Synthesis of Tumor-Inhibiting Complex Salts Containing the Anion *trans*-Tetrachlorobis(indazole)ruthenate(III) and Crystal Structure of the Tetraphenylphosphonium Salt

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Dedicated to Prof. Dirk Walther on the occasion of his 60th birthday

Keywords: Ruthenium / Coordination chemistry / Paramagnetic complexes / Magnetic properties / Ion exchange / Antitumor agents / Colon tumors

Indazolium *trans*-tetrachlorobis(indazole)ruthenate(III) exhibits excellent results against different tumor models in vitro and in vivo. To improve the water solubility necessary for the introduction of this tumor-inhibiting compound into clinical trials, we synthesized the corresponding sodium salt in a two-step ion exchange via the tetramethylammonium salt. The sodium salt shows a 35-fold higher solubility in water relative to the indazolium salt. We also synthesized the *n*-butylammonium, *n*-octylammonium, and tetraphenylphosphonium salts, all of which showed improved solubility in organic solvents. The X-ray crystal structure of the latter could be solved, proving the *trans* configuration of the complex anion. In spite of the paramagnetic Ru^{III} center an assignement of the coordinated indazole protons could be made with the help of a COSY experiment.

Introduction

The development of ruthenium complexes as an alternative to platinum-based tumor inhibitors is of special interest. Antitumor and antimetastatic activity was found for different Ru^{II} and Ru^{III} complexes.[1–7] Ruthenium(III) complexes of the general formula $HL[RuCl_4L_2]$, where L is a heterocyclic ligand bound to ruthenium through nitrogen and HL the protonated ligand, show remarkable activity against different tumor models in vitro and in vivo. They exhibit excellent activity especially against autochthonous colorectal tumors in rats, with a tumor reduction of 70% to 90%.[8][9] This autochthonous tumor induced by intrarectal application of acetoxymethylnitrosamine (AMMN) is comparable to human colon tumors in its histological appearance and behavior toward chemotherapeutics. The metal-based antitumor drug *cisplatin* is completely inactive in this model. Furthermore, the Ru^{III} complexes show antiproliferative activity in two human colon cancer cell lines (SW707 and SW948).[10] The most promising complex contains two *trans*-standing indazole (L = ind) ligands. It exhibits antineoplastic effects on proliferation of clonogenic cells from freshly explanted human tumors in a capillary soft agar cloning system.[11] The problem with compound **1**, $HInd[RuCl_4ind_2]$ (see Figure 1),[12] is its poor water solubility, making a formulation for clinical trials difficult. To solve this problem, we synthesized new complex salts by ion exchange of the indazolium cation against a variety of cations. The complex anion, responsible for antitumor activity, remains unchanged. Especially the sodium salt **2** shows a much better water solubility, while the corresponding tetraphenylphosphonium salt, of which the crystal structure could be resolved, and the tetraalkylammonium salts are much more soluble in organic solvents, which might be of interest for further reactions with these complex salts.

Results and Discussion

Exchange of the indazole cation in the complex salt **1**, $HInd[RuCl_4ind_2]$, against a tetraalkylammonium or tetraphenylphosphonium cation can be achieved by adding the corresponding chloride salt to a nearly saturated solution of **1** in water (see Figure 1). Immediate precipitation of the complex salts **4**, **5**, or **6**, even less soluble in water than **1**, occurs. In the case of the tetramethylamonium salt **3** methanol is used as solvent instead of water because **3** is more soluble in water than **1**.

The more hydrophobic the substituents of the cation, the more soluble in organic solvents are the corresponding Ru-complex salts. Not surprisingly the tetraoctylammonium salt **5** exhibits the best solubility in less polar solvents like chloroform.

These solubility characteristics can be used in synthesizing the sodium salt **2**, $Na[RuCl_4ind_2]$, that cannot be obtained directly from **1**. Addition of sodium tetraphenylbo-

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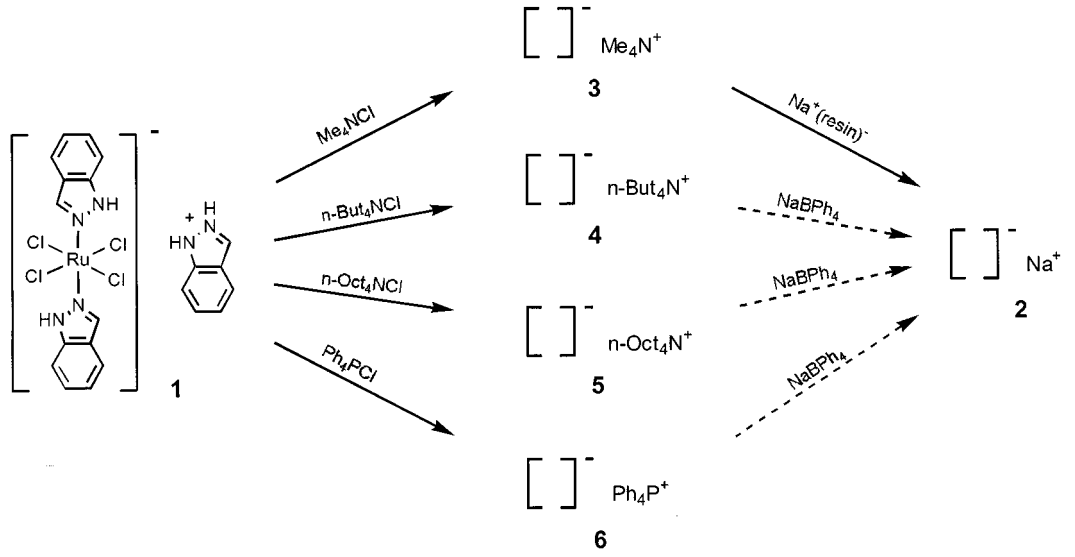

Figure 1. Synthesis of the complex salts **3**, **4**, **5**, and **6** ([ ]$^-$ represents the complex [$RuCl_4ind_2$]$^-$) and synthesis pathways from **1**, HInd[$RuCl_4ind_2$], to **2**, Na[$RuCl_4ind_2$]

rate to a solution of the complex salts **3**, **4**, **5**, or **6** in solvents like methanol, acetone or acetonitrile leads to precipitation of the corresponding tetraphenylborate salts, for example tetraphenylphosphonium tetraphenylborate in the case of **6**. The sodium salt **2** stays in solution and can be precipitated by addition of diethyl ether. Unfortunately, pure products cannot be obtained reproducibly. The best results were obtained with the tetraphenylphosphonium salt **6** in acetonitrile.

A more advantageous method of synthesizing the sodium salt **1** makes use of cation exchange resins. This method was only successful when the tetramethylammonium salt **3**, already more soluble in water than the indazolium salt **1**, was used. The sodium salt could not be prepared directly from the indazolium salt. Thus, a solution of **3** in water was mixed with a Dowex cation exchange resin preloaded with sodium. To avoid hydrolysis of the complex, the solution was frozen immediately after ion exchange, and water was removed under vacuum. After this lyophilization process the product **2**, sodium *trans*-tetrachlorobis(indazole)ruthenate(III), is obtained as a trihydrate. Its solubility in water (0.018 mol/l) is about 35 times higher than that of **1**.

The ^{1}H-NMR spectra of the complex salts show high-field shifts and peak broadening for the protons of the coordinated indazole ligands, because of the paramagnetic Ru^{III} center. In a [D_3]acetonitrile solution of the sodium salt **2** the signals for the protons at position 1 and 3 of the heterocycle, nearest to the Ru^{III} center, can be detected at a chemical shift of about $\delta = -7$ and -12, respectively. The signal at $\delta = -7$ can be assigned to the protons at N1 of the indazole rings, because it disappears due to rapid exchange upon addition of water. The other signals at $\delta = 2.45$ (2 H, at C4 or C7), 2.63 (2 H, at C7 or C4), 3.18 (2 H, at C5 or C6), and 4.32 (2 H, at C6 or C5), represent the protons at a greater distance from the paramagnetic Ru^{III} center. They were assigned in pairs with the help of a COSY experiment (see Figure 2).

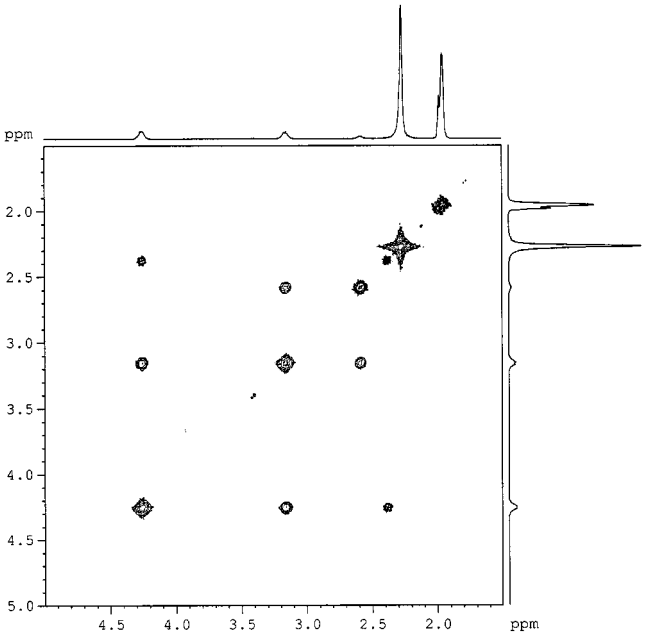

Figure 2. Detail of the COSY spectrum of **2**, Na[$RuCl_4ind_2$], in [D_3]acetonitrile, showing the signals at $\delta = 2.45$, 2.63, 3.18, and 4.32 that represent the indazole protons further from the paramagnetic Ru^{III} center (the signal at $\delta = 2.45$ in the projections is overlapped by the water signal of the solvent) than the two nearest protons, which cannot be detected in the COSY experiment.

In ^{13}C-NMR measurements the signals of the two quaternary carbons and the carbon beneath the coordinated nitrogen of each indazole ligand could not be detected. The detectable carbons at $\delta = 118.07$ (C5 or C6), 114.72 (C6 or C5), 98.29 (C4 or C7), and 97.77 (C7 or C4) could also be assigned in pairs because of the corresponding cross peaks in a H,C-correlated spectrum (HMQC, spectrum not shown).

The X-ray crystal structure of the tetraphenylphosphonium salt was solved, proving the *trans* configuration of

the complex anion $[RuCl_4ind_2]^-$ (see Figure 3, crystallographic data are collected in Table 1). The Ru atom is in the center of an octahedron. The two planes of the *trans* indazole ligands, bound through the N2 nitrogen, are twisted. The longest Ru−Cl bond is formed between Cl(2) and the Ru center [2.3723(8) Å], whereas the Ru−Cl(1) [2.3627(7) Å], Ru−Cl(3) [2.3618(7) Å] and especially the Ru−Cl(4) [2.3586(8) Å] bonds are slightly, but significantly shorter. The longer Ru−Cl(2) bond is due to hydrogen bonding between the Cl(2) and the N(4) of one indazole ligand. The N(4)−Cl(2) distance is 3.105 Å. The distance between Cl(2) and the hydrogen at the N(4) of the indazole ring, H(2), is 2.441 Å [N(4)−H(2): 1.094 Å]. Cl(2), Ru, N(3), N(4), and H(2) are nearly in a plane.

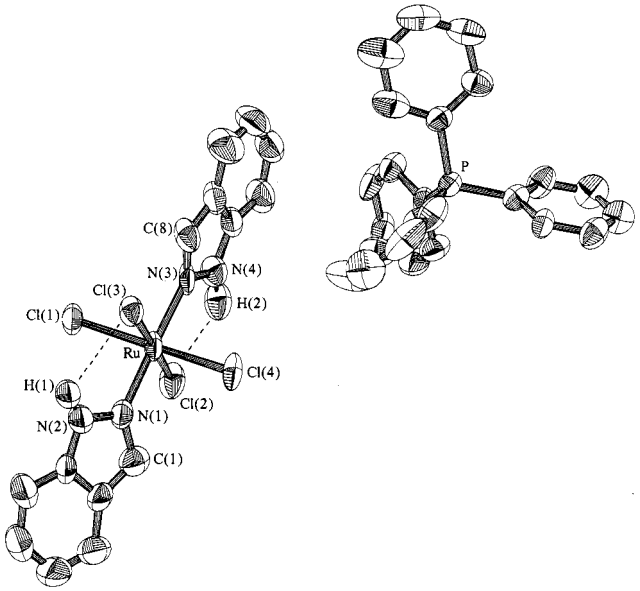

Figure 3. Perspective view of the crystal structure of **6**, $Ph_4P[RuCl_4ind_2]$. Selected bond lengths [Å] and angles [deg]: Ru−Cl(1) 2.3627(7), Ru−Cl(2) 2.3723(8), Ru−Cl(3) 2.3618(7), Ru−Cl(4) 2.3586(8), Ru−N(1) 2.0517(21), Ru−N(3) 2.0711(22), N(1)−N(2) 1.3498(31), N(3)−N(4) 1.3466(29), N(1)−C(1) 1.3338(36), N(3)−C(8) 1.3065(39), N(1)−Ru−N(3) 178.33(8), N(1)−Ru−Cl(1) 90.33(6), N(1)−Ru−Cl(2) 89.81(6), N(1)−Ru−Cl(3) 89.80(6), N(1)−Ru−Cl(4) 89.63(6), N(3)−Ru−Cl(1) 90.89(6), N(3)−Ru−Cl(2) 89.07(7), N(3)−Ru−Cl(3) 91.37(6), N(3)−Ru−Cl(4) 89.20(6), Cl(1)−Ru−Cl(2) 89.85(3), Cl(1)−Ru−Cl(3) 87.96(3), Cl(1)−Ru−Cl(4) 177.44(2), Cl(2)−Ru−Cl(3) 177.78(2), Cl(2)−Ru−Cl(4) 92.71(3), Cl(3)−Ru−Cl(4) 89.48(3)

In contrast, N(2) of the other indazole ligand exhibits only weak interactions with the chlorine Cl(3) through its H(1) atom [N(2)−Cl(3): 3.212 Å, Cl(3)−H(1): 2.750 Å, N(2)−H(1): 0.853 Å]. The N(2)−Cl(1) distance is 3.426 Å. Cl(4) is not involved in any hydrogen bonding and therefore exhibits the shortest Ru−Cl bond length.

In general, the Ru−Cl and Ru−N [Ru−N(1): 2.0517(21) Å, Ru−N(3): 2.0711(22) Å] bond lengths, as well as the bond lengths of the indazole rings, lie in the same range as those of the corresponding 1-methylindazole complex, the crystal structure of which has already been published[12]. The phosphorus of the tetraphenylphosphonium counterion is tetrahedrally coordinated by the phenyl rings, as could be expected

Experimental Section

Materials: All solvents and reagents were used as received and were of analytical grade. Indazolium *trans*-tetrachlorobis(indazole)ruthenate(III), $HInd[RuCl_4ind_2]$, was prepared as described previously[12].

Infrared Spectra: Infrared spectra were recorded on a Perkin−Elmer FTIR 2000 IR spectrophotometer.

NMR Spectra: The ^1H-, ^{13}C-, and 2D NMR experiments were performed at 400.13 MHz (^1H) and 100.61 MHz (^{13}C) on a Bruker DPX 400 spectrometer at 24 °C.

The gradient selected COSY and the HMQC (inverse H,C-correlation with BIRD selection and GARP decoupling in phase-sensitive mode using TPPI) experiments were performed with standard Bruker pulse programs.

X-ray Structure Determination: A single crystal of the tetraphenylphosphonium salt with the approximate dimensions of 0.30 × 0.25 × 0.15 mm was used for X-ray measurement on a Nonius KappaCCD diffractometer (Mo-*Kα* radiation) at room temperature. Denzo-SMN software was utilized for the data evaluation. The structure was solved by direct methods (SHELXS-97)[13] and refined (SHELXL-97)[14] including the positions of all hydrogen atoms. A summary of the crystal data and of the refinement procedures is given in Table 1. Atomic coordinates and displacement parameters are deposited in the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-112417.

Elemental Analyses: C,H,N analysis were carried out on a Perkin−Elmer 2400 CHN Elemental Analyzer. Cl was analyzed by argentometry.

Preparation of Compounds. Sodium *trans*-Tetrachlorobis(indazole)ruthenate(III) Trihydrate, $Na[RuCl_4ind_2] \cdot 3\ H_2O$ (2): A solution of $Me_4N[RuCl_4ind_2]$ (**3**; 100 mg, 0.18 mmol) in water (200 mL) was mixed with a Dowex 50WX2 acidic cation-exchange resin preloaded with sodium for 20 minutes. After filtration, the solution was immediately frozen with liquid nitrogen and lyophilized. The sodium salt was obtained as a voluminous, brown powder. Yield: 80 mg (89%). − $C_{14}H_{12}Cl_4N_4NaRu \cdot 3\ H_2O$ (556.19): calcd. C 30.23, H 3.26, Cl 25.50, N 10.07; found: C 30.20, H 2.62, Cl 25.47, N 9.80. − ^1H NMR (400 MHz, [D$_3$]acetonitrile): δ = 4.32 (2 H), 3.18 (2 H), 2.63 (2 H), 2.45 (2 H), −7.1 (2 H), −12.9 (2 H). − ^{13}C NMR (100 MHz, [D$_3$]acetonitrile): δ = 118.07, 114.72, 98.29, 97.77. IR (CsI): $\tilde{\nu}$ = 3459 s, 3316 s, 2925 w, 1627 vs, 1511 m, 1439 w, 1382 m, 1356 vs, 1280 w, 1241 s, 1154 m, 1124 m, 1085 s, 1004 m, 967 m, 900 w, 868 w, 838 m, 782 w, 750 vs, 667 s, 616 w, 435 m, 321 s, 291 m, 215 m cm^{-1}. − Thermogravimetric analysis (Mettler-Toledo TGA 850): The loss of one mol equivalent of water was achieved by heating up to 130 °C (nitrogen atmosphere). Further weight loss is observed at temperatures above 200 °C, resulting in decomposition of the complex.

Sodium *trans*-Tetrachlorobis(indazole)ruthenate(III), $Na[RuCl_4ind_2]$: $NaB[C_6H_5]_4$ (600 mg, 1.75 mmol) was added to a solution of **6** ($Ph_4P[RuCl_4ind_2]$, 500 mg, 0.61 mmol) in acetonitrile (25 mL). The precipitated $Ph_4PB[C_6H_5]_4$ was filtered off after stirring for five minutes. The sodium salt was precipitated by addition of diethyl ether to the filtrate. After standing at 4 °C for 30 minutes, $Na[RuCl_4ind_2]$ was filtered and dried in vacuum over P_2O_5. Yield: 266 mg (87%). − $C_{14}H_{12}Cl_4N_4NaRu$ (502.15): calcd. C, 33.49, H 2.41, N 11.16, Cl 28.24; found: C 33.09, H 2.67, N 11.04, Cl 26.79. − ^1H NMR (400 MHz, [D$_3$]acetonitrile): δ(cation) = 7.94 (4 H), 7.71 (m, 16 H); δ(anion) = 4.55 (2 H), 3.27 (2 H), 2.84 (2 H), 2.59 (2 H), −7.0 (2 H), −12.5 (2 H).

Table 1. Crystallographic data for $Ph_4P[RuCl_4ind_2]$ (**6**)

Empirical formula	$C_{38}H_{32}Cl_4N_4PRu$	$2\theta_{max}$[°]	53
space group	*P*1bar	measured reflections	13471
a [Å]	11.000(2)	unique data set	6802
b [Å]	13.503(2)	$R_{int.}$	0.017
c [Å]	14.471(2)	data with $F_o>4\sigma(F_o)$	5573
α [°]	65.42(1)	variables	562
β [°]	82.80(1)	*R*1 [for $F_o>4\sigma(F_o)$]	0.033
γ [°]	67.93(1)	*wR*2 [for all F_o^2]	0.088
V [Å^3]	1810.2	$R1 = \Sigma\|\|F_o\| - \|F_c\|\|/ \Sigma\|F_o\|$	
Z	2	$wR2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma wF_o^4]^{1/2}$	
ρ_{calc} [gcm^{-3}]	1.50	$w = 1/[\sigma^2(F_o^2) + (0.045\times P)^2 + 0.3\times P]$	
μ(Mo-*Kα*) [$^{-1}$]	8.1	$P = \{[\max \text{ of } (0 \text{ or } F_o^2)] + 2F_c^2\}/3$	

Crystal−detector distance: 28 mm, 180 frames with 2° φ scan range and 2 × 150 s exposure time per frame.

Tetramethylammonium *trans*-Tetrachlorobis(indazole)ruthenate(III), $Me_4N[RuCl_4ind_2]$ (3): Tetramethylammonium chloride (368 mg, 3.36 mmol) was added to $HInd[RuCl_4ind_2]$ (500 mg, 0.84 mmol) in methanol (150 mL). After stirring for 30 min, the formed precipitate was filtered, washed with water and dried under vacuum over phosphorus pentaoxide. Yield: 326 mg (70%). − $C_{18}H_{24}Cl_4N_5Ru$ (553.1): calcd. C 39.07, H 4.37, Cl 25.63, N 12.66; found: C 38.90, H 4.29, Cl 25.52, N 12.36. − ^{1}H NMR (400 MHz, [D$_3$]acetonitrile): δ(cation) = 3.16 (s, 12 H); δ(anion) = 4.54 (2 H), 3.27 (2 H), 2.83 (2 H), 2.58 (2 H), −5.81 (2 H), −10.89 (2 H). − ^{13}C NMR (100 MHz, [D$_3$]acetonitrile): δ(cation) = 59.24; δ(anion) = 118.12, 113.91, 98.12, 97.81. − IR (CsI): $\tilde{\nu}$ = 3460 m, 3293 s, 3013 m, 1627 s, 1560 w, 1509 m, 1483 s, 1438 w, 1380 w, 1356 vs, 1276 w, 1239 s, 1149 w, 1119 w, 1082 m, 1002 m, 945 vs, 866 w, 836 w, 750 vs, 669 s, 522 m, 455 w, 435 m, 336 m, 321 s, 291 m, 266 w, 218 m cm^{-1}.

Tetra(*n*-butyl)ammonium *trans*-Tetrachlorobis(indazole)ruthenate(III), $(n\text{But})_4N[RuCl_4ind_2]$ (4): $HInd[RuCl_4ind_2]$ (200 mg, 0.34 mmol) was suspended in water (100 mL) and acetonitrile (5 mL) by ultrasonic treatment and then dissolved in water (400 mL). Tetra(*n*-butyl)ammonium chloride (186 mg, 0.69 mmol) was added to this solution and precipitation occurred immediately. To complete the reaction, the mixture was stirred overnight. The precipitate was filtered, washed with water, and dried under vacuum over phosphorus pentaoxide. Yield: 216 mg (89%). − $C_{30}H_{48}Cl_4N_5Ru$ (721.63): calcd. C 49.93, H 6.70, Cl 19.65, N 9.71; found: C 49.57, H 6.46, Cl 19.67, N 9.53. − ^{1}H NMR (400 MHz, [D$_3$]acetonitrile): δ(cation) = 3.20 (8 H), 1.76 (8 H), 1.40 (8 H), 1.01 (12 H); δ(anion) = 4.55 (2 H), 3.26 (2 H), 2.83 (2 H), 2.57 (2 H), −7.0 (2 H), −12.3 (2 H). − ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ(cation) = 59.36, 24.39, 20.26, 14.53; δ(anion) = 118.39, 114.69, 99.79, 96.28. − IR (CsI): $\tilde{\nu}$ = 3307 s, 2960 s, 2874 m, 2360 m, 1626 s, 1506 w, 1478 vs, 1442 m, 1381 m, 1354 vs, 1275 w, 1243 s, 1152 s, 1089 m, 1002 m, 963 m, 838 m, 749 vs, 670 s, 628 s, 556 s, 434 m, 333 m, 320 s, 289 m, 217 m cm^{-1}.

Tetra(*n*-octyl)ammonium *trans*-Tetrachlorobis(indazole)ruthenate(III), $(n\text{Oct})_4N[RuCl_4ind_2]$ (5): To a solution of $HInd[RuCl_4ind_2]$ (250 mg, 0.42 mmol) in water (800 mL), prepared analogously to the above-mentioned procedure, were added tetra(*n*-octyl)ammonium chloride (420 mg, 0.84 mmol) in water (30 mL) and ethyl acetate (1 mL) to aid solution. After stirring for three days a green agglutinated precipitate formed and was filtered, washed with methanol, and dried under vacuum over phosphorus pentaoxide. Yield: 234 mg (59%). − $C_{46}H_{80}Cl_4N_5Ru$ (946.06): calcd. C 58.39, H 8.52, Cl 14.99, N 7.40; found: C 57.85, H 8.11, Cl 14.42, N 7.69. − ^{1}H NMR (400 MHz, $CDCl_3$): δ(cation) = 2.91 (8 H), 1.47 (16 H), 1.19 (32 H), 0.83 (12 H); δ(anion) = 4.11 (2 H), 3.11 (2 H), 2.40 (2 H), 2.27 (2 H), −7.7 (2 H), −14.3 (2 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ(cation) = 32.13, 30.19, 29.56, 29.02, 28.38, 23.04, 21.81, 14.55; δ(anion) = 116.88, 116.22, 99.40, 95.33. − IR (CsI): $\tilde{\nu}$ = 3296 s, 3096 w, 2955 s, 2926 vs, 2856 s, 1626 m, 1504 w, 1466 s, 1375 m, 1353 s, 1269 w, 1242 m, 1149 w, 1114 w, 1083 m, 998 w, 954 w, 830 w, 746 s, 671 m, 547 w, 442 w, 433 w, 328 s, 283 m, 218 m cm^{-1}.

Tetraphenylphosphonium *trans*-Tetrachlorobis(indazole)ruthenate(III), $Ph_4P[RuCl_4ind_2]$ (6): Tetraphenylphosphonium chloride (190 mg, 0.5 mmol) was added to a solution of $HInd[RuCl_4ind_2]$ (150 mg, 0.25 mmol) in water (500 mL), prepared analogously to the above-mentioned procedure, which resulted in immediate precipitation. After stirring overnight the precipitate was filtered and washed with water. Afterwards the crude product was dissolved in acetone and reprecipitated by addition of diethyl ether. The ocher-yellow precipitate was washed with diethyl ether/acetone (1:1) and dried under vacuum over phosphorus pentaoxide. Yield: 82 mg (40%). − $C_{38}H_{32}Cl_4N_4PRu$ (818.56): calcd. C 55.76, H 3.94, Cl 17.32, N 6.84; found: C 55.55, H 3.77, Cl 17.19, N 6.65. − ^{1}H NMR (400 MHz, [D$_3$]acetonitrile): δ(cation) = 7.94 (4 H), 7.71 (m, 16 H); δ(anion) = 4.54 (2 H), 3.26 (2 H), 2.82 (2 H), 2.58 (2 H), −7.1 (2 H), −12.5 (2 H). − ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ(cation) = 136.88, 135.60 (d), 131.86 (d), 118.88 (d); δ(anion) = 118.42, 114.71, 99.82, 96.26. − IR (CsI): $\tilde{\nu}$ = 3475 s, 3351 s, 3057 m, 1626 s, 1584 m, 1508 m, 1482 m, 1437 vs, 1380 m, 1358 s, 1277 m, 1164 m, 1108 vs, 1087 w, 996 s, 962 m, 837 m, 764 vs, 723 vs, 690 vs, 666 s, 528 vs, 440 w, 435 w, 336 m, 321 s, 282 m, 216 m cm^{-1}. − Crystals for X-ray diffraction were obtained by slowly evaporating an acetonitrile solution.

Acknowledgments

The assistance of Mrs. Rosa Strobl in preparing the manuscript is gratefully acknowledged.

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Received March 2, 1999
[I99077]