

appropriate solvent. The materials obtained and the solvents employed are summarized in Table II together with the analytical data. Elemental analyses except for copper were performed by Huffman Laboratories, Wheatridge, CO. The materials were stable enough to be handled in air. As long as TTF was in excess, the composition of the materials obtained was independent of reaction conditions, such as the TTF:CuX₂ ratio. A typical method of preparation of each of the materials is described below.

(TTF)₂CuCl₂. A solution of 11 mg (0.065 mmol) of CuCl₂·2H₂O in 1.5 mL of methanol was added with stirring to 29 mg (0.14 mmol) of TTF dissolved in 3 mL of methanol under a nitrogen atmosphere. Deep purple crystalline powders were formed. After the resulting mixture was stirred for ca. 1 h, the precipitate was collected on a filter, washed with ethanol, and dried under vacuum.

(TTF)₇(CuCl₂)₃. An acetonitrile solution of CuCl₂·2H₂O (0.076 mmol in 2.5 mL) was added with stirring to TTF (0.177 mmol) dissolved in acetonitrile (2.5 mL) under a nitrogen atmosphere. After the resulting mixture was stirred for ca. 1 h, the precipitate formed was collected on a filter, washed with acetonitrile, and dried under vacuum.

(TTF)₅(CuBr₂)₃. A methanol solution of CuBr₂ (0.054 mmol in 1 mL) was added with stirring to a methanol solution of TTF (0.111 mmol in 2.5 mL) under a nitrogen atmosphere. After the resulting mixture was stirred for ca. 1 h, the precipitate formed was collected, washed with ethanol, and dried under vacuum.

(TTF)₄(CuBr₂)₃. A tetrahydrofuran (THF) solution of CuBr₂ (0.078 mmol in 5 mL) was added with stirring to TTF (0.16 mmol) dissolved in THF (2.5 mL) under a nitrogen atmosphere. After the resulting mixture was stirred for ca. 1 h, the precipitate formed was collected on a filter, washed with THF, and dried under vacuum.

(TTF)₆CuBr₄. An acetonitrile solution of CuBr₂ (0.072 mmol in 1 mL) was added with stirring to 0.156 mmol of TTF dissolved in acetonitrile (2 mL) under a nitrogen atmosphere. The resulting mixture was stirred for ca. 1 h. The precipitate formed was collected on a filter, washed with acetonitrile, and dried under vacuum.

Physical Measurements. The electrical conductivity was determined on the compressed pellets by van der Pauw's 4-probe method²⁸ in a temperature range of 100–300 K. The thermoelectric power of the pellets

was determined against copper metal with platinum contacts at 300 K.

The ESR spectra were recorded by means of a Varian E-3 spectrometer. Diphenylpicrylhydrazyl was employed as a calibrant for determining *g* values.

The IR spectra of the compounds in Nujol mulls were recorded with a Perkin-Elmer 1420 spectrophotometer. The nature of the spectra observed was independent of mull-preparation techniques.

The X-ray photoelectron spectra were obtained with a Vacuum Generators ESCALAB MK II spectrometer (East Grinstead, U.K.). The pressure in the sample chamber did not exceed 5×10^{-10} Torr during the experiments. All samples were irradiated with Al K α X-rays (1486.6 eV). The sample powders were mixed with ultrapure powdered graphite in a ratio of 15:1 and pressed onto indium foil. The binding energies of the photoelectrons were determined by assuming that the carbon 1s electrons had a binding energy of 284.6 eV. Throughout each of the experiments, no significant outgassing of the samples was detected, and no other indications of sample decomposition were observed. The data were recorded digitally, and all peak scans were signal-averaged until an acceptable signal:noise ratio was obtained.

The magnetic susceptibility was determined by means of a Faraday balance²⁹ in the temperature range 100–300 K. Sodium chloride (-0.52×10^{-6} emu g⁻¹) was used as a calibrant.²⁹ The molar susceptibility was corrected for diamagnetic contributions (10^{-6} emu mol⁻¹) from TTF (-99),³⁰ Cl⁻ (-26), and Br⁻ (-36).³¹

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Registry No. TTF, 31366-25-3; (TTF)₂CuCl₂, 99639-32-4; (TTF)₇(CuCl₂)₃, 104034-45-9; (TTF)₅(CuBr₂)₃, 99639-34-6; (TTF)₄(CuBr₂)₃, 104034-46-0; (TTF)₆CuBr₄, 104034-48-2; CuCl₂, 7447-39-4; CuBr₂, 7789-45-9.

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Synthesis and Structure of [Rhodamine 123]₂PtCl₄·4H₂O: The First Tetrachloroplatinate(II) Salt with Anticancer Activity

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The preparation and characterization of bis(Rhodamine 123)tetrachloroplatinate(II) tetrahydrate, [RH(123)]₂PtCl₄·4H₂O (A), is described. Crystals of A are monoclinic C2/c with *a* = 13.318 (3) Å, *b* = 21.702 (5) Å, *c* = 15.485 (3) Å and β = 94.11 (2)° and have four formula units in the unit cell. The structure was determined by standard methods and refined to *R*₁ = 0.066, *R*₂ = 0.087 on the basis of 5101 independent reflections. Data were measured with use of Mo K α radiation and a Syntex P2₁ diffractometer. There are strong π ··· π interactions between the cation molecules, and the structure is stabilized by an extensive hydrogen-bonding network. There is no structural or spectral evidence for covalent interaction between the Pt atoms and the dye molecules. This result is discussed in light of the anticancer properties of the compound.

Introduction

Although a variety of Pt complexes have been shown to possess clinical anticancer properties, none of these compounds are selectively taken up by tumors.¹ There is great interest in finding

active Pt compounds that are targeted to tumors. Chen et al. have recently shown that the cationic dye Rhodamine 123 (RH(123)) is selectively retained in the mitochondria of carcinoma cells compared to normal cells in tissue culture.² The chemical structure of the RH(123) cation is shown in Figure 1. In an attempt to form a complex of RH(123) and Pt, the reaction of

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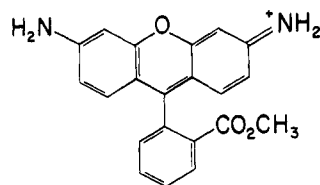


Figure 1. The Rhodamine 123 cation (schematic).

Table I. Crystal Data

compd	[C ₂₁ H ₁₇ N ₂ O ₃ ⁺] ₂ [PtCl ₄ ²⁻]·4H ₂ O, C ₄₂ H ₄₂ Cl ₄ N ₄ O ₁₀ Pt
fw	1099.7
cryst size, mm	0.05 × 0.10 × 0.50
systematic absences	<i>hkl</i> , <i>h</i> + <i>k</i> = 2 <i>n</i> + 1; <i>h</i> 0 <i>l</i> , <i>l</i> = 2 <i>n</i> + 1
space group	C2/c, No. 15
unit cell parameters, Å and deg	<i>a</i> = 13.318 (3), <i>b</i> = 21.702 (5), <i>c</i> = 15.485 (3), β = 94.11 (2)
<i>V</i> , Å ³	4464 (1)
<i>Z</i>	4
ρ_{calcd} , ρ_{obsd} , g cm ⁻³	1.64, 1.67 (2)
linear abs coeff, cm ⁻¹	36.0
abs corr factor limits	1.06–1.40
max 2θ, deg; reflns collected	55; <i>h</i> , <i>k</i> , ± <i>l</i>
std reflns (esd)	1,5,-3 (0.019), 263 (0.023)
temp, °C	22
no. of reflns collected	5457
<i>R</i> _{merg}	0.0236
no. of independent reflns	5101
no. with <i>I</i> > 3σ _{<i>I</i>} , used	2424
no. with 3σ _{<i>I</i>} > <i>I</i> > 0	2033
no. with <i>I</i> < 0, rejected	644
final <i>R</i> ₁ , ^a <i>R</i> ₂ ^a	0.066, 0.087
final shift/error max (av)	0.125, 0.010
<i>x</i> (secondary extinction)	-0.00028
final diff map peak, valley, e Å ⁻³	+2.17, ^b -1.20 ^b
weighting scheme	<i>w</i> = (σ _{<i>F</i>} ² + 0.0025 <i>F</i> ₀ ²) ⁻¹
error in an obsn of unit wt	1.30

^a *R*₁ = Σ||*F*₀| - |*F*_{*hkl*}||/Σ|*F*₀|; *R*₂ = [Σ*w*(|*F*₀| - |*F*_{*hkl*})|²/Σ*wF*₀²]^{1/2}.

^b Near the platinum atom position.

the dye with K₂PtCl₄ was performed. The product of this reaction possesses in vivo anticancer and radiosensitizer activity in mice not shown by either [RH(123)]Cl or K₂PtCl₄.³⁻⁵ Moreover, the compound is selectively taken up by Lewis lung carcinoma cells in mice.⁶ The identification of this material as a tetrachloroplatinate (II) salt of RH(123) and its spectral and structural characterization are described in this paper. To our knowledge, [RH(123)]₂PtCl₄·4H₂O is the first tetrachloroplatinate(II) salt to show in vivo anticancer and radiosensitizer activity.

Experimental Section

Rhodamine 123 chloride (Fisher) and K₂PtCl₄ (Johnson Matthey) were used as received. Infrared spectra were recorded on both Nicolet 7199-FT-IR and Perkin-Elmer Model 283 spectrophotometers. The samples were ground with KBr at a concentration of approximately 1% by weight and then pressed into pellets. Spectra were calibrated with polystyrene. For the region 500–100 cm⁻¹, the samples were prepared as Nujol mulls on polyethylene plates. ¹H (dimethylformamide-*d*₇; internal standard) and ¹⁹⁵Pt (aqueous Na₂[PtCl₆] external standard) NMR spectra were obtained by using an IBM AF-80 multinuclear NMR spectrometer. Elemental analysis was performed by Atlantic Microlab Inc., Atlanta, GA.

Preparation of [Rhodamine 123]₂PtCl₄·4H₂O. Rhodamine 123 chloride (1.50 g, 3.94 mmol) was dissolved in water (700 mL). To this red solution was added K₂PtCl₄ (0.82 g, 1.98 mmol) dissolved in water (125 mL). A red precipitate formed immediately. The reaction mixture was stirred for 30 min and the product collected by suction filtration. The

Table II. Atomic Positional Parameters (×10⁴) and Temperature Factors (Å² × 10³)

atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{eq} ^a
C(1a)	3691 (8)	6710 (5)	4648 (7)	36 (6)
C(1)	3667 (10)	6280 (5)	3949 (8)	45 (8)
C(2)	3723 (10)	6466 (7)	3100 (8)	50 (8)
C(3)	3792 (8)	7117 (6)	2915 (8)	40 (8)
C(4)	3836 (9)	7547 (5)	3587 (7)	39 (7)
C(4a)	3794 (8)	7348 (5)	4423 (7)	33 (6)
C(5a)	3774 (7)	7639 (5)	5901 (7)	27 (6)
C(5)	3826 (9)	8128 (5)	6479 (8)	39 (7)
C(6)	3739 (8)	7994 (5)	7360 (8)	39 (7)
C(7)	3639 (9)	7373 (6)	7634 (8)	42 (7)
C(8)	3605 (8)	6905 (5)	7066 (7)	37 (7)
C(8a)	3668 (8)	7018 (5)	6171 (7)	33 (6)
C(9)	3630 (8)	6554 (5)	5533 (8)	37 (7)
C(1')	3407 (10)	5901 (5)	5760 (7)	41 (8)
C(2')	4171 (9)	5471 (5)	6011 (7)	38 (6)
C(3')	3911 (11)	4859 (6)	6214 (8)	52 (8)
C(4')	2868 (11)	4683 (6)	6129 (10)	60 (8)
C(5')	2134 (11)	5115 (6)	5916 (10)	62 (9)
C(6')	2384 (10)	5727 (6)	5721 (9)	49 (8)
C(7')	5234 (10)	5652 (5)	6066 (8)	44 (7)
C(8')	6942 (11)	5380 (7)	6482 (14)	85 (13)
O	3831 (6)	7790 (3)	5052 (5)	37 (5)
O(1)	5852 (8)	5238 (4)	6436 (7)	67 (7)
O(2)	5524 (7)	6143 (4)	5822 (8)	73 (7)
N(3)	3821 (8)	7302 (6)	2088 (6)	50 (6)
N(6)	3768 (8)	8471 (5)	7936 (7)	47 (7)
Pt	0	5478.4 (3)	7500	50.2 (5)
Cl(1)	692 (4)	4731 (2)	8387 (4)	99 (4)
Cl(2)	781 (5)	6225 (2)	8342 (2)	125 (5)
O(3)	1383 (9)	3116 (5)	5203 (6)	77 (8)
O(4)	1516 (9)	8124 (5)	9688 (7)	82 (8)

$$U_{\text{eq}} = \frac{1}{3}(U_{11} + U_{22} + 2U_{13} \cos \beta).$$

red solid was washed with water (50 mL), 1 N HCl (50 mL), ethanol (50 mL), and ether (50 mL) and dried in vacuo. Yield of [RH(123)]₂PtCl₄·4H₂O: 1.7 g, 78% based on Pt. Crystals for X-ray structural analysis were obtained by slow evaporation of an acetone/water (4:1 v/v) solution of the title salt to which a few drops of 2 N HCl had been added. Anal. Calcd for C₄₂H₄₂Cl₄N₄O₁₀Pt: C, 45.87; H, 3.86; Cl, 12.89; N, 5.10. Found: C, 45.56; H, 3.89; Cl, 12.63; N, 4.96. Electronic spectrum (dimethylacetamide) [λ, nm (ε, L mol⁻¹ cm⁻¹): 515 (1.7 × 10⁵), 480 (sh), 333 (1.5 × 10⁴). IR (KBr) (cm⁻¹): ν_{N-H} 3200 (s), ν_{Pt-Cl} 320 (m). ¹H NMR (dimethylformamide-*d*₇) (ppm): 3.63 (sharp singlet), 5.01 (broad singlet), 7.02–8.36 (complex multiplet). ¹⁹⁵Pt NMR (9:1 sulfolane/D₂O v/v) (ppm): -1466.

Collection of the Data. A dark red acicular crystal was used for X-ray studies and was mounted along the needle axis. Precession photographs revealed the crystal symmetry and unit cell parameters were obtained from a least-squares fit of 15 reflections in the range 20.4° < 2θ < 27.7° recorded on a P₂ diffractometer with use of graphite-monochromated Mo Kα radiation (0.71069 Å). Crystal data and other numbers related to data collection are summarized in Table I. The density was determined by flotation in a chloroform–carbon tetrabromide mixture. Intensities were also measured with use of the P₂ diffractometer and a coupled θ(crystal)–2θ(counter) scan. The methods of selection of scan rates and initial data treatment have been described.^{7,8} Corrections were made for Lorentz–polarization effects but not for absorption. On the basis of the maximum and minimum dimensions of the crystal and by treating it as a cylindrical specimen, we estimate the maximum error in *F*₀ due to absorption to be <7.0%.

Solution of the Structure. The platinum atom was found from a three-dimensional Patterson synthesis to lie on a twofold axis, and subsequent least-squares refinement and electron density difference syntheses revealed all the non-hydrogen atoms. Further refinement using of full-matrix least-squares and all atoms with anisotropic temperature factors minimized Σ*w*(|*F*₀| - |*F*_{*hkl*}|)² and was terminated when the maximum shift/error fell below 0.2. No attempt was made to locate the hydrogen atoms. Corrections were made for extinction with the method of SHELX.⁹

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Table III. Selected Interatomic Distances (Å) and Angles (deg)

C(1a)-C(1)	1.43 (2)	C(1)-C(2)	1.38 (2)	C(2)-C(3)	1.45 (2)
C(3)-C(4)	1.40 (2)	C(4)-C(4a)	1.37 (2)	C(4a)-O	1.36 (1)
C(5a)-C(5)	1.39 (2)	O-C(5a)	1.36 (1)	C(5)-C(6)	1.41 (2)
C(6)-C(7)	1.42 (2)	C(7)-C(8)	1.34 (2)	C(8)-C(8a)	1.42 (2)
C(8a)-C(9)	1.41 (2)	C(9)-C(1a)	1.42 (2)	C(1a)-C(4a)	1.44 (2)
C(5a)-C(8a)	1.42 (1)	C(9)-C(1')	1.50 (2)	C(1')-C(2')	1.41 (2)
C(2')-C(3')	1.42 (2)	C(3')-C(4')	1.44 (2)	C(4')-C(5')	1.38 (2)
C(5')-C(6')	1.41 (2)	C(6')-C(1')	1.41 (2)	C(2')-C(7')	1.47 (2)
C(7')-O(1)	1.32 (2)	C(7)-O(2)	1.20 (1)	O(1)-C(8')	1.48 (2)
C(3)-N(3)	1.35 (2)	C(6)-N(6)	1.37 (1)	Pt-Cl(1)	2.28 (5)
Pt-Cl(2)	2.277 (4)				
C(1a)-C(1)-C(2)	122 (1)	C(1)-C(2)-C(3)	119 (1)	C(2)-C(3)-C(4)	120 (1)
C(3)-C(4)-C(4a)	120 (1)	C(4)-C(4a)-O	117 (1)	C(4a)-O-C(5a)	121.3 (8)
O-C(5a)-C(5)	115.9 (9)	C(5a)-C(5)-C(6)	118 (1)	C(5)-C(6)-C(7)	120 (1)
C(6)-C(7)-C(8)	121 (1)	C(7)-C(8)-C(8a)	121 (1)	C(8)-C(8a)-C(9)	124 (1)
C(8a)-C(9)-C(1a)	120 (1)	C(9)-C(1a)-C(1)	125 (1)	C(2)-C(3)-N(3)	119 (1)
C(4)-C(3)-N(3)	121 (1)	C(4)-C(4a)-C(1a)	123 (1)	O-C(4a)-C(1a)	120.1 (9)
O-C(5a)-C(8a)	121.6 (9)	C(5)-C(5a)-C(8a)	123 (1)	C(5)-C(6)-N(6)	118 (1)
C(7)-C(6)-N(6)	121 (1)	C(8)-C(8a)-C(5a)	118 (1)	C(9)-C(8a)-C(5a)	118 (1)
C(9)-C(1a)-C(4a)	119 (1)	C(1)-C(1a)-C(4a)	116 (1)	C(8a)-C(9)-C(1')	121 (1)
C(1a)-C(9)-C(1')	119 (1)	C(9)-C(1')-C(2')	123 (1)	C(9)-C(1')-C(6')	117 (1)
C(6')-C(1')-C(21)	121 (1)	C(1')-C(2')-C(3')	120 (1)	C(2')-C(3')-C(4')	119 (1)
C(3')-C(4')-C(5')	120 (1)	C(4')-C(5')-C(6')	121 (1)	C(5')-C(6')-C(1')	119 (1)
C(1')-C(2)-C(7)	121 (1)	C(3')-C(2')-C(7')	119 (1)	C(2')-C(7')-O(1)	114 (1)
C(2')-C(7')-O(2)	123 (1)	O(1)-C(7')-O(2)	122 (1)	C(7')-C(1)-C(8')	117 (1)
Cl(2)-Pt-Cl(1)	90.7 (2)				
N(6)...Cl(1)	3.52 (1)	N(3)...Cl(2)	3.32 (1)	O(3)...Cl(2)	3.27 (1)
N(3)...O(4)	2.91 (2)	O(4)...O(2)	2.77 (2)	O(3)...O(4)	2.79 (2)
N(6)...O(3)	3.00 (2)				

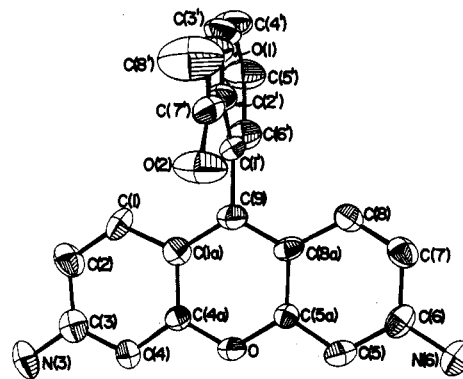
Throughout the refinement, scattering curves were taken from ref 10 and anomalous dispersion corrections from ref 11 were applied to the curves for platinum and chlorine. The atom parameters for non-hydrogen atoms are listed in Table II.

Results and Discussion

The reaction of K_2PtCl_4 and RH(123) results in the formation of the salt $[RH(123)]_2PtCl_4 \cdot 4H_2O$, which is slightly soluble in water and readily soluble in polar organic solvents such as dimethylformamide and sulfolane.

The infrared spectrum of $[RH(123)]_2PtCl_4 \cdot 4H_2O$ and of RH(123) show no significant differences (wavenumbers the same, small changes in intensity probably resulting from different concentrations) with the following exceptions: a band at 320 cm^{-1} is the same as for the $(NH_4)_2PtCl_4$ spectra, and there are no new bands typical of Pt-N bonding. There are a sharpening and a small shift to higher wavenumber of the ν_{NH} band at 3200 cm^{-1} . $\Delta = 100\text{ cm}^{-1}$ in the $PtCl_4^{2-}$ salt relative to that in the chloride salt of RH(123) (3160 cm^{-1} , $\Delta = 180\text{ cm}^{-1}$). The 515- and 333-nm bands in the electronic spectrum of the $PtCl_4^{2-}$ salt are unchanged from the corresponding bands in the chloride salt. Similarly, the only difference in the 1H NMR spectrum of $[RH(123)]_2PtCl_4 \cdot 4H_2O$ compared to $[RH(123)]Cl$ is the signal at 5.01 ppm due to the lattice water molecules.

$[RH(123)]_2PtCl_4 \cdot 4H_2O$ exhibits a single peak at -1466 ppm in its ^{195}Pt NMR spectrum (compared to -1494 ppm for K_2PtCl_4 in the same solvent). This relatively minor change in the Pt chemical shift is consistent with no covalent interaction between the dye molecule and the Pt atom.¹² In summary, there is no spectral evidence for coordination of Rhodamine 123 to platinum



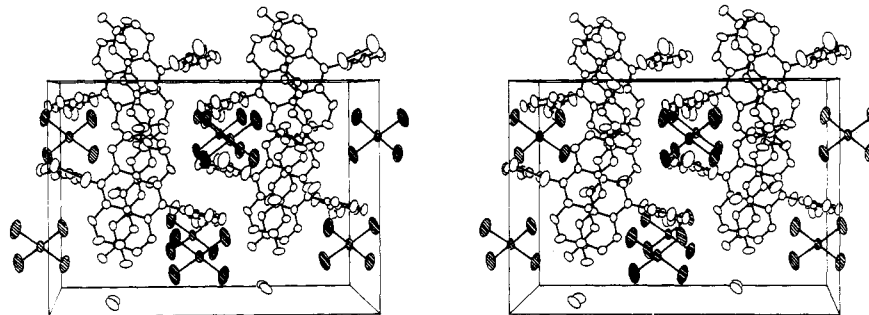


Figure 3. Packing within the unit cell. *b* and *c* are parallel to the bottom and sides of the page, and the view is down *a*. The PtCl₄²⁻ groups are indicated by shadowing of the atoms.

that the xanthine protons, which are parallel to the *bc* plane, overlap, thus giving strong $\pi\cdots\pi$ interactions (ring–ring distance ~ 3.4 Å). Any pair of cations is separated from the nearest *c* translationally equivalent pair by a pair of pairs of (four) water molecules. In the *c* direction, the chains of pairs of cations along the *a* direction are interleaved by pairs of cations related by the *c* glide. The methyl benzoate portions of the cations lie close to the $y = 0$ and $y = 1/2$ planes and are arranged such that a methyl benzoate group on a cation at $y = 1/4$ lies adjacent to an inversion-related methyl benzoate group on a molecule at $y = 3/4$, again giving a strong $\pi\cdots\pi$ interaction (ring–ring distance ~ 3.4 Å). The methyl benzoate groups thus form columns at $x = 0, y = 0$ and $x = 1/2, y = 1/2$. Along the *a* direction these columns are separated by the PtCl₄²⁻ cations at $x = 1/2, y = 0$ and $x = 0, y = 1/2$. The anions are tilted so that they are roughly 45° to both the xanthine and methyl benzoate portions of the cation.

In addition to the $\pi\cdots\pi$ interactions and the cation–anion charge interactions, there is an extensive hydrogen-bonding network stabilizing the crystal, although the bonds are of only medium strength.¹⁹ It is important to note, particularly in light of the anticancer activity of this compound, that there are no strong interactions between the cation and anion.

The [RH(123)]₂PtCl₄·4H₂O salt exhibits biological properties not shown by either ion alone. Farrell et al. have shown that the related compound [ethidium]₂PtCl₄ is less toxic to mice than ethidium bromide but has equal trypanocidal activity.²⁰ Similarly, [RH(123)]₂PtCl₄ is less toxic to mice than [RH(123)]Cl.⁴ Recently, one of our groups studied the in vitro uptake of [RH(123)]₂PtCl₄·4H₂O (labeled with γ -emitting ^{195m}Pt) in the human squamous cell carcinoma cell line, SCC-25. Molar uptake of

RH(123) (as measured by fluorescence) was twice that of Pt (as measured by γ counting), suggesting that the ion pairs were getting into the cells intact.²¹

Rhodamine dyes have been used for some time in colorimetric analyses to extract anionic metal species (e.g. ReO₄⁻, InBr₄⁻, and AuCl₄⁻) from aqueous to organic phases.^{22,23} In [RH(123)]₂PtCl₄·4H₂O the cationic dye molecule may “extract” the reactive PtCl₄²⁻ anion into the lipophilic membranes of cells. Once inside cells, PtCl₄²⁻ could react with a variety of nucleophiles causing extensive cross-linking between nucleic acids and/or proteins.

Conclusions

The reaction of K₂PtCl₄ with [RH(123)]Cl in water leads to the precipitation of the salt [RH(123)]₂PtCl₄·4H₂O. This formulation is confirmed by elemental analysis, by IR, electronic, and NMR spectroscopy, and by X-ray crystallography. Work is in progress to further characterize the anticancer properties of this and related compounds.

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Registry No. [RH(123)]₂PtCl₄·4H₂O, 104114-29-6; K₂PtCl₄, 10025-99-7.

Supplementary Material Available: Tables of anisotropic temperature factors, least-squares planes, and dihedral angles (2 pages); a table of calculated and observed structure factors (25 pages). Ordering information is given on any current masthead page.

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