

Crystal and Molecular Structure of *cis*-[Pt(NH₃)₂(Guo)₂]Cl_{3/2}(ClO₄)_{1/2}·7H₂O and Anticancer Activity of *cis*-[Pt(NH₃)₂(PuO)₂]Cl₂ Complexes

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The crystal and molecular structure of the reaction product of *cis*-dichlorodiammineplatinum(II) and guanosine, *cis*-[Pt(NH₃)₂(Guo)₂]²⁺ (Guo = guanosine), has been determined by a complete three-dimensional X-ray diffraction study. The colorless salt, *cis*-[Pt(NH₃)₂(Guo)₂]Cl_{3/2}(ClO₄)_{1/2}·7H₂O, crystallizes as regular octahedra in the tetragonal space group *P*4₁2₁2 with *a* = 17.850 (9) Å, *c* = 24.411 (7) Å, and *V* = 7778 (6) Å³ with 8 formulas/unit cell. The structure was refined by least-squares techniques to a final error index *R*₁ = 0.042 with a unique set of 1964 data. No hydrogen atoms were located. The platinum atom is bound to the N₇ position of each guanosine at distances of 1.99 (1) and 2.02 (1) Å. The platinum–ammine distances are 2.09 (1) and 2.07 (1) Å. The angles about the platinum atom are all close to 90°, and the platinum atom is in the coordination plane formed by the four nitrogens. The dihedral angle between the planar guanine rings is 74°. The guanine rings form dihedral angles of 74 and 70° with the platinum coordination plane. Because of the anti orientation of the two guanosine ligands, the platinum center is chiral. The complex cations stack along the fourfold screw axis in the configuration of a right-handed helix which is stabilized by base-stacking interactions between the guanine rings of adjacent complex cations and the intermolecular hydrogen bonds. The antitumor activity of *cis*-Pt(NH₃)₂Cl₂ is proposed to result from distortion induced in the DNA structure when platinum binds to adjacent bases in the same strand. A low but significant degree of antitumor activity is reported for complexes of the type *cis*-[Pt(NH₃)₂(PuO)₂]Cl₂ for Puo = guanosine, inosine, and xanthosine.

Introduction

Since discovery of the antitumor activity of *cis*-dichlorodiammineplatinum(II) (*cis*-DDP) by Rosenberg and VanCamp,² there has been considerable interest in the interactions of this class of square-planar platinum complexes with DNA and its purine and pyrimidine constituents. However, only a few crystallographic studies have been reported,³⁻⁵ including the ethylenediamine analogue of the complex reported here, [Pt(en)(Guo)₂]²⁺.⁴ Since *cis*-Pt(NH₃)₂Cl₂ has greater antitumor activity than Pt(en)Cl₂, we felt it would be interesting to compare the structures of the reaction products of these two compounds with guanosine.

Experimental Section

Materials. Guanosine was obtained from Sigma Chemical Co., and K₂PtCl₄ was obtained from Strem Chemical Co., Inc. Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz. *cis*-Dichloroammineplatinum(II) was synthesized by the method of Kauffman.⁶

Instrumentation. Proton and ¹³C NMR spectra were obtained with a Varian Associates XL-100-15 NMR spectrometer equipped with Digilab Fourier transform accessories. Ultraviolet spectra were obtained with a Beckman Acta CIII spectrophotometer, and CD spectra were obtained with a Cary Model 61 spectrophotometer.

Synthesis. The reaction product of *cis*-DDP with 2 mol of guanosine was obtained by the method reported by Kong and Theophanides.⁷ Elemental analysis was performed on the product recrystallized three times from water. Anal. Calcd for PtC₂₀N₁₂O₁₂H₃₂Cl₂·7H₂O: C, 23.44; H, 4.53; N, 16.40; Cl, 6.92. Found: C, 22.85; H, 3.58; N, 16.17; Cl, 6.53.

Physical Measurements. The chloride salt of the compound has a maximum in the UV spectrum at 259 nm with log ε_{max} = 4.36 at

pH 6.0 and concentration of 9.7 × 10⁻⁶ M. Uncomplexed guanosine has a maximum at 253 nm with log ε_{max} = 4.13 at pH 6.1 and concentration 6.25 × 10⁻⁵ M. The platinum complex has previously been reported to have a maximum at 256 nm with log ε_{max} = 3.37 for pH 5.7 and concentration 4.1 × 10⁻⁵ M.⁷

The ¹H NMR spectrum exhibits resonances at -5.96 (H₁) and -8.45 ppm (H₈) relative to internal DSS. The H₈ resonance exhibits broad ¹⁹⁵Pt-¹H coupling of 24 Hz. The remaining ribose resonances appear in three groups between -3.8 and -4.8 ppm. The proton-noise-decoupled ¹³C spectrum exhibits resonances at -101.2 (C₆), -98.9 (C₂), -94.9 (C₄), -84.4 (C₈), -58.8 (C₅), -33.3 (C₁), -30.1 (C₄), -18.6 (C₂), -14.6 (C₃), and -5.6 ppm (C₅) relative to an internal reference of (CH₃)₄NCl. Assignments were made from those reported by Kotowycz⁸ for aqueous guanosine 5'-monophosphate and are supported by the off resonance spectrum. Due to base stacking interactions between complexes in solution, the chemical shifts are concentration dependent. Those reported here are for ~0.1 M solution.

Optical rotation measurements gave a value for the molecular rotation [Φ]_D = -226.0 (9)° mol⁻¹ for a 2 g/100 mL solution of the platinum complex at pH 6.9. Guanosine at 2 g/100 mL in 0.1 M NaOH had [Φ]_D = -196 (4)° mol⁻¹ (lit. value [Φ]_D = -171° mol⁻¹; calculated from [α]_D = -60.5° g⁻¹).⁹ The polarimeter calibration was checked with D(+)-tartaric acid. The CD spectrum showed only the effect expected from free, monomeric guanosine.

X-ray Data Collection. Attempts to obtain crystals of *cis*-[Pt(NH₃)₂(Guo)₂]Cl₂ by slow evaporation of aqueous solutions yielded glassy, gummy substances but no crystals. However, clear, regular octahedral crystals of *cis*-[Pt(NH₃)₂(Guo)₂]Cl_{3/2}(ClO₄)_{1/2}·7H₂O were obtained from aqueous solutions to which perchlorate anions had been added. A single crystal measuring 0.16 mm per side was mounted so that the crystal axis did not coincide with the diffractometer φ axis. A Syntex P1 four-circle computer-controlled diffractometer with graphite monochromatized Mo Kα radiation (Kα₁, λ = 0.709 30 Å; Kα₂, λ = 0.713 59 Å) and a scintillation detector with a pulse height analyzer was used for preliminary experiments and the measurements of diffraction intensities. Except as otherwise noted, the procedure used has previously been reported.^{10,11} The cell constants and their standard deviations were determined by a least-squares treatment of the angular coordinates of 15 independent reflections with 2θ values

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up to 14°. A $2\theta:\theta$ scan mode was used with minimum and maximum scan rates of 1° min^{-1} to $24^\circ \text{ min}^{-1}$ in 2θ . The intensities of three check reflections were remeasured every 100 reflections during data collection. These showed only random variations within the end of the reflections. Reflections were measured for all $hkl > 0$ and $3^\circ < 2\theta < 45^\circ$. The observed intensities were corrected for Lorentz and polarization effects.¹² An absorption correction was applied¹³ which approximated the shape of the crystal by a $6 \times 6 \times 6$ grid.¹⁴ The linear absorption coefficient, μ , was calculated from the total cross sections of the elements¹⁵ to be 40.29 cm^{-1} . Transmission coefficients ranged from 0.620 to 0.646. Of the 5680 reflections measured, 3515 had intensities greater than three times their standard deviation, and only these were used in subsequent calculations. A tetragonal space group was confirmed by the equality of the hkl and khk structure factors, and these were merged by taking a simple average to form a unique set of 1964 data. The standard deviation for each of the averaged structure factors was calculated according to $\sigma(F_o) = [(\sigma_{hkl})^2/2 + (\sigma_{khk})^2/2]^{1/2}$. The averaged structure factors agreed within three times their least-squares standard deviations in 93% of the cases, and the maximum deviation was 9.7 times the least-squares standard deviation.

Crystal Data. *cis*-[Pt(NH₃)₂(Guo)₂]Cl_{3/2}(ClO₄)_{1/2}·7H₂O crystallizes in the tetragonal system with systematic absences indicating the space group $P4_12_12$ with $a = 17.850(9) \text{ \AA}$, $c = 24.411(7) \text{ \AA}$, $V = 7778(6) \text{ \AA}^3$, $d_{\text{calc}} = 1.75 \text{ g cm}^{-3}$ for a molecular weight of 1024.7 and 8 formulas/unit cell, $d_{\text{obsd}}(\text{floatation}) = 1.80 \text{ g cm}^{-3}$. The numbers in parentheses are estimated standard deviations in the least-significant digit given for the corresponding parameter.

Structure Determination

The position of the platinum atom was determined with the help of a three-dimensional Patterson function. The positions of all other nonhydrogen atoms were found by successive cycles of Fourier refinement using the fast-Fourier algorithm.¹⁶ Block diagonal least-squares refinement¹⁷ was performed with anisotropic thermal parameters for all atoms. No hydrogen atoms were located. The atomic scattering factors for Pt²⁺, Cl⁻, Cl⁰ (ClO₄), O⁰, N⁰, and C⁰ were used.¹⁸ Corrections were made to Pt²⁺, Cl⁻, and Cl⁰ for anomalous dispersion effects.¹⁹ The final error indices were $R_1 = 0.042$ and $R_2 = 0.041$, and the "goodness of fit" is 0.79. The definitions for R_1 , R_2 , the goodness of fit, and the assigned weights can be found in ref 20. The number of observations used in the least-squares calculations is 1964 (m) and the total number of parameters is 518 (s), yielding an overdetermination ratio ($m:s$) of 3.8.

In the final cycles of least-squares refinement, all shifts in atomic positional and thermal parameters were less than their esd, except for two of the perchlorate chlorine parameters where some disorder is manifested in the form of large deviations. In this case the largest shift in position was 318% of the esd for x and the largest shift in a thermal parameter was 220% of the esd for β_{13} . The largest peak on the final difference Fourier map with an estimated esd of 0.05 e \AA^{-3} was 0.8 e \AA^{-3} located close to the platinum atom.

The final positional and thermal parameters, together with their standard deviations are presented in Table I. An ORTEP²¹ drawing

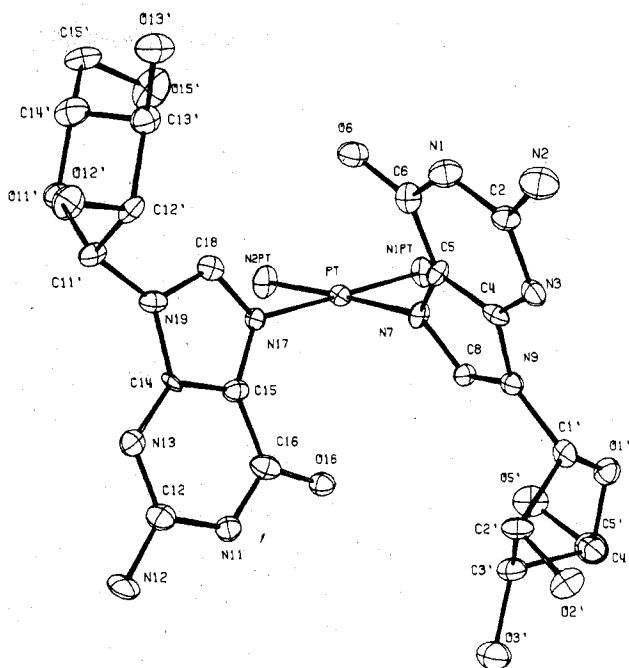


Figure 1. Molecular structure and labeling of *cis*-[Pt(NH₃)₂(Guo)₂]²⁺. Atoms are represented by 20% probability ellipsoids.

of the structure of the complex cation is shown in Figure 1. The bond lengths and bond angles for the complex cation are shown in Tables II and III, respectively. In the text subscripted atom numbers, i.e., N₇, refer to a general guanosine position in accord with the usual nomenclature. Nonsubscripted numbers refer to particular atoms in the crystal structure, i.e., both N7 and N17 are at the N₇ position of guanosine.

Discussion

Complex Cation. The complex cation consists of a Pt(II) ion bound in a planar fashion (Table IV) to the nitrogen atoms of four ligands, two ammines and two guanosines. The *cis* geometry of the Pt(NH₃)₂Cl₂ starting material is retained in the product. The platinum ion is bound to the N₇ position of guanosine, as was found previously in similar complexes of guanosine^{4,5} and inosine 5'-monophosphate.³ While the angles about the platinum are all close to 90°, it is interesting to note that the angle between the two bulky guanosine groups is the smallest. This is probably a crystal-packing effect due to the intermolecular base-stacking interaction between complex cations along the fourfold screw axis, *vide infra*.

The guanine bases are planar to less than 1.8σ for the N7 plane and 1.6σ for the N17 plane with only random deviations from the mean planes, Table IV. The interior angles about N1, 126 (2)°, N11, 123 (2)°, N3, 114 (2)°, and N13, 117 (2)°, indicate²² that guanine is protonated at the expected N₁ position in both cases. Platinum coordination to the N₇ position of guanosine does not produce significant distortions in the ring geometry.

The dihedral angles describing the ribose conformation²³ are given in Table V. The glycosidic bond C₁-N₉ has the anti conformation with $\chi_{\text{CN}} = 139.3$ and $\chi_{\text{CN}} = 144.4^\circ$. The C₅-O₅ bond has the gauche, gauche conformation with $\phi_{\text{OO}} = -63.4^\circ$, $\phi_{\text{OC}} = 51.6^\circ$, $\phi_{\text{OO}'} = -63.0^\circ$, and $\phi_{\text{OC}'} = 55.1^\circ$. There is a weak hydrogen-bonding interaction between O₅ and C₈ with O5'-C8 = 3.38 Å and O15'-C18 = 3.27 Å which may help stabilize this conformation. The ribose ring has the

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Table I. Fractional Atomic Coordinates ($\times 10^4$) and Thermal Parameters ($\times 10^4$) for *cis*-[Pt(NH₃)₂(Guo)₂]Cl_{3/2}(ClO₄)_{1/2}·7H₂O^a

atom	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}	occ ^b
Pt	4.7 (5)	4712.8 (3)	52.3 (2)	22.5 (3)	24.7 (3)	11.34 (8)	1.9 (2)	-0.8 (1)	-0.9 (2)	
N1Pt	-1140 (7)	4753 (8)	-122 (6)	16 (4)	31 (6)	26 (3)	15 (4)	-12 (3)	-4 (4)	
N2Pt	-44 (10)	5818 (7)	307 (7)	38 (6)	16 (5)	34 (4)	10 (5)	-7 (5)	-7 (3)	
O6	929 (8)	4251 (9)	-1161 (4)	44 (7)	36 (8)	14 (2)	5 (4)	3 (3)	0 (3)	
O1'	-938 (7)	1669 (7)	381 (5)	27 (5)	33 (5)	21 (3)	-4 (4)	-1 (3)	6 (3)	
O2'	445 (8)	762 (7)	756 (6)	42 (6)	31 (5)	24 (3)	3 (4)	9 (3)	11 (3)	
O3'	33 (10)	1501 (8)	1678 (5)	60 (7)	47 (6)	17 (3)	-1 (6)	-5 (4)	7 (3)	
O5'	-1542 (10)	2789 (11)	1105 (7)	50 (8)	53 (9)	26 (4)	21 (6)	7 (4)	2 (4)	
N1	1066 (10)	3004 (11)	-1384 (7)	35 (7)	37 (8)	17 (3)	10 (6)	11 (4)	3 (4)	
N2	1307 (10)	1809 (11)	-1668 (7)	42 (8)	48 (8)	18 (4)	16 (6)	9 (4)	-1 (4)	
N3	646 (8)	1991 (9)	-876 (6)	21 (5)	35 (6)	12 (3)	-5 (5)	-5 (3)	-5 (3)	
N7	42 (10)	3635 (7)	-158 (6)	37 (6)	10 (4)	18 (3)	-5 (5)	-1 (4)	-5 (3)	
N9	-58 (8)	2403 (7)	-60 (5)	18 (4)	28 (5)	11 (2)	-2 (4)	-0 (4)	1 (3)	
C2	995 (11)	2264 (11)	-1302 (7)	27 (8)	26 (9)	12 (3)	10 (6)	1 (4)	1 (4)	
C4	352 (9)	2523 (10)	-541 (6)	11 (5)	42 (8)	7 (3)	7 (5)	-0 (3)	-1 (4)	
C5	392 (9)	3285 (9)	-592 (7)	20 (6)	15 (6)	15 (3)	0 (5)	9 (4)	-2 (4)	
C6	788 (10)	3566 (12)	-1050 (9)	21 (7)	28 (7)	21 (4)	10 (6)	-4 (4)	-3 (5)	
C8	-236 (9)	3093 (9)	127 (6)	26 (6)	16 (5)	11 (3)	5 (4)	3 (4)	-3 (3)	
C1'	-187 (8)	1676 (10)	201 (7)	8 (7)	37 (7)	16 (3)	-1 (4)	1 (3)	-2 (4)	
C2'	321 (11)	1534 (10)	677 (6)	32 (6)	35 (8)	10 (3)	12 (6)	-8 (4)	-8 (4)	
C3'	-201 (12)	1798 (11)	1150 (7)	37 (9)	37 (8)	13 (3)	-1 (6)	5 (4)	10 (4)	
C4'	-990 (12)	1554 (14)	958 (8)	25 (8)	49 (10)	14 (4)	-7 (7)	4 (4)	2 (5)	
C5'	-1643 (13)	1980 (17)	1180 (12)	22 (9)	71 (14)	26 (6)	2 (8)	3 (5)	10 (7)	
O16	530 (8)	3723 (7)	1194 (5)	29 (6)	33 (5)	13 (2)	2 (4)	3 (3)	2 (3)	
O11'	3012 (7)	5662 (7)	-388 (5)	33 (5)	28 (5)	15 (2)	1 (4)	4 (3)	0 (5)	
O12'	3970 (8)	4308 (7)	-731 (6)	40 (6)	28 (5)	23 (3)	-1 (4)	3 (3)	-2 (3)	
O13'	3194 (8)	4682 (8)	-1663 (5)	57 (6)	39 (6)	16 (3)	7 (5)	7 (3)	5 (3)	
O15'	1842 (11)	6163 (11)	-1068 (9)	43 (8)	52 (8)	48 (6)	15 (7)	16 (6)	17 (5)	
N11	1746 (10)	3588 (10)	1409 (5)	27 (7)	29 (7)	14 (3)	-1 (5)	3 (4)	-1 (3)	
N12	3015 (9)	3394 (11)	1664 (6)	35 (6)	59 (8)	7 (3)	-3 (6)	-1 (3)	3 (4)	
N13	2762 (9)	4065 (8)	880 (6)	32 (6)	23 (5)	13 (3)	-3 (5)	2 (4)	-8 (3)	
N17	1114 (6)	4657 (8)	206 (5)	10 (4)	31 (5)	12 (2)	-2 (4)	3 (3)	3 (3)	
N19	2335 (8)	4775 (8)	101 (5)	33 (5)	28 (6)	10 (3)	5 (4)	4 (3)	1 (3)	
C12	2538 (13)	3680 (13)	1298 (9)	33 (9)	35 (10)	12 (4)	4 (8)	4 (5)	-4 (5)	
C14	2229 (8)	4353 (9)	556 (5)	6 (5)	36 (7)	5 (2)	2 (4)	-4 (3)	1 (3)	
C15	1486 (10)	4270 (10)	617 (7)	31 (7)	22 (6)	13 (3)	5 (5)	1 (4)	2 (4)	
C16	1198 (14)	3879 (12)	1079 (8)	42 (11)	38 (9)	12 (3)	13 (8)	-2 (5)	-3 (4)	
C18	1629 (10)	4911 (10)	-101 (7)	33 (7)	18 (6)	13 (3)	14 (6)	1 (4)	-8 (4)	
C11'	3039 (9)	4940 (10)	-189 (6)	41 (7)	12 (6)	13 (3)	-3 (6)	7 (3)	-2 (4)	
C12'	3190 (10)	4422 (10)	-661 (7)	20 (7)	22 (6)	18 (4)	-3 (5)	9 (4)	10 (4)	
C13'	2893 (11)	4900 (12)	-1146 (7)	36 (8)	31 (9)	17 (4)	-1 (7)	4 (4)	0 (4)	
C14'	3077 (12)	5681 (14)	-978 (9)	27 (8)	48 (11)	21 (4)	18 (7)	13 (5)	14 (6)	
C15'	2592 (15)	6329 (14)	-1203 (9)	54 (12)	40 (11)	16 (4)	8 (9)	13 (6)	21 (6)	
Cl1	2360 (8)	2360 (8)	0	26 (5)	26 (5)	23 (2)	2 (2)	1 (2)	-1 (2)	0.88 (4) ^c
OC11	2970 (15)	2242 (26)	281 (17)	48 (13)	211 (33)	84 (14)	-22 (13)	-13 (9)	35 (16)	1.0 (1)
OC12	1755 (22)	2266 (28)	266 (20)	153 (26)	348 (47)	143 (24)	90 (27)	91 (19)	159 (28)	1.4 (1)
Cl2	1650 (4)	2732 (3)	2546 (3)	56 (3)	37 (3)	18 (1)	4 (2)	0 (2)	3 (1)	0.92 (2)
Cl3	3460 (12)	1869 (10)	2420 (5)	143 (12)	95 (9)	31 (3)	34 (7)	6 (5)	-9 (4)	0.69 (4)
OW1	506 (11)	375 (12)	4438 (7)	62 (9)	71 (9)	28 (4)	-0 (7)	16 (5)	-1 (5)	1.00 ^d
OW2	4929 (9)	4640 (8)	4450 (7)	47 (6)	49 (6)	31 (3)	-7 (7)	-4 (4)	8 (4)	1.00 ^d
OW3	563 (33)	1924 (26)	4174 (20)	162 (40)	87 (26)	62 (17)	11 (21)	35 (18)	-4 (14)	0.7 (1)
OW4	320 (17)	1888 (14)	3105 (15)	106 (15)	68 (11)	87 (11)	-3 (10)	16 (11)	-5 (9)	1.00 ^d
OW5	4692 (26)	2372 (22)	2585 (15)	93 (27)	70 (20)	29 (10)	-33 (16)	12 (12)	8 (10)	0.52 (8)
OW6	425 (55)	4113 (26)	3872 (14)	571 (99)	142 (25)	39 (7)	-159 (45)	-3 (24)	-8 (11)	1.00 ^d
OW7	3945 (27)	1832 (22)	4494 (22)	201 (32)	110 (21)	142 (20)	24 (21)	-136 (24)	-10 (17)	1.00 ^d
OW8	1526 (44)	3046 (51)	4673 (22)	381 (67)	449 (84)	86 (17)	-272 (60)	121 (28)	-131 (33)	1.00 ^d

^a See Figure 1 for the identities of the atoms. Estimated standard deviations in the least-significant digit given are in parentheses. The thermal ellipsoid is of the form $\exp[-(h^2\beta_{11} + k^2\beta_{22} + l^2\beta_{33} + 2hk\beta_{12} + 2hl\beta_{13} + 2kl\beta_{23})]$. ^b Refined occupancy parameters. ^c The perchlorate chlorine atom occupies Wyckoff position 4a, of which there are four per unit cell. There are $(4)(0.88) = 3.52$ (16) ClO₄⁻ ions per cell. ^d The occupancy of these positions refined to within 3σ of 100. In the final structure factor calculation these parameters were set equal to 1.0.

envelope conformation C₃-endo with C2' 0.046 Å below the C4'-O1'-C1' plane and C3' 0.553 Å above the plane. The corresponding distances in the other ribose ring are 0.110 and 0.456 Å, respectively.

While the platinum(II) ion lies in the coordination plane, the purine rings do not lie in this plane but are twisted from it in opposite directions to relieve steric crowding. The dihedral angle between the coordination plane and the plane of the N7 ring is 74°, and that formed with N17 plane is 70°. Thus the complex has an anti conformation, in which the two guanosines are oriented toward opposite sides of the platinum coordination plane, and is chiral. The absolute configuration can be de-

termined because the absolute configuration of the β-D-ribose moiety is known.²⁴ The absolute configuration is illustrated in Figure 1 and in Figure 2 which is a view perpendicular to the pseudo-twofold axis of the molecule.

Significant bond distances for the ammine complex are compared to the values reported for the corresponding ethylenediamine complex⁴ in Table VI. Although one-quarter of the counterions are different in the two compounds, the lack of significant interactions between the complex cation and the

Table II. Bond Lengths (Å)

N1Pt-Pt	2.09 (1)	Cl1-OC11	1.31 (3)
N2Pt-Pt	2.07 (1)	Cl1-OC12	1.27 (4)
N7-Pt	1.99 (1)	N17-Pt	2.02 (1)
N1-C2	1.34 (3)	N11-C12	1.45 (3)
C2-N2	1.33 (3)	C12-N12	1.34 (3)
C2-N3	1.31 (2)	C12-N13	1.29 (3)
N3-C4	1.36 (2)	N13-C14	1.34 (2)
C4-C5	1.37 (2)	C14-C15	1.34 (2)
C5-C6	1.42 (3)	C15-C16	1.42 (3)
C6-O6	1.28 (3)	C16-O16	1.26 (3)
C6-N1	1.38 (3)	C16-N11	1.37 (3)
C5-N7	1.38 (2)	C15-N17	1.39 (2)
N7-C8	1.29 (2)	N17-C18	1.27 (2)
C8-N9	1.35 (2)	C18-N19	1.38 (2)
N9-C4	1.40 (2)	N19-C14	1.36 (2)
N9-Cl'	1.46 (2)	N19-Cl1'	1.47 (2)
Cl'-C2'	1.50 (2)	C11'-C12'	1.50 (2)
C2'-O2'	1.41 (2)	C12'-O12'	1.42 (2)
C2'-C3'	1.56 (2)	C12'-C13'	1.55 (3)
C3'-O3'	1.46 (2)	C13'-O13'	1.42 (2)
C3'-C4'	1.55 (3)	C13'-C14'	1.49 (3)
C4'-C5'	1.49 (3)	C14'-C15'	1.55 (3)
C5'-O5'	1.47 (4)	C15'-O15'	1.41 (3)
C4'-O1'	1.43 (2)	C14'-O11'	1.44 (2)
O1'-Cl'	1.41 (2)	O11'-C11'	1.38 (2)

Table III. Bond Angles (Degrees)

N1-Pt-N2	89.3 (6)	Pt-N7-C8	124.9 (12)
N1-Pt-N7	90.8 (6)	Pt-N7-C5	130.6 (13)
N7-Pt-N17	88.2 (5)	Pt-N17-C15	129.0 (12)
N2-Pt-N17	91.8 (6)	Pt-N17-C18	125.7 (11)
N1-C2-N3	122.2 (18)	N11-C12-N13	120.7 (19)
N1-C2-N2	117.5 (18)	N11-C12-N12	117.0 (18)
N2-C2-N3	120.4 (18)	N12-C12-N13	122.2 (20)
C2-N3-C4	113.7 (15)	C12-N13-C14	116.7 (17)
N3-C4-C5	128.4 (14)	N13-C14-C15	126.4 (14)
C4-C5-C6	116.7 (15)	C14-C15-C16	119.9 (16)
C5-C6-N1	112.8 (17)	C15-C16-N11	113.2 (17)
C5-C6-O6	127.2 (18)	C15-C16-O16	129.1 (18)
O6-C6-N1	120.0 (18)	O16-C16-N11	117.4 (19)
C6-N1-C2	126.3 (18)	C16-N11-C12	122.9 (16)
C4-C5-N7	110.0 (15)	C15-C15-N17	109.8 (14)
C6-C5-N7	132.3 (16)	C16-C15-N17	130.1 (16)
C5-N7-C8	104.3 (12)	C15-N17-C18	104.9 (14)
N7-C8-N9	114.2 (14)	N17-C18-N19	113.0 (15)
C8-N9-C4	105.5 (13)	C18-N19-C14	105.3 (14)
N9-C4-C5	104.8 (14)	C15-C14-N19	106.9 (14)
N9-C4-N3	126.9 (16)	N19-C14-N13	126.7 (15)
C4-N9-Cl'	125.6 (13)	C14-N19-C11'	128.6 (14)
C8-N9-Cl'	128.6 (13)	C18-N19-C11'	125.1 (13)
N9-Cl'-O1'	107.1 (13)	N19-C11'-O11'	109.1 (12)
N9-Cl'-C2'	113.1 (13)	N19-C11'-C12'	113.5 (14)
Cl'-C2'-O2'	111.6 (14)	C11'-C12'-O12'	110.9 (14)
Cl'-C2'-C3'	99.3 (13)	C11'-C12'-C13'	100.7 (14)
O2'-C2'-C3'	106.7 (15)	O12'-C12'-C13'	108.8 (14)
C2'-C3'-C4'	103.6 (14)	C12'-C13'-C14'	103.2 (16)
C2'-C3'-O3'	112.0 (16)	C12'-C13'-O13'	113.3 (16)
O3'-C3'-C4'	115.3 (15)	O13'-C13'-C14'	114.6 (17)
C3'-C4'-C5'	117.2 (19)	C13'-C14'-C15'	118.5 (18)
C3'-C4'-O1'	101.5 (16)	C13'-C14'-O11'	103.6 (17)
C5'-C4'-O1'	109.7 (18)	C15'-C14'-O11'	109.1 (17)
C4'-C4'-O5'	111.0 (21)	C14'-C15'-O15'	106.9 (20)
C4'-O1'-Cl'	111.8 (15)	C14'-O11'-C11'	111.8 (14)
O1'-Cl'-C2'	109.4 (14)	O11'-C11'-C12'	108.1 (14)
ClO2-Cl1-ClO1	115 (3)	ClO2-Cl1-ClO2'	92 (3)
ClO2-Cl1-ClO1'	104 (3)	ClO1-Cl1-ClO1'	123 (2)

perchlorate and iodide anions in the ammine and ethylenediamine structures, respectively, justifies this comparison. The platinum-amine bond is seen to be longer in the ammine complex than in the ethylenediamine complex. This means that ethylenediamine is more strongly bound than ammonia, as expected due to the increased basicity of alkyl-substituted amines toward the soft platinum(II) ion. The strength of the platinum-amine bond affects the strength of the platinum-guanosine bond which is also longer in the ammine complex

Table IV. Deviations (Å) of Atoms from Least-Squares Planes

	plane 1	plane 2	plane 3
N7	0.025	N17	0.012
C8	-0.026	C18	-0.030
N9	0.003	N19	0.024
C4	0.002	C14	0.004
C5	-0.004	C15	-0.024
C6	0.001	C16	0.017
N1	-0.009	N11	0.014
C2	-0.007	C12	-0.014
N3	0.014	N13	-0.003
N2	-0.006 ^a	N12	0.040 ^a
O6	0.071 ^a	O16	-0.049 ^a
Cl1'	0.146 ^a	Cl11'	-0.131 ^a
Pt	0.238 ^a	Pt	-0.090 ^a
δ	0.015	0.019	0.035
A	0.8483	-0.0108	-0.1888
B	-0.0012	0.8363	-0.2871
C	0.5295	0.5481	0.9392
D	-0.1736	7.1949	-2.2836

^a Atoms not defining plane.

Table V. Dihedral Angles (Deg) Characterizing the Ribose Ring Conformation

	Guo	N7	N17	Guo	N7	N17
ϕ_{OO}	-63.37	-63.03	τ_1	-23.89	-24.11	
ϕ_{OC}	51.64	55.13	τ_2	35.81	34.30	
χ_{CN}	139.28	144.42	τ_3	-35.56	-32.42	
ψ	82.29	82.91	τ_4	21.42	18.35	
τ_0	-1.87	-4.43				

Table VI. Comparison of Distances (Å) in *cis*-[Pt(NH₃)₂(Guo)₂]²⁺ and [Pt(en)(Guo)₂]²⁺

interaction	<i>cis</i> -[Pt(NH ₃) ₂ (Guo) ₂] ²⁺	[Pt(en)(Guo) ₂] ²⁺
Pt-N1Pt	2.089 (13)	2.036 (17)
Pt-N2Pt	2.070 (13)	
Pt-N7	1.992 (12)	1.967 (15)
Pt-N17	2.018 (12)	
O6-N2Pt ^a	2.897	
O16-N1Pt ^a	2.943	2.84
Guo-Guo ^b	3.34 (4)	3.31
	3.37 (4)	

^a Intercationic hydrogen-bond distance. ^b Interplanar distance of guanines from adjacent cations.

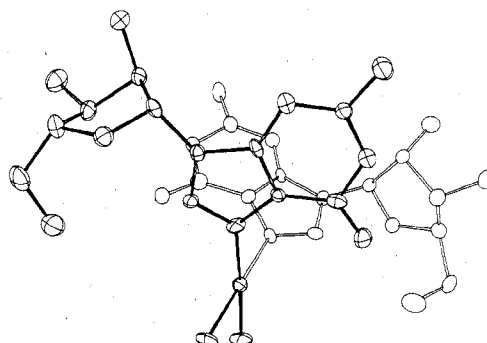


Figure 2. View of the complex cation perpendicular to the pseudotwofold axis of the molecule.

than in the ethylenediamine complex. This could be due to a difference in the trans influence of ammonia and ethylenediamine or to some back-donation of electron density into the π^* orbitals of the guanine ring.

The lengths of the intermolecular hydrogen bonds (vide infra) between the carbonyl oxygens and amines on the adjacent complex cations are also seen to be greater for the

amine than for the ethylenediamine complex. The explanation for this must consider two opposing factors. Compared to ammonia, the electron-releasing alkyl substituent of ethylenediamine will produce additional negative charge on the nitrogen, decreasing the acidity of the hydrogens and therefore the hydrogen-bonding ability. However, the stronger platinum–ethylenediamine bond will decrease the electron density on the nitrogen, making the hydrogens more acidic and therefore increasing the hydrogen-bonding ability. Apparently the strength of the platinum–ethylenediamine bond makes the greater contribution, and the ethylenediamine complex has significantly stronger hydrogen bonds than the ammine complex. The greater hydrogen-bonding ability expected for ammonia has been postulated as a possible explanation for the greater antitumor activity of *cis*-dichlorodiammineplatinum(II) relative to that of dichloroethylenediamineplatinum(II).^{25,26} In fact, the opposite trend is true.

Chu and Tobias²⁷ have suggested that base stacking between the purines stabilizes the complex *cis*-[Pt(NH₃)₂(Ino)₂]²⁺. The most effective base-stacking interaction occurs when the planes of the bases are parallel to each other and falls to zero when the bases are perpendicular to each other. In the former case the dihedral angle between the planes of the bases is 0° while it is 90° in the latter. In this structure the dihedral angle between the two purine planes is 74° while that in the analogous ethylenediamine complex is 71°.⁴ Apparently a more favorable base-stacking interaction occurs in *cis*-[Pt(NH₃)₂(IMP)₂]²⁺ where the dihedral angle between planes is 43°.³ However the large dihedral angles observed in all three of these structures, coupled with the fact that the structures are anti which minimizes overlap between the rings, indicate that base stacking does not contribute significantly to the stabilization of these complexes. Still, the close proximity of the purine bases with their associated ring currents would produce significant differences in the NMR chemical shifts of *cis*-[Pt(NH₃)₂(PuO)(H₂O)]²⁺ and *cis*-[Pt(NH₃)₂(PuO)₂]²⁺ as observed by Tobias.²⁷

While intramolecular base stacking does not appear to be important in these compounds, all of these structures exhibit extensive intermolecular base stacking. This intermolecular base stacking may well have an effect on the observed geometry of the complex cation and may be the reason that the angle between the bulky guanosine groups, N7–Pt–N17, is the smallest of the angles in the platinum coordination sphere. Intermolecular base stacking also occurs in solution as evidenced by the concentration dependence of the ¹H NMR of these molecules.

As a result of this intermolecular base stacking and of the intermolecular hydrogen bonding, the complex cations are stacked with the platinum atoms lying just off the 4₁ screw axis. The Pt–Pt distance is 6.15 Å, eliminating the possibility of metal–metal interaction as is expected for a colorless compound. The configuration is that of a right-handed helix, with the helix axis coincident with the screw axis, Figure 3. The distances which characterize the intermolecular base stacking in this helix are listed in Table VI.

Anions and Waters. The unusual solvate and counterion stoichiometry exhibited in this compound is similar to that found in other platinum(II)–nucleoside complexes.^{3–5} For substantiation of the stoichiometry, the occupancy parameters of all atoms except those of the complex cation were refined and are presented in Table I. Those for which the occupancy parameter was within 3σ of full occupancy were assigned an occupancy of 1.00. The stoichiometry reported is the sum of the occupancy parameters rounded off to the nearest 0.5.

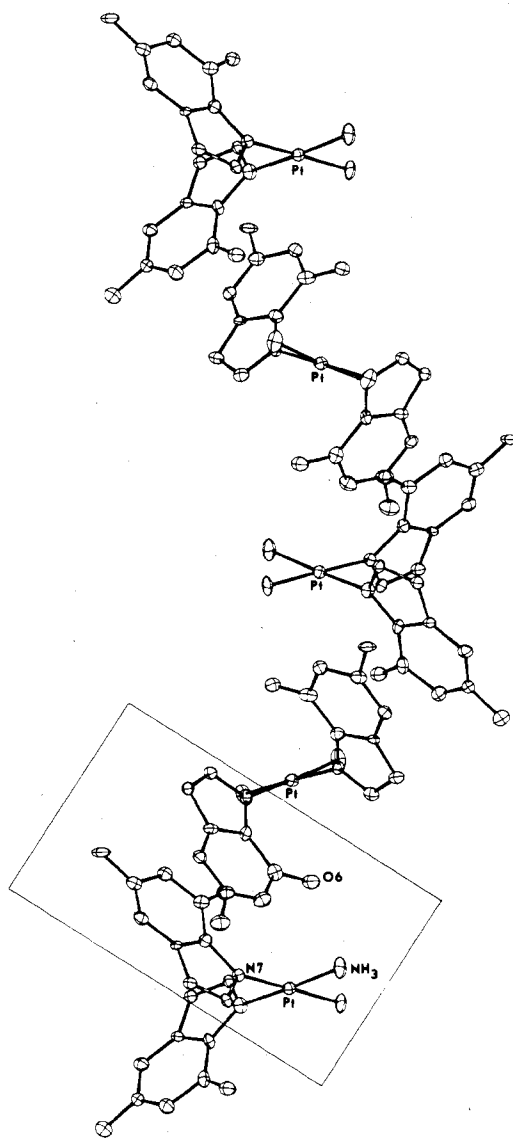


Figure 3. View of the stacking arrangement of the complex cation along the fourfold screw axis.

On the basis of electron density alone, a chloride atom with half-occupancy cannot be differentiated from an oxygen atom with full occupancy. Therefore it was necessary to assign the Cl3 position on the basis of hydrogen-bonding distances. The assigned position places Cl3 too close (2.41 Å) to OW5; however, both of these atoms have only half-occupancy so that the two positions are not simultaneously occupied.

The perchlorate anion is situated at Wyckoff position 4a with twofold point symmetry, requiring location of only half of the anion. The perchlorate exhibits some disorder which is manifested as abnormal occupancy and thermal parameters. Perchlorate anions often exhibit some degree of disorder, and because the perchlorate has no direct significance in this structure, no further attempt was made to resolve this disorder.

As would be expected from the large number of hydrogen-bond donors and acceptors in the cation, the anions and the solvates, there is extensive hydrogen bonding in this crystal. Most of the strongest hydrogen bonds involving the cation are shown in Figure 4, and all of the hydrogen-bond distances are listed in Table VII. Nearly all potential hydrogen-bond donors and acceptors take part in such an interaction. In general the hydrogen bond interactions of the two nonequivalent guanosine moieties involve similar donors or acceptors and similar distances, although differences do occur. Six of the eight water

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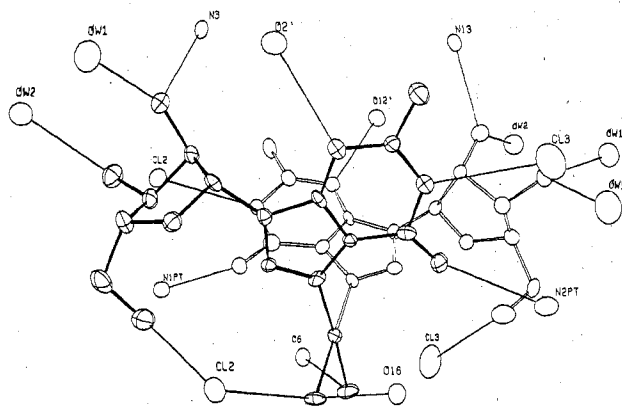


Figure 4. A view of the cation showing the strong hydrogen bonds.

Table VII. Possible Hydrogen-Bonding Interactions A-H...B

A	asymmetric unit	B	asymmetric unit	A-B dist, Å
N1Pt	1/2 - y, 1/2 + x, 1/4 + z	Cl2	x, y, z	3.24
N1Pt	1/2 - y, 1/2 + x, 1/4 + z	O16	x, y, z	2.94
N1Pt	1 - y, -x, 1/2 - z	OW7	x, y, z	3.05
N2Pt	x, y, z	O6	1/2 - y, 1/2 + x, 1/4 + z	2.90
N2Pt	x, y, z	OW5	1/2 - x, 1/2 + y, 1/4 - z	3.00
N2Pt	-y, -x, 1/2 - z	OW7	x, y, z	3.26
N1	x, y, z	Cl3	y, x, -z	3.02
N11	x, y, z	Cl2	x, y, z	3.17
N2	x, y, z	O3'	y, x, -z	3.19
N2	x, y, z	Cl2	y, x, -z	3.33
N12	x, y, z	O13'	y, x, -z	3.00
N12	x, y, z	Cl3	x, y, z	3.38
O2'	y, x, -z	N3	x, y, z	2.78
O12'	y, x, -z	N13	x, y, z	2.79
O3'	1/2 - y, 1/2 + x, 1/4 + z	OW2	x, y, z	2.73
O13'	x, y, z	OW1	1/2 - x, 1/2 + y, 1/4 - z	2.72
O5'	x, y, z	Cl2	-1/2 + y, 1/2 - x, -1/4 + z	3.06
O15'	x, y, z	Cl3	1/2 - x, 1/2 + y, 1/4 - z	3.12
OW1	x, y, z	OW1	y, x, 1 - z	2.76
OW1	x, y, z	O2'	-y, -x, 1/2 - z	2.74
OW2	1 - x, 1 - y, -1/2 + z	O12'	x, y, z	2.75
OW2	x, y, z	OW2	y, x, 1 - z	2.78
OW3	x, y, z	OW1	x, y, z	2.84
OW3	x, y, z	OW4	x, y, z	2.65
OW4	x, y, z	Cl2	x, y, z	3.13
OW4	1/2 + x, 1/2 - y, 3/4 - z	OW2	x, y, z	2.82
OW5	x, y, z	OW3	1/2 + x, 1/2 - y, 3/4 - z	2.70
OW5	y, x, -z	O13'	x, y, z	2.69
OW6	x, y, z	O16	1/2 - y, 1/2 + x, 1/4 + z	2.98
OW7	1/2 - x, 1/2 + y, 1/4 - z	O15'	x, y, z	2.92
OW7	y, x, 1 - z	OW8	x, y, z	2.65
OW8	x, y, z	O5'	1/2 - y, 1/2 + x, 1/4 + z	2.97
OW8	x, y, z	OW3	x, y, z	2.91

molecules are hydrogen bonded to the cation while the other two participate in hydrogen bonds between waters and to a chloride ion.

Antitumor Activity. The complex *cis*-[Pt(NH₃)₂(Guo)₂]Cl₂ and its inosine and xanthosine analogues exhibit a low but

Table VIII. Antitumor Screening Results^a

compd	dosage, mg/kg	injections/day	T:C, %
<i>cis</i> -[Pt(NH ₃) ₂ (Guo) ₂] ²⁺	800	1/4	129
<i>cis</i> -[Pt(NH ₃) ₂ (Ino) ₂] ²⁺	400	1/4	130
<i>cis</i> -[Pt(NH ₃) ₂ (Xao) ₂] ²⁺	800	1/4	134

^a Results from the National Cancer Institute using their standard P388 protocol.

significant degree of antitumor activity, Table VIII.²⁸ In addition they possess high solubility and low toxicity relative to the neutral complexes such as *cis*-DDP. Although screening of these compounds is in a preliminary stage, the activity appears to increase over the series guanosine ≤ inosine < xanthosine. The toxicity appears to increase over the series inosine ≤ guanosine < xanthosine so that the xanthosine derivative is significantly more toxic than the other two compounds. Toxicity is somewhat alleviated with a regimen of one injection every 4 days, allowing larger doses to be administered with greater efficacy.

Until recently only neutral complexes had been found to exhibit a significant antitumor activity and neutrality has been proposed as a necessary criterion for activity.²⁵ However, the platinum blue complexes are an exception to this criterion.²⁹ In addition, a cationic complex obtained from the reaction between dichloroethylenediamineplatinum(II) and cytosine arabinoside has recently been reported which also shows promise as an antitumor agent.³⁰ Thus, the *cis*-[Pt(NH₃)₂(Puo)₂]Cl₂ complexes are part of a family of cationic complexes of Pt(II) which exhibit anticancer activity. Electrical neutrality is not therefore a necessary condition for antitumor activity of platinum complexes.

It was initially thought that the activity of *cis*-Pt(NH₃)₂Cl₂ resulted from the formation of interstrand DNA cross-links,³¹⁻³³ but evidence now indicates otherwise.^{32,34,35} It has been suggested, instead, that the platinum binds to adjacent bases in the same strand, which produces significant local distortion in the DNA.³⁶⁻³⁹ Upon replication this distortion of the DNA structure could lead to damage in the daughter strand and cell death.

The results of this structural study provide some structural parameters for a Guo-Pt-Guo link envisioned by this mechanism. While the N₇ positions of adjacent guanosines in the same strand of DNA are 3.86-4.15 Å apart,⁴⁰ they are drawn together to 2.79 Å in this structure. Thus binding of the platinum in such a manner would force the two N₇ positions together by about 1 Å. In addition, while the planes of adjacent purine bases are parallel⁴¹ in DNA, binding to the

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platinum disrupts this relationship. Therefore intrastrand binding of a platinum ion across the N₇ position of two adjacent guanosines would significantly distort the structure of DNA at the binding site.

While the trans compound is also known to bind to DNA,³³ presumably at the N₇ position of guanosine, it is unable to bind to an adjacent guanosine due to the trans location of the second binding site. Thus upon binding to DNA, the trans complex

leaves the DNA structure unaltered. We propose that the essential difference between *cis*-Pt(NH₃)₂Cl₂ and *trans*-Pt(NH₃)₂Cl₂ is the ability of the former to induce a localized distortion in the DNA structure which the trans complex cannot accomplish.

Registry No. *cis*-[Pt(NH₃)₂(Guo)₂]Cl_{3/2}(ClO₄)_{1/2}·7H₂O, 71911-91-6; *cis*-[Pt(NH₃)₂(Ino)₂]Cl₂, 50883-28-8; *cis*-[Pt(NH₃)₂(Xao)₂]Cl₂, 50790-43-7; *cis*-DDP, 15663-27-1.

Supplementary Material Available: A listing of structure factor amplitudes (12 pages). Ordering information is given on any current masthead page.

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Trinuclear "Crown-like" Metal Complexes: An Unusual Product of Reaction of Activated Alkynes with Dinuclear Thiolato-Bridged Iridium Complexes

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The present work, supported by chemical, spectroscopic, and crystallographic studies, depicts the occurrence of oxidative additions of alkynes on initially nonbonded Ir(I) atoms of dinuclear complexes. Starting from [Ir(μ-S-*t*-Bu)(CO)L]₂ complexes, we obtained trinuclear complexes (L = CO) or dinuclear complexes (L = P(OCH₃)₃) both with a metal-metal bond (Ir(II)-Ir(II)). Special attention is devoted to the trinuclear species which exhibits a remarkable "crown-like" structure as shown by a crystal structure determination of [Ir₃(μ-S-*t*-Bu)₃(μ-C₄F₆)(CO)₆].

Introduction

In many dinuclear complexes, the alkyne ligand is μ-bridged to the metal atoms: the C-C bond is either perpendicular to the metal-metal axis as in Co₂(CO)₆(RC₂R)¹ or parallel as in [Fe(μ-SCF₃)(CO)₃]₂C₄F₆.^{2,3}

In iridium(I) chemistry, an original dinuclear complex [Ir(μ-Cl)(C₈H₁₂)(C₄F₆)₂] has been recently reported;⁴ in this complex, alkyne (and alkene) ligands are coordinated to the same metal atom.

As part of our continuing interest in the coordination chemistry of new iridium carbonyl compounds [Ir(μ-S-*t*-Bu)(CO)L]₂ (L = CO or P(OCH₃)₃) recently described,⁵ we have investigated the reaction of hexafluorobut-2-yne and dimethylacetylene dicarboxylate with these complexes. We now report the synthesis and the characterization of an unusual type of trinuclear iridium complex.

Experimental Section

Physical Measurements. The infrared spectra were recorded with a Perkin-Elmer 225 grating apparatus. Hexadecane solution or cesium bromide dispersions were used. In the ν_{CO} region of interest, the spectra were calibrated by water vapor lines. Proton NMR spectra have been run on Varian A60A and fluorine NMR spectra run on a Perkin-Elmer R10. Microanalyses were carried out by the Service Central de Microanalyses du CNRS. Melting points were determined in air. Molecular weights were determined by tonometry in benzene by using a Mechrolab apparatus. Magnetic measurements were obtained by using the Faraday method with HgCo(SCN)₄ as standard (χ_g = 16.44 × 10⁻⁶ cgsu).

Preparation of Complexes. [Ir(μ-S-*t*-Bu)(CO)₂]₂ (I) and [Ir(μ-S-*t*-Bu)(CO)(P(OCH₃)₃)₂] (II) were prepared as previously described.⁵

Preparation of [Ir₃(μ-S-*t*-Bu)₃(μ-C₄F₆)(CO)₆] (III). In a typical reaction, 1.012 g of I (ca. 1.5 mmol) was transferred to a thick glass reaction vessel fitted with a Teflon stopcock. It was evacuated and cooled to -196 °C, and pentane (ca. 20 mL) and hexafluorobut-2-yne (ca. 0.2 g) were condensed in. The reaction mixture was then allowed

to warm-up slowly to room temperature and was stirred overnight. The solution was then evaporated under reduced pressure. By crystallization at -40 °C in toluene, lemon yellow crystals were obtained and vacuum dried. A 0.950-g amount of product was obtained: yield ~80%; mp 148 °C; χ_M = -509.9 × 10⁶ cgsu.

Anal. Calcd for Ir₃C₂₂H₂₇O₆S₃F₆: C, 22.50; H, 2.30; S, 8.18; F, 9.70. Found: C, 22.26; H, 2.30; S, 8.05; F, 9.80. Molecular weight: calcd, 1174; found, 1180.

Preparation of [Ir₃(μ-S-*t*-Bu)₃(μ-C₂(CO₂CH₃)₂)(CO)₆] (IV). To a solution of 1.012 g of I (1.5 mmol) in 20 mL of pentane was added 0.142 g (0.123 mL) of C₂(CO₂CH₃)₂. The solution was stirred overnight. By crystallization at -40 °C in pentane, orange crystals (0.922 g, yield ~80%) were obtained and dried in vacuo; mp 142 °C dec.

Anal. Calcd for Ir₃C₂₄H₃₃O₁₀S₃: C, 24.98; H, 2.86; S, 8.33. Found: C, 25.08; H, 2.95; S, 8.03. Molecular weight: calcd, 1153; found, 1172.

Preparation of [Ir₂(μ-S-*t*-Bu)₂(μ-C₄F₆)(CO)₂(P(OCH₃)₃)₂] (V). In a typical reaction 0.867 g (ca. 1 mmol) of II⁵ was transferred to a thick glass reaction vessel fitted with a Teflon stopcock. It was evacuated and cooled to -196 °C and pentane (ca. 50 mL) and the alkyne (ca. 0.2 g) were condensed in. The reaction mixture was then allowed to warm slowly to room temperature and was stirred overnight. The solution was evaporated under reduced pressure. By crystallization at -40 °C in a CH₂Cl₂-hexane (1:1) mixture, lemon yellow crystals were obtained and vacuum dried. A 0.800-g amount of product was obtained: yield ~80%; mp 165 °C dec; χ_M = -430.1 × 10⁻⁶ cgsu; λ_{max} 315 nm (ε 7480 M⁻¹ cm⁻¹ (in CH₂Cl₂ solution)).

Anal. Calcd for Ir₂C₂₀H₃₆O₈P₂S₂F₆: C, 23.34; H, 3.50; S, 6.23; F, 11.07. Found: C, 23.59; H, 3.57; S, 6.22; F, 11.10. Molecular

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