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Antitumor Agents

The "Complex-in-a-Complex" Cations $[(acac)_2M\subset Ru_6(p\text{-}iPrC_6H_4Me)_6(tpt)_2(dhbq)_3]^{6+}$: A Trojan Horse for Cancer Cells**

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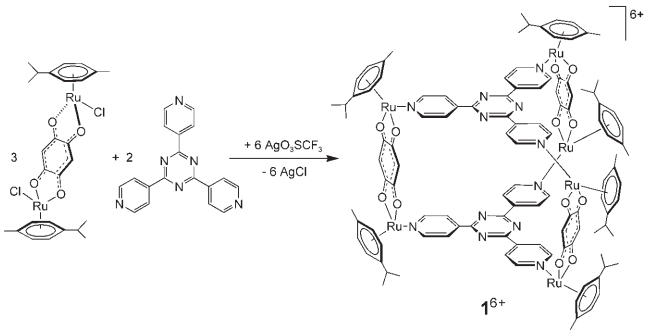
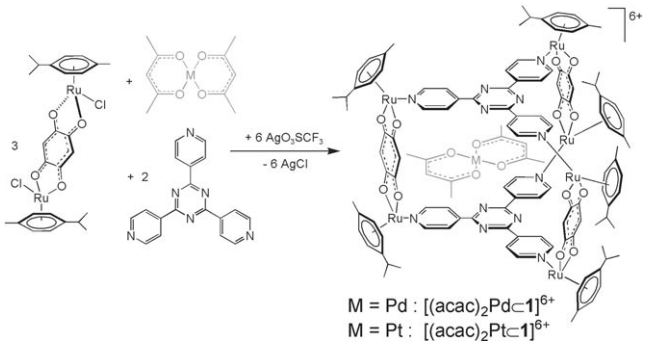
The directed synthesis of organometallic cage molecules for the assembly of molecular nano-objects is a topical area of chemical research.[1] By combining the "molecular clip" strategy developed by Stang[2] with the "molecular paneling" strategy pioneered by Fujita,[3] we recently synthesized trigonal-prismatic cage molecules in which six (η^6-arene)ruthenium or (η^5-pentamethylcyclopentadienyl)rhodium units are held together by two trigonal 2,4,6-tris(pyridin-4-yl)-1,3,5-triazine (tpt) panels and three dichloro[4] or oxalato[5] bridges. We have now extended this principle to construct the larger cationic hexanuclear metalloprism $[Ru_6(p\text{-}iPrC_6H_4Me)_6(tpt)_2(dhbq)_3]^{6+}$ ($\mathbf{1}^{6+}$), which incorporates *p*-cymene ruthenium building blocks and is bridged by 2,5-dihydroxy-1,4-benzoquinonato (dhbq) ligands and connected by two tpt subunits (Scheme 1).



Scheme 1. Synthesis of $[\mathbf{1}](O_3SCF_3)_6$.

The hexametallic cation $\mathbf{1}^{6+}$ was prepared from the dinuclear complex $[Ru_2(p\text{-}iPrC_6H_4Me)_2(dhbq)Cl_2]$[6] and tpt in the presence of AgO_3SCF_3. The cationic complex was isolated and characterized as its triflate salt $\mathbf{1}\text{-}(OSO_2CF_3)_6$ in 75% yield. The assembly of $\mathbf{1}^{6+}$ can also be achieved in the presence of $[Pd(acac)_2]$ or $[Pt(acac)_2]$ (acac = acetylacetonato) to give the "complex-in-a-complex" cations $[(acac)_2Pd\subset\mathbf{1}]^{6+}$ and $[(acac)_2Pt\subset\mathbf{1}]^{6+}$ without affecting the overall yield (Scheme 2). Cations $[(acac)_2Pd\subset\mathbf{1}]^{6+}$ and $[(acac)_2Pt\subset\mathbf{1}]^{6+}$ were both isolated as their triflate salts.



Scheme 2. Synthesis of $[(acac)_2Pd\subset\mathbf{1}](O_3SCF_3)_6$ and $[(acac)_2Pt\subset\mathbf{1}](O_3SCF_3)_6$.

The formation of $[(acac)_2Pd\subset\mathbf{1}]^{6+}$ and $[(acac)_2Pt\subset\mathbf{1}]^{6+}$ can easily be monitored by ^{1}H NMR spectroscopy and their molecular structure established by one-dimensional ^{1}H ROESY experiments. The CH and Me signals of the acetylacetato ligands in the ^{1}H NMR spectra of $[(acac)_2Pd\subset\mathbf{1}]^{6+}$ and $[(acac)_2Pt\subset\mathbf{1}]^{6+}$ are shifted upfield by about 1.7 ppm relative to the free complexes in $[D_6]$acetone (see the Supporting Information). One-dimensional ^{1}H ROESY experiments confirmed the molecular structure of cations $[(acac)_2Pd\subset\mathbf{1}]^{6+}$ and $[(acac)_2Pt\subset\mathbf{1}]^{6+}$. Thus, intense cross-peaks are observed between the protons of the encapsulated complex (H_{acac} and Me_{acac}) and the protons of the cage molecule (H_{tpt}, H_{cym}, H_{dhbq}) in close proximity (see Supporting Information).

The molecular structure of $[(acac)_2Pt\subset\mathbf{1}]^{6+}$ was confirmed by single-crystal X-ray structure analysis of $[(acac)_2Pt\subset\mathbf{1}](O_3SCF_3)_6$ (Figure 1).[7] The structure shows the $[Pt(acac)_2]$ complex to be held between the triazine units of the tpt ligands. It is clear from the van der Waals representation of the "complex-in-a-complex" cation that the $Pt(acac)_2$ complex is indeed encapsulated in $\mathbf{1}^{6+}$; the separation between platinum and triazine-centroid being 3.4 Å. The {Ru_2-

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

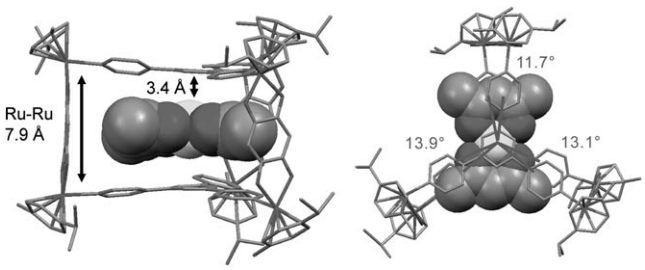

Figure 1. Molecular structure of $[(acac)_2Pt\subset\mathbf{1}]^{6+}$; side view and top view.

$(dhbq)^{2+}$} clips are tilted out of the plane of the tpt subunits by as much as 14° to accommodate the $[Pt(acac)_2]$ complex within the cavity of $\mathbf{1}^{6+}$.

To examine the stability of the cage in solution, we recorded the ^{1}H NMR spectra in D_2O at elevated temperatures (Figure 2). The ^{1}H NMR spectra of $\mathbf{1}^{6+}$, $[(acac)_2Pd\subset\mathbf{1}]^{6+}$, and $[(acac)_2Pt\subset\mathbf{1}]^{6+}$ in D_2O show no signal changes, thereby indicating the stability of the cage. The $[M(acac)_2]$ complexes are only (partially) released after a prolonged period, with the palladium complex being released to a greater extent.

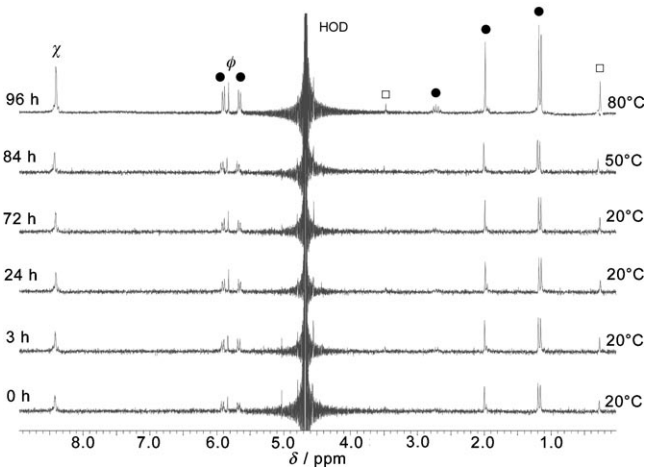

Figure 2. ^{1}H NMR spectra of $[(acac)_2Pd\subset\mathbf{1}]^{6+}$ (D_2O, 200 MHz) at elevated temperature (□ acac, ϕ dhbq, χ tpt, ● *p*-*i*PrC_6H_4Me).

Given the well-established anti-cancer activity of platinum compounds[8] and the promising anti-cancer potential of ruthenium complexes,[9] several of which are currently undergoing clinical evaluation,[10] we studied the cytotoxicity of the two "complex-in-a-complex" cations $[(acac)_2Pd\subset\mathbf{1}]^{6+}$ and $[(acac)_2Pt\subset\mathbf{1}]^{6+}$ with respect to the empty hexaruthenium cage **1** and the free acetylacetonato complexes $[Pd(acac)_2]$ and $[Pt(acac)_2]$ against A2780 human ovarian cancer cells.

One of the main challenges in cancer chemotherapy is to develop drugs that are selective towards cancer cells in order to reduce the general toxicity and consequently the side effects of the compound. One such targeting method involves using large carrier compounds which release the drug once inside a cancer cell, since large compounds selectively accumulate in cancer cells owing to the "enhanced permeability and retention effect".[11] Herein, $\mathbf{1}^{6+}$ represents the carrier compound and its high charge also potentially facilitates uptake in cancer cells.[12] We found that cisplatin can also be encapsulated within $\mathbf{1}^{6+}$, but it rapidly leaches from the hydrophobic pocket in water. However, the more hydrophobic complexes $[M(acac)_2]$ (M = Pd, Pt) are strongly immobilized within $\mathbf{1}^{6+}$, while being almost insoluble in water in their free form under ambient conditions. Indeed, the cytotoxicity data of the compounds described herein is in complete correlation with their observed solubility/stability properties (Table 1). The free $[M(acac)_2]$ complexes, which

Table 1: Cytotoxicity of the complexes in human A2780 ovarian cancer cells.

Complex	IC_{50}[a] [μM]
$[Pt(acac)_2]$	inactive
$[Pd(acac)_2]$	inactive
$\mathbf{1}^{6+}$	23
$[(acac)_2Pt\subset\mathbf{1}]^{6+}$	12
$[(acac)_2Pd\subset\mathbf{1}]^{6+}$	1

[a] IC_{50}: drug concentration necessary for 50% inhibition of cell viability.

are virtually insoluble in water (the palladium species being slightly more soluble), show no cytotoxic effects on the A2780 human ovarian cancer cells. However, while the cage complex $\mathbf{1}^{6+}$ is moderately cytotoxic, both "complex-in-a-complex" species $[(acac)_2M\subset\mathbf{1}]^{6+}$ are more active, with the platinum-containing species being about twice as active as the empty cage and the palladium entrapped species being more than one order of magnitude more cytotoxic; indeed, the IC_{50} value of 1 μM for $[(acac)_2Pd\subset\mathbf{1}]^{6+}$ is extremely low in comparison to other platinum and ruthenium complexes. The higher cytotoxicity of $[(acac)_2Pd\subset\mathbf{1}]^{6+}$ with respect to that of $[(acac)_2Pt\subset\mathbf{1}]^{6+}$ may suggest that the palladium complex is more easily released from the hexaruthenium cage $\mathbf{1}^{6+}$ than the platinum complex. Once inside a cell, the hexaruthenium cage may open and release the $[M(acac)_2]$ complex to the biological target. A more detailed study of this mode of action is in progress.

A large number of polynuclear metal complexes have been evaluated as putative anticancer agents.[13] In general, these complexes are based on metal centers connected through bridging ligands or metal centers connected to macromolecular supports. However, to our knowledge, the "Trojan horse" strategy described herein represents the first example in which a relatively hydrophobic complex encapsulated within a hydrophobic pocket of a metal-containing host functions in a synergic fashion by accelerated release inside a cancer cell.

Experimental Section

All organic solvents were saturated with nitrogen prior to use. $[Pd(acac)_2]$, $[Pt(acac)_2]$, and 2,5-dihydroxy-1,4-benzoquinone ($dhbqH_2$) were purchased from Fluka. 2,4,6-Tris(pyridin-4-yl)-1,3,5-triazine (tpt)[14] and $[Ru_2(p\text{-}i\text{Pr}C_6H_4Me)_2(dhbq)Cl_2]$[6] were prepared according to published methods. NMR spectra were recorded with a Varian 200 MHz or Bruker 400 MHz spectrometer. IR spectra were

recorded with a Perkin–Elmer 1720X FT-IR spectrometer (4000–400 cm^{-1}). Microanalyses were performed by the Laboratory of Pharmaceutical Chemistry, University of Geneva (Switzerland).

1-$(O_3SCF_3)_6$: A mixture of $[Ru_2(p\text{-}i\text{Pr}C_6H_4Me)_2(dhbq)Cl_2]$ (60 mg, 0.09 mmol) and AgO_3SCF_3 (46 mg, 0.18 mmol) in MeOH (20 mL) was stirred at room temperature for 2 h, then filtered. The ligand tpt (18.4 mg, 0.06 mmol) was then added to the red filtrate and the mixture stirred at room temperature for 48 h. The solvent was then removed under vacuum. The dark residue was taken up in CH_2Cl_2 (20 mL) and, after filtration, the solution was concentrated (3 mL) and diethyl ether added to precipitate a red solid. Yield: 75 mg (75%). ^{1}H NMR (400 MHz, [D$_6$]acetone): $\delta = 8.75$ (dd, $^3J_{H,H} = 5.36$ Hz, $^4J_{H,H} = 1.56$ Hz, 12H; H_α), 8.68 (dd, $^3J_{H,H} = 5.36$ Hz, $^4J_{H,H} = 1.56$ Hz 12H; H_β), 6.24 (d, $^3J_{H,H} = 6.32$ Hz, 12H; H_{ar}), 6.03 (d, $^3J_{H,H} = 6.32$ Hz, 12H; H_{ar}), 5.87 (s, 6H; H_q), 3.00 (sept, $^3J_{H,H} = 6.92$ Hz, 6H; CH), 2.28 (s, 18H; CH_3), 1.41 ppm (d, $^3J_{H,H} = 6.92$ Hz, 36H; CH_3); $^{13}C\{^1H\}$ NMR (100 MHz, [D$_6$]acetone): $\delta = 170.04$, 154.86, 144.66, 125.15, 123.26, 120.24, 104.42, 102.16, 99.53, 84.19, 82.72, 31.57, 21.98, 17.63 ppm; IR: $\tilde{\nu} = 1635$(s), 1524(s), 1377(m), 1259(s), 1161(m), 1031(m), 639(s) cm^{-1}. C,H,N analysis (%) calcd for $C_{120}H_{114}F_{18}N_{12}O_{30}S_6Ru_6$ (3345.0): C 43.09, H 3.44, N 5.02; found: C 42.96, H 3.33, N 4.86.

$[(acac)_2M\subset\mathbf{1}](O_3SCF_3)_6$: A mixture of $[Ru_2(p\text{-}i\text{Pr}C_6H_4Me)_2(dhbq)Cl_2]$ (60 mg, 0.09 mmol) and AgO_3SCF_3 (47 mg, 0.18 mmol) in MeOH (20 mL) was stirred for 2 h, then filtered. [M(acac)$_2$] (M = Pd, 10 mg, 0.03 mmol; M = Pt, 13 mg, 0.03 mmol) and tpt (18 mg, 0.06 mmol) were added to the red filtrate to give a red solution. The mixture was stirred at room temperature for 15 h and the solvent removed under vacuum. The dark residue was taken up in CH_2Cl_2 (20 mL) and, after filtration, the solution was concentrated (3 mL) and diethyl ether added to precipitate a red solid.

$[(acac)_2Pd\subset\mathbf{1}](O_3SCF_3)_6$: Yield: 75 mg (69%). ^{1}H NMR (400 MHz, [D$_6$]acetone): $\delta = 8.68$ (dd, $^3J_{H,H} = 6.04$ Hz, 24H; py), 6.23 (d, $^3J_{H,H} = 5.60$ Hz, 12H; $Ar_{p\text{-cym}}$), 6.02 (d, $^3J_{H,H} = 5.60$ Hz, 12H; $Ar_{p\text{-cym}}$), 5.88 (s, 6H), 3.68 (s, 2H; CH), 2.95 (sept, $^3J_{H,H} = 6.80$ Hz, 6H; CH), 2.26 (s, 18H; CH_3), 1.40 (d, $^3J_{H,H} = 6.80$ Hz, 36H; CH_3), 0.44 ppm (s, 12H, CH_3); $^{13}C\{^1H\}$ NMR (100 MHz, [D$_6$]acetone): $\delta =$ 184.06, 182.87, 170.03, 158.24, 143.37, 124.16, 122.15, 121.38, 105.32, 103.52, 101.09, 84.66, 82.34, 32.14, 24.28, 22.56, 18.22 ppm; IR: $\tilde{\nu} =$ 1688(s), 1526(s), 1439(s), 1223(s), 1092(s), 1032(m), 981(m), 908(s), 896(s), 846(m) cm^{-1}. C,H,N analysis (%) calcd for $C_{130}H_{128}F_{18}N_{12}O_{34}PdRu_6S_6$ (3649.7): C 42.78, H 3.54, N 4.61; found: C 42.53, H 3.17, N 4.53.

$[(acac)_2Pt\subset\mathbf{1}](O_3SCF_3)_6$: Yield: 70 mg (62%). ^{1}H NMR (400 MHz, [D$_6$]acetone): $\delta = 8.66$ (s, 24H; py), 6.22 (d, $^3J_{H,H} = 6.40$ Hz, 12H; $Ar_{p\text{-cym}}$), 6.02 (d, $^3J_{H,H} = 6.40$ Hz, 12H; $Ar_{p\text{-cym}}$), 5.90 (s, 6H), 3.77 (s, 2H; CH), 2.98 (sept, $^3J_{H,H} = 7.00$ Hz, 6H; CH), 2.26 (s, 18H; CH_3), 1.38 (d, $^3J_{H,H} = 7.00$ Hz, 36H; CH_3), 0.30 ppm (s, 12H; CH_3); $^{13}C\{^1H\}$ NMR (100 MHz, [D$_6$]acetone): $\delta = 184.94$, 184.46, 170.53, 155.29, 145.66, 125.83, 124.08, 120.88, 105.12, 102.72, 100.17, 84.76, 83.32, 32.14, 24.46, 22.27, 18.31 ppm; IR: $\tilde{\nu} = 1709$(s), 1526(s), 1340(s), 1208(s), 1093(s), 1032(m), 831(s) cm^{-1}. C,H,N analysis (%) calcd for $C_{130}H_{128}F_{18}N_{12}O_{34}PtRu_6S_6$ (3738.3): C 41.77, H 3.45, N 4.50; found: C 41.56, H 3.40, N 4.33.

Human A2780 ovarian carcinoma cells were obtained from the European Centre of Cell Cultures (ECACC, Salisbury, UK) and maintained in culture as described by the provider. The cells were routinely grown in RPMI 1640 medium containing 10% foetal calf serum (FCS) and antibiotics at 37°C and 6% CO_2. For the growth inhibition tests, the cells were seeded in 96-well plates and grown for 24 h in complete medium. The complexes were diluted to the required concentration and added to the cell culture for 72 h incubation. Solutions of the compounds were applied by diluting a freshly prepared stock solution of the corresponding compound in aqueous RPMI medium (20 mM). The MTT test was performed in the last 2 h without changing the culture medium. Following drug exposure, MTT (Sigma) was added to the cells at a final concentration of 0.2 mg mL^{-1} and incubated for 2 h, then the culture medium was aspirated and the violet formazan precipitate dissolved in 0.1N HCl in 2-propanol. The optical density was quantified at 540 nm using a multiwell plate reader (iEMS Reader MF, Labsystems, US), and the percentage of surviving cells was calculated from the ratio of absorbance of treated to untreated cells. The IC_{50} values for the inhibition of cell growth were determined by fitting the plot of the percentage of surviving cells against the drug concentration using a sigmoidal function (Origin v7.5).

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[6] See the Supporting Information for the synthesis and characterization of $[Ru_2(p\text{-}i\text{Pr}C_6H_4Me)_2(dhbq)Cl_2]$.

[7] X-ray data for $[(acac)_2Pt\subset\mathbf{1}](O_3SCF_3)_6$: $C_{130}H_{128}F_{18}N_{12}O_{34}PtRu_6S_6$, $M = 3738.31$, monoclinic, space group $P2_1/c$ (no. 14), $a = 28.076(2)$, $b = 18.1010(7)$, $c = 32.747(2)$ Å, $\beta = 108.085(5)°$, $V = 15819.7(15)$ Å^3, $T = 173(2)$ K, $Z = 4$, $\rho_{calcd} = 1.570$ g cm^{-3}, $\lambda(Mo_{K\alpha}) = 0.71073$ Å, 22950 reflections measured, 8529 unique ($R_{int} = 0.2046$) which were used in all calculations. The structure was solved by direct methods (SHELXL-97; G. M. Sheldrick, *SHELXL-97*, University of Göttingen, Göttingen, Germany (1999)) and refined by full-matrix least-squares methods on F^2 with 1792 parameters. $R_1 = 0.0752$ ($I > 2\sigma(I)$) and $wR_2 = 0.1660$, GOF = 0.887; max./min. residual electron density 1.181/−1.719 e Å^{-3}. CCDC-673229 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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