2): δ = 9.03 (d, J = 2.0 Hz, 1H), 8.83 (d, J = 1.1 Hz, 1H), 8.73 (d, J = 1.1 Hz, 1H), 8.57 (s, 1H), 8.52 (s, 1H), 8.50 (s, 1H), 8.22 (t, J = 1.9 Hz, 1H), 7.91 (m, 3H), 7.81 (t, J = 1.8 Hz, 1H), 7.59 (m, 2H), 7.52 (t, J = 1.1 Hz, 1H), 1.14 (s, 15H). **^{13}C{^{1}H} NMR** (100 MHz, CD_2Cl_2): δ = 163.4, 157.5, 155.9, 155.8, 151.7, 150.9, 150.0, 140.9, 137.8, 137.1, 133.1, 130.1, 130.0, 129.8, 129.0, 128.6, 128.5, 127.9, 127.8, 124.5, 120.3, 89.7 (Cp*-CCH$_3$), 8.1 (Cp*-CH$_3$).

X-ray Crystal Structure Determination: Crystals of **1**, **2**, and **4** suitable for X-ray diffraction studies were obtained by crystallization from dichloromethane/methanol/*iso*-hexane mixtures at ambient temperature. Crystals were selected by means of a polarization microscope, mounted on a MiTeGen MicroLoop, and investigated with a Bruker D8 Venture TXS diffractometer using Mo-Kα radiation (λ = 0.71073 Å). The frames were integrated with the Bruker SAINT software package.[23] Data were corrected for absorption effects using the Multi-Scan method (SADABS).[24] The structures were solved by direct methods and refined by full-matrix least-squares calculations on F^2 using the Bruker SHELXTL Software package.[25] The figures have been drawn at the 25% ellipsoid probability level using ORTEP.[26] The H atoms and hexafluoridophosphate anions respectively, in the Figures 1–3 have been omitted for more clarity. Details of the crystal data, data collection, structure solution, and refinement parameters of compound **1**, **2**, and **4** are summarized in Table 2. Crystallographic data (excluding structure factors) for the structures 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 upon quoting the depository number CCDC-2248848 (**1**), CCDC-2248849 (**2**), and CCDC-2248850 (**4**) (Fax: +44-1223-336-033; E-Mail: deposit@ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk).

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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[1] a) P. Zhang, P. J. Sadler, *J. Organomet. Chem.* **2017**, *839*, 5; b) K. J. Franz, N. Metzler-Nolte, *Chem. Rev.* **2019**, *119*, 727; c) C. N. Morrison, K. E. Prosser, R. W. Stokes, A. Cordes, N. Metzler-Nolte, S. M. Cohen, *Chem. Sci.* **2020**, *11*, 1216; d) E. J. Anthony, E. M. Bolitho, H. E. Bridgewater, O. W. L. Carter, J. M. Donnelly, C. Imberti, E. C. Lant, F. Lermyte, R. J. Needham, M. Palau, P. J. Sadler, H. Shi, F.-X. Wang, W.-Y. Zhang, Z. Zhang, *Chem. Sci.* **2020**, *11*, 12888; e) M. Patra, G. Gasser, N. Metzler-Nolte, *Dalton Trans.* **2012**, *41*, 6350; f) C. G. Hartinger, N. Metzler-Nolte, P. J. Dyson, *Organometallics* **2012**, *31*, 5677; g) G. Gasser, N. Metzler-Nolte, *Curr. Opin. Chem. Biol.* **2012**, *16*, 84; h) G. Gasser, I. Ott, N. Metzler-Nolte, *J. Med. Chem.* **2011**, *54*, 3; i) T. S. Prathima, B. Choudhury, M. Ahmad, K. Chanda, M. M. Balamurali, *Coord. Chem. Rev.* **2023**, *490*, 215231; j) G. Backman-Blanco, H. Valdés, M. T. Ramírez-Apan, P. Cano-Sanchez, S. Hernandez-Ortega, A. L. Orjuela, J. Alí-Torres, A. Flores-Gaspar,

R. Reyes-Mártinez, D. Morales-Morales, *J. Inorg. Biochem.* **2020**, *211*, 111206.
[2] a) J. Li, L. Guo, Z. Tian, M. Tian, S. Zhang, K. Xu, Y. Qian, Z. Liu, *Dalton Trans.* **2017**, *46*, 15520; b) H. Zhang, L. Guo, Z. Tian, M. Tian, S. Zhang, Z. Xu, P. Gong, X. Zheng, Z. Liu, *Chem. Commun.* **2018**, *54*, 4421; c) J. M. Hearn, G. M. Hughes, I. Romero-Canelón, A. F. Munro, B. Rubio-Ruiz, Z. Liu, N. O. Carragher, P. J. Sadler, *Metallomics* **2018**, *10*, 93.
[3] D.-L. Ma, C. Wu, K.-J. Wu, C.-H. Leung, *Molecules* **2019**, *24*, 2739.
[4] R. M. Lord, P. C. McGowan, *Chem. Lett.* **2019**, *48*, 916.
[5] a) W.-Y. Zhang, S. Banerjee, C. Imberti, G. J. Clarkson, Q. Wang, Q. Zhong, L. S. Young, I. Romero-Canelón, M. Zeng, A. Habtemariam, P. J. Sadler, *Inorg. Chim. Acta* **2020**, *503*, 119396; b) S. Banerjee, P. J. Sadler, *RSC Chem. Biol.* **2021**, *2*, 12.
[6] L. Biancalana, H. Kostrhunova, L. K. Batchelor, M. Hadiji, I. Degano, G. Pampaloni, S. Zacchini, P. J. Dyson, V. Brabec, F. Maschetti, *Inorg. Chem.* **2021**, *60*, 9529.
[7] a) M. I. Murillo, C. Gaiddon, R. Le Lagadec, *Frontiers Chem.* **2022**, *10*, 967337; b) L. Zhang, N. Montesdeoca, J. Karges, H. Xiao, *Angew. Chem.* **2023**, *135*, e202300662; *Angew. Chem. Int. Ed.* **2023**, *62*, e202300662; c) K. Peng, Y. Zheng, W. Xia, Z.-W. Mao, *Chem. Soc. Rev.* **2023**, *52*, 2790.
[8] a) M. Graf, H.-C. Böttcher, K. Sünkel, S. Thavalingam, N. Metzler-Nolte, R. Czerwieniec, *Z. Anorg. Allg. Chem.* **2021**, *647*, 306 and references cited therein; b) M. Graf, H.-C. Böttcher, N. Metzler-Nolte, S. Thavalingam, P. Mayer, *Z. Anorg. Allg. Chem.* **2022**, *648*, e202200206.
[9] M. Graf, J. Ochs, N. Metzler-Nolte, P. Mayer, H.-C. Böttcher, *Z. Anorg. Allg. Chem.* **2023**, *649*, e202200382.
[10] M.-T. Youinou, R. Ziessel, *J. Organomet. Chem.* **1989**, *363*, 197.
[11] M. A. Scharwitz, I. Ott, Y. Geldmacher, R. Gust, W. S. Sheldrick, *J. Organomet. Chem.* **2008**, *693*, 2299.
[12] P. Govindaswamy, J. Canivet, B. Therrien, G. Süss-Fink, *J. Organomet. Chem.* **2007**, *692*, 3664.
[13] J. M. Gichumbi, S. J. Zamisa, H. B. Friedrich, *Z. Kristallogr. NCS* **2020**, *235*, 1403.
[14] H. Aneetha, P. S. Zacharias, B. Srinivas, G. H. Lee, Y. Wang, *Polyhedron* **1999**, *18*, 299.
[15] E. W. Abel, V. S. Dimitrov, N. S. Long, K. G. Orrell, A. G. Osborne, V. Šik, M. B. Hursthouse, M. A. Mazid, *J. Chem. Soc., Dalton Trans.* **1993**, 291.
[16] E. W. Abel, V. S. Dimitrov, N. S. Long, K. G. Orrell, A. G. Osborne, H. M. Pain, V. Šik, M. B. Hursthouse, M. A. Mazid, *J. Chem.Soc., Dalton Trans.* **1993**, 597.
[17] E. W. Abel, K. G. Orrell, A. G. Osborne, H. M. Pain, V. Šik, *J. Chem.Soc., Dalton Trans.* **1994**, 111.
[18] O. S. Taniya, D. S. Kopchuk, A. F. Khasanov, I. S. Kovalev, S. Santra, G. V. Zyryanov, A. Majee, V. N. Charushin, O. N. Chupakhin, *Coord. Chem. Rev.* **2021**, *442*, 213980.
[19] a) A. H. Wang, J. Nathans, G. van der Marel, J. H. van Boom, A. Rich, *Nature* **1978**, *276*, 471; b) J. Li, R. Liu, J. Jiang, X. Liang, G. Huang, D. Yang, H. Chen, L. Pan, Z. Ma, *J. Inorg. Biochem.* **2020**, *25*, 111165; c) K. W. Jennette, S. J. Lippard, G. A. Vassiliades, W. R. Bauer, *Proc. Nat. Acad. Sci.* **1974**, *71*, 3839.
[20] a) B. M. Zeglis, V. C. Pierre, J. K. Barton, *Chem. Commun.* **2007**, 4565; b) A. Draksharapu, A. J. Boersma, M. Leising, A. Meetsma, W. R. Browne, G. Roelfes, *Dalton Trans.* **2015**, *44*, 3647.
[21] C. White, A. Yates, M. P. Maitlis, *Inorg. Synth.* **1992**, *29*, 228.
[22] M. A. Matell, J. W. Kampf, M. Sanford, *Organometallics* **2018**, *37*, 3240.
[23] Bruker (2012). SAINT AXS Inc., Madison, Wisconsin, USA.
[24] G. M. Sheldrick (1996). SADABS. University of Göttingen, Germany.
[25] G. M. Sheldrick, *Acta Crystallogr.* **2015**, *A71*, 3.
[26] L. J. Farrugia, *J. Appl. Crystallogr.* **2012**, *45*, 849.

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