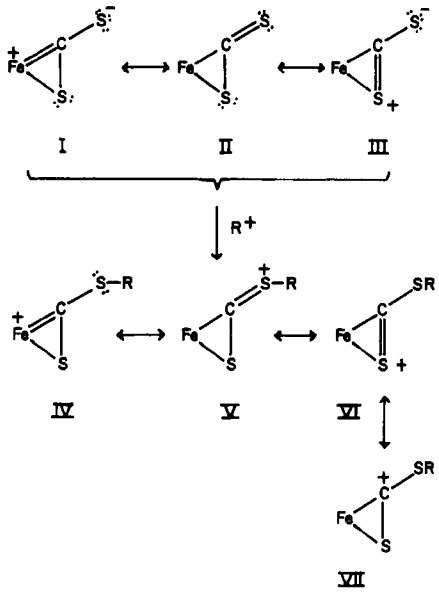
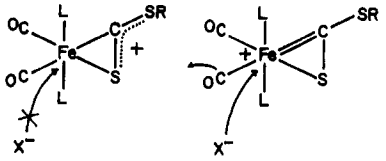
Scheme II



Scheme III



out that the Fe(η^2-CS_2) group in a derivative of type **1** is modified in a similar though less pronounced fashion by attachment of a manganese atom to the uncoordinated sulfur site. Thus in $(PhMe_2P)_2(CO)_2FeCS_2Mn(CO)_2(C_5H_5)$[7] the Fe–C distance is 1.939 (6) Å, with C–S(1) of 1.658 (6) Å and C–S(2) of 1.642 (6) Å.

In order to adequately account for the structural features, electronic charge distribution, and reactivity of the precursor **1c**, we earlier suggested contributions from canonical forms I–III to the ground state description of this molecule. Pictorially, alkylation of these forms by R^+ would lead to the valence-bond representations IV–VI (Scheme II). Additionally the reasonable carbonium ion structure VII might be expected to contribute to the electronic structure of **5e**. The detailed comparison of structural parameters for **5e** and **1c** outlined above suggests that form IV makes a substantially greater contribution to **5e** than the corresponding form I to **1c** and that the weight given to structures with double-bond character in the uncoordinated C–S bond is reduced from **1c** to **5e**. These conclusions regarding the electronic structure of **5e** have significance for the chemistry of compounds **4** and **5**. Thus for molecules of this type with strong donor ligands (**4d,e** and **5d,e**) displacement of CO and coordination of halide ion are facilitated by stabilization of the positive charge on iron (form IV) while for the weak donor ligands $P(OMe)_3$ and PPh_3 (**4a,b** and **5a,b**) those forms with the positive charge localized on the ligand predominate (Scheme III).

Registry No. **1a**, 64424-66-4; **1b**, 64424-68-6; **1c**, 64424-59-5; **1d**, 64424-57-3; **1e**, 64424-58-4; **2b**, 72598-18-6; **3b**, 76648-71-0; **4a**, 71004-17-6; **4b**, 71004-19-8; **4d**, 71004-23-4; **4e**, 71004-25-6; **5c**, 76648-73-2; **5d**, 76648-75-4; **5e**, 76648-77-6; **6d**, 76704-54-6; **6e**, 71004-27-8; **7d**, 76648-78-7; **7e**, 76648-79-8; MeI, 74-88-4; $PhCH_2Bu$, 100-39-0.

Supplementary Material Available: A listing of observed and calculated structure factor amplitudes (16 pages). Ordering information is given on any current masthead page.

Contribution from the Institute for Materials Research, McMaster University, Hamilton, Ontario, L8S 4M1, Canada

Crystal and Molecular Structures of *cis*- and *trans*-Dichlorobis(cyclobutylamine-*N*)platinum(II), $PtCl_2(C_4H_7NH_2)_2$, and Some Comments on the Conversion of Cis to Trans

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Received August 26, 1980

The X-ray crystal structures of the cis and trans forms of dichlorobis(cyclobutylamine-*N*)platinum(II) have been determined. The cis form, monoclinic $P2_1/c$, has cell dimensions a = 5.975 (2) Å, b = 20.459 (8) Å, c = 11.512 (2) Å, and β = 116.18 (2)° and has 4 formula units in the cell. The crystal structure was determined by standard methods and refined to R_1 = 0.0515 and R_2 = 0.0635 on the basis of 1852 independent reflections. The trans form is also monoclinic $P2_1/c$ with a = 7.760 (2) Å, b = 9.319 (3) Å, c = 8.621 (2) Å, and β = 97.61 (2)° and has 2 formula units in the cell. The crystal structure, which was determined similarly, refined to R_1 = 0.0281 and R_2 = 0.0333 on the basis of 1383 independent reflections. The crystal structure, which was determined similarly, refined to R_1 = 0.0281 and R_2 = 0.0333 on the basis of 1383 independent reflections. Both data sets were collected by using Mo Kα radiation and a Syntex $P2_1$ diffractometer. Bond lengths (Pt–N range 2.047 (8)–2.06 (3) Å, Pt–Cl range 2.298 (3)–2.326 (9) Å) are similar in the two compounds and agree with values for other amine complexes. Both compounds were prepared by the same preparative method but with different crystallization procedures. It is shown that recrystallization from acetone causes facile cis to trans isomerization.

Introduction

Platinum amine complexes of the type *cis*-$PtCl_2(RNH_2)_2$, where R is a cyclic alkyl group, have been shown[1,2] to have a much better therapeutic index against certain cancers in animals than the first platinum anticancer drug, *cis*-dichlorodiammineplatinum(II).[3] This is caused primarily by a decrease in toxicity of the drug as ring size increases. The corresponding trans analogues are inactive. Attempts to

(1) Connors, T. A.; Jones, M.; Ross, W. C. J.; Braddock, P. D.; Khokhar, A. R.; Tobe, M. L. *Chem.-Biol. Interact.* **1972**, *5*, 415.
(2) Braddock, P. D.; Connors, T. A.; Jones, M.; Khokhar, A. R.; Melzack, D. H.; Tobe, M. L. *Chem.-Biol. Interact.* **1975**, *11*, 145.
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0020-1669/81/1320-1817$01.25/0

Table I

	cis-$PtCl_2(C_4H_7NH_2)_2$	*trans*-$PtCl_2(C_4H_7NH_2)_2$
cryst size	*a*	plate $1\bar{0}0$, $\bar{1}00$ (0.028 mm apart) $1\bar{1}1$, $\bar{1}1\bar{1}$ (0.08 mm apart) 011, $01\bar{1}$ (0.08 mm apart)
systematic absences	$0k0, k \neq 2n$ $h0l, l \neq 2n$	$0k0, k \neq 2n$ $h0l, l \neq 2n$
space group	$P2_1/c$	$P2_1/c$
unit cell parameters		
a, Å	5.975 (2)	7.760 (2)
b, Å	20.459 (8)	9.319 (3)
c, Å	11.512 (2)	8.621 (2)
β, deg	116.18 (2)	97.61 (2)
vol, Å^3	1262.9 (7)	617.9 (3)
Z	4	2
ρ_{calcd}, g cm^{-3}	2.15	2.19
ρ_{obsd}, g cm^{-3}	2.16 (1)	2.17 (2)
linear abs coeff, cm^{-1}	113	123
abs coeff limits	1.2996–1.4259	1.3889–2.7296
std reflctns (esd, %)	−1,−1,0 (3.4)	104 (1.7)
	1,−1,−2 (5.6)	011 (1.8)
	022 (4.5)	0,3,−1 (1.7)
no. of independent reflctns[b]	1852	1383
with $I > 3\sigma(I)$	743	803
with $3\sigma(I) > I > \sigma(I)$ ($F_o < F_c$)	84	38
with $3\sigma(I) > I > \sigma(I)$ ($F_o > F_c$)	281	105
with $I < \sigma(I)$	744	437
final R_1 (obsd) (all)	0.0457 (0.0515)	0.0269 (0.0281)
final R_2 (obsd) (all)	0.0614 (0.0635)	0.0328 (0.0333)
final shift in esd		
max	0.0037	0.5752
av	0.0002	0.0693
g, extinction coefficient	1.52×10^{-8}	-4.52×10^{-9}
final difference map highest peak, e/Å^3 (location)	1.9 (0.13, 0.25, 0) 1.9 (0.48, 0.25, 0)	0.8 (0.025, 0.113, 0)
lowest valley, e/Å^3 (location)	−1.1 (0.36, 0.25, 0)	−0.9 (0.1, −0.005, −0.05)
weighting scheme[c]	$[\sigma^2 + (0.03F_o)^2]^{-1}$	$[\sigma^2 + (0.025F_o)^2]^{-1}$
error in an observn of unit weight	1.3473	0.9087
anal. calcd (obsd), %		
N	6.9 (6.7)	6.9 (7.4)
C	23.5 (24.3)	23.5 (23.7)
H	4.4 (4.8)	4.4 (4.6)
fw	408.24	408.24

[a] See Figure 1. [b] Most of the unobserved reflections occurred above $2\theta = 35°$ for the trans compound. For the cis compound most of the unobserved reflections occurred for $l = 2n + 1$. [c] The values 0.03 and 0.025 were chosen to make $\langle w(|F_o| - |F_c|)^2 \rangle$ locally independent of F_o and $(\sin\theta)/\lambda$.

correlate therapeutic index with aqueous solubility or lipid solubility were inconclusive, leading to the postulate that the changes in therapeutic index must be structure related.[1,2] As a result, the structures of a number of these complexes have been investigated.[4-9] A surprising result is that, in a number of cases, literature preparations for the cis isomer apparently gave the trans isomer.[4,6,7,9] This was the case with the cyclobutylamine complex, and thus we have investigated the reason for this. We report this work here.

Experimental Section

***cis*-Dichlorobis(cyclobutylamine-*N*)platinum(II), *cis*-$PtCl_2(C_4H_7NH_2)_2$.** The procedure of Connors et al.[1] was used but with roughly one-fourth quantities (cyclobutylamine, 0.187 g, 2.63×10^{-3} mol; K_2PtCl_4, 0.529 g, 1.27×10^{-3} mol; water, 20 mL) to give a yellow powder.

Roughly one-third of the solid was dissolved in dimethylformamide (20 mL) at room temperature, and any undissolved solid was removed by filtration. HCl (0.1 N) was added dropwise until the solution was faintly cloudy. A few drops of dimethylformamide was added to remove the cloudiness, and the solution was placed in the refrigerator overnight. Pale yellow crystals were collected.

***trans*-Dichlorobis(cyclobutylamine-*N*)platinum(II), *trans*-$PtCl_2(C_4H_7NH_2)_2$.** The same procedure[1] was used as for the cis compound (cyclobutylamine, 0.2 g, 2.8×10^{-3} mol; K_2PtCl_4, 0.58 g, 1.4×10^{-3} mol; water, 20 mL). The solid was recrystallized by dissolving in boiling acetone (30 mL). The solution was cooled to room temperature, and any residual solid was removed by filtration. Three to four drops of extra acetone was added to the filtrate. The filtrate was placed in an Erlenmeyer flask (125 mL) which was covered with aluminum foil with a few holes punched in the top. The solution was allowed to evaporate slowly in a refrigerator (0 °C) (7–28 days), yielding the product as pale yellow crystals.

Collection of the X-ray Data. Crystals of the two compounds were selected after examination under a polarizing microscope for homogeneity. Precession photographs showed both crystals were monoclinic. Unit cell parameters were obtained from least-squares fit of χ, Φ, and 2θ for 15 reflections for each compound in the range $19° < 2\theta < 27°$ recorded on a Syntex $P2_1$ diffractometer using graphite-monochromated Mo Kα radiation (λ 0.71069 Å at 21 °C). Crystal data and other numbers related to data collection are summarized in Table I. Densities were obtained by flotation in an aqueous zinc bromide solution. Intensity data were recorded on a Syntex $P2_1$ diffractometer using a coupled θ(crystal)–2θ(counter) scan. The methods of selection of scan rate and initial data treatment have been described.[10,11] Corrections were made for Lorentz–polarization effects

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(5) Zanotti, G.; Del Pra, A.; Bombieri, G.; Tamburro, A. M. *Acta Crystallogr., Sect. B* **1978**, *B34*, 2138.
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(8) Howard-Lock, H. E.; Lock, C. J. L.; Zvagulis, M., be submitted for publication in *Can. J. Chem.*
(9) Lock, C. J. L.; Zvagulis, M. *Acta Crystallogr.* **1980**, *B36*, 2140.

Table II. Positional and Thermal Parameters ($Å^2$) and Anisotropic Temperature Factors[a] ($Å^2$) for *trans*-Dichlorobis(cyclobutylamine-*N*)platinum(II), $PtCl_2(C_4H_7NH_2)_2$ ($\times 10^3$)

atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt	0.0	0.0	0.0	34.5 (3)	25.9 (2)	21.9 (2)	0.2 (6)	7.4 (1)	−0.6 (8)
Cl	44.8 (4)	243.8 (3)	5.8 (4)	72 (2)	30 (1)	37 (1)	−5 (1)	15 (2)	−2 (1)
N	−86 (1)	6 (2)	214.3 (9)	47 (5)	34 (4)	26 (3)	22 (8)	8 (3)	6 (8)
C(1)	−279 (1)	1 (2)	204 (1)	40 (4)	48 (5)	40 (5)	−4 (11)	17 (4)	16 (12)
C(2)	−366 (2)	15 (2)	356 (1)	53 (6)	41 (9)	51 (5)	9 (7)	27 (4)	12 (7)
C(3)	−508 (2)	105 (2)	264 (2)	44 (7)	69 (9)	74 (10)	11 (6)	18 (6)	−6 (7)
C(4)	−374 (2)	144 (2)	149 (2)	52 (7)	78 (10)	53 (8)	11 (7)	15 (6)	20 (7)
H(1)	−45 (27)	−60 (20)	273 (26)						
H(2)	−50 (28)	101 (21)	251 (27)						
$U = 60$ Å^2									
$U = 60$ Å^2									

[a] Anisotropic temperature factors U_{ij} were obtained from $\beta_{ij} = 2\pi^2 \mathbf{b}_i \mathbf{b}_j U_{ij}$, where the β_{ij}'s appear as a temperature effect of the form $\exp[-(\beta_{11}h^2 + \ldots + 2\beta_{12}hk + \ldots)]$ and $\mathbf{b}_i$ and $\mathbf{b}_j$ are the reciprocal lattice vectors.

Table III. Positional and Thermal Parameters ($Å^2$) and Anisotropic Temperature Factors[a] ($Å^2$) for *cis*-Dichlorobis(cyclobutylamine-*N*)platinum(II), $PtCl_2(C_4H_7NH_2)_2$ ($\times 10^3$)

atom	x	y	z	U	atom	x	y	z	U
Pt	299.3 (2)	249.3 (1)	501.9 (1)		C(3)	−49 (8)	439 (2)	654 (4)	100 (14)
Cl(1)	105 (2)	318.9 (5)	325.8 (8)		C(4)	−138 (8)	369 (2)	660 (4)	96 (13)
Cl(2)	547 (2)	208.0 (5)	411.1 (8)		C(5)	444 (8)	120 (2)	624 (4)	95 (13)
N(1)	84 (5)	280 (1)	590 (3)	61 (7)	C(6)	506 (10)	65 (3)	718 (5)	124 (17)
N(2)	472 (4)	187 (1)	657 (2)	49 (6)	C(7)	315 (9)	17 (3)	616 (5)	130 (18)
C(1)	−23 (7)	345 (2)	567 (4)	87 (12)	C(8)	214 (10)	85 (3)	551 (5)	128 (18)
C(2)	143 (8)	404 (2)	609 (4)	88 (12)					

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt	60.1 (7)	69.7 (8)	38.0 (5)	−2 (2)	22.9 (4)	−2 (1)
Cl(1)	88 (7)	89 (7)	50 (5)	14 (6)	33 (5)	12 (5)
Cl(2)	75 (6)	105 (7)	49 (5)	−3 (5)	36 (4)	−10 (5)

[a] Anisotropic temperature factors U_{ij} were obtained from $\beta_{ij} = 2\pi^2 \mathbf{b}_i \mathbf{b}_j U_{ij}$, where the β_{ij}'s appear as a temperature effect of the form $\exp[-(\beta_{11}h^2 + \ldots + 2\beta_{12}hk + \ldots)]$ and $\mathbf{b}_i$ and $\mathbf{b}_j$ are the reciprocal lattice vectors.

and absorption.

Solution of the Structure. Both structures were solved in the same way. The coordinates of the platinum atom were found from a three-dimensional Patterson synthesis, and a series of full-matrix least-squares refinements, followed by three-dimensional difference syntheses, revealed all the nonhydrogen atoms. After refinement, the temperature factors of the platinum and chlorine atoms, for the cis compound and all nonhydrogen atoms for the trans compound, which were previously isotropic, were made anisotropic. Tests were made at each stage to show the use of increased parameters was significant.[12] Attempts were made to find hydrogen atoms for the trans complex. A difference map showed a number of peaks about 1 e/Å^3. Some of these were in geometrically acceptable positions, but others were not. In addition, it was not possible to find hydrogen atoms in all the expected positions. Ultimately, only the two hydrogen atoms attached to the nitrogen atom, which could be involved in hydrogen bonding, were included in the refinement. Only their positional parameters were refined: the temperature factors were fixed at approximately 50% greater than that of the nitrogen atom. No attempt was made to find the hydrogen atoms for the cis complex. Further refinement using full-matrix least squares minimizing $\sum w(|F_o| - |F_c|)^2$ was terminated when the maximum shift/error was 0.5 for the hydrogen atoms and 0.2 for the other atoms. Corretions were made for secondary extinction with the method of Larson.[13] Throughout the refinement, the scattering curves were taken from ref 14, and anomalous dispersion corrections from ref 15 were applied to the curves for platinum and chlorine. The atom parameters are listed in Tables II and III.[16]

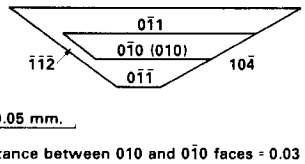

Figure 1. Crystal of *cis*-dichlorobis(cyclobutylamine-*N*)platinum(II).

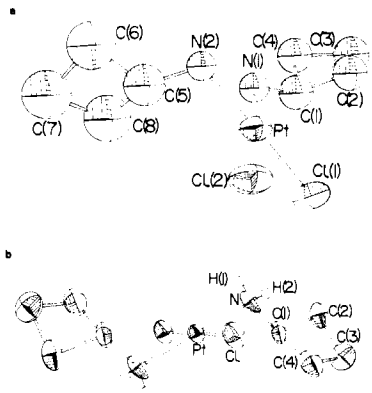

Figure 2. (a) *cis*-Dichlorobis(cyclobutylamine-*N*)platinum(II). (b) *trans*-Dichlorobis(cyclobutylamine-*N*)platinum(II).

(10) Hughes, R. P.; Krishnamachari, N.; Lock, C. J. L.; Powell, J.; Turner, G. *Inorg. Chem.* **1977**, *16*, 314.
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Table IV. Selected Interatomic Distances (Å) and Angles (Deg) for *cis*- and *trans*-$PtCl_2(C_4H_7NH_2)_2$

Distances

atoms	cis	trans	atoms	cis	trans	atoms	cis
Pt-Cl(1)	2.326 (9)	2.298 (3)	N(1)-C(1)	1.45 (5)	1.49 (1)	N(2)-C(5)	1.41 (5)
Pt-Cl(2)	2.32 (1)		C(1)-C(2)	1.51 (6)	1.56 (2)	C(5)-C(6)	1.48 (7)
Pt-N(1)	2.06 (3)	2.047 (8)	C(2)-C(3)	1.61 (8)	1.52 (2)	C(6)-C(7)	1.57 (7)
Pt-N(2)	2.06 (2)		C(3)-C(4)	1.54 (6)	1.57 (2)	C(7)-C(8)	1.56 (7)
N-H(1)		0.8 (2)	C(4)-C(1)	1.58 (7)	1.57 (3)	C(8)-C(5)	1.44 (7)
N-H(2)		1.0 (2)					

Hydrogen Bond Distances[a]

atoms	cis	atoms	trans	atoms	trans
Cl(1)...N(2)^{i}	3.41 (2)	Cl..H(1)^{iv}	2.6 (2)	Cl..N^{ii}	3.48 (1)
Cl(1)...N(1)^{ii}	3.34 (3)	Cl..H(2)^{ii}	2.7 (2)	Cl..N^{iv}	3.42 (1)
Cl(2)...N(1)^{iii}	3.30 (3)				

Angles

atoms	cis	trans	atoms	cis	trans	atoms	cis
Cl(1)-Pt-Cl(2)	90.2 (4)	180.0	Pt-N(1)-C(1)	121 (3)	113.0 (6)	Pt-N(2)-C(5)	115 (2)
Cl(1)-Pt-N(1)	93.5 (8)	91.2 (5)	N(1)-C(1)-C(2)	120 (3)	119.4 (8)	N(2)-C(5)-C(6)	125 (4)
Cl(1)-Pt-N(2)	179.3 (8)	88.8 (5)	N(1)-C(1)-C(4)	116 (4)	115 (1)	N(2)-C(5)-C(8)	127 (4)
Cl(2)-Pt-N(1)	176.1 (8)	88.8 (5)	C(1)-C(2)-C(3)	89 (4)	89 (1)	C(5)-C(6)-C(7)	93 (4)
Cl(2)-Pt-N(2)	89.3 (9)	91.2 (5)	C(2)-C(3)-C(4)	86 (3)	88 (1)	C(6)-C(7)-C(8)	79 (4)
N(1)-Pt-N(2)	87 (1)	180.0	C(3)-C(4)-C(1)	89 (4)	86 (1)	C(7)-C(8)-C(5)	95 (4)
Pt-N-H(1)		113 (17)	C(4)-C(1)-C(2)	88 (3)	87 (1)	C(8)-C(5)-C(6)	86 (4)
Pt-N-H(2)		102 (15)	C(1)-N-H(1)		108 (15)		
H(1)-N-H(2)		114 (18)	C(1)-N-H(2)		107 (14)		

[a] Atoms are related to those in Tables II and III as follows: (i) $x-1, {}^1/_2-y, z-{}^1/_2$; (ii) $x, {}^1/_2-y, z-{}^1/_2$; (iii) $1+x, y, z$; (iv) $-x, {}^1/_2+y, {}^1/_2-z$.

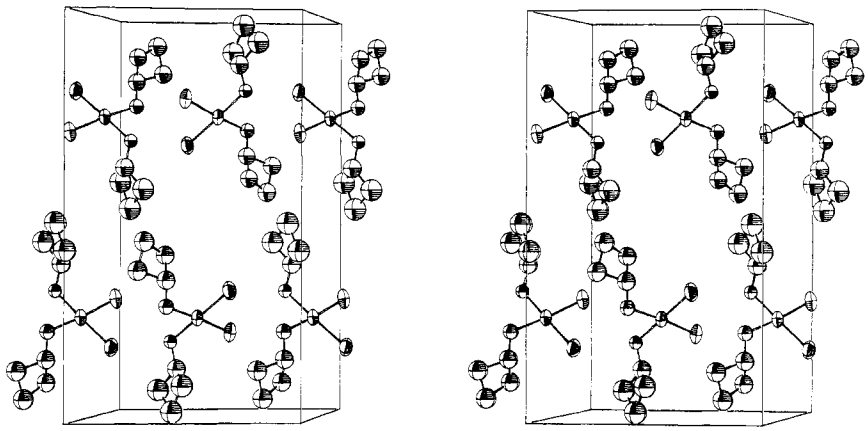

Figure 3. Packing of *cis*-dichlorobis(cyclobutylamine-*N*)platinum(II) within the unit cell. *c* and *b* are parallel to the top and side of the page, respectively, and the view is down *a**.

Results and Discussion

cis-Dichlorobis(cyclobutylamine-*N*)platinum(II) is shown in figure 2a and the corresponding trans compound in Figure 2b. Selected interatomic distances and angles are compared in Table IV. Pt–N distances are very similar for the two compounds, as are Pt–Cl distances, and lie well within the

Table V. Least-Squares Plane and Torsional and Dihedral Angles in *cis*- and *trans*-$PtCl_2(C_4H_7NH_2)_2$

plane [*cis*-$PtCl_2(C_4H_7NH_2)_2$]	dist from Plane, Å
PtCl(1)Cl(2)N(1)N(2)[a]	Pt, 0.02; Cl(1), 0.01; Cl(2), −0.01; N(1), −0.01; N(2), 0.01

atoms	cis	trans	atoms	cis
Torsional Angles, Deg				
PtN(1)C(1)C(2)	64	−176	PtN(2)C(5)C(6)	−167
PtN(1)C(1)C(4)	−168	−75	PtN(2)C(5)C(8)	53
N(1)C(1)C(2)C(3)	141	141	N(2)C(5)C(6)C(7)	−154
C(1)C(2)C(3)C(4)	−22	−24	C(5)C(6)C(7)C(8)	19
C(2)C(3)C(4)C(1)	20	24	C(6)C(7)C(8)C(5)	−20
C(3)C(4)C(1)C(2)	−22	−24	C(7)C(8)C(5)C(6)	21
C(4)C(1)C(2)C(3)	21	24	C(8)C(5)C(6)C(7)	−21
N(1)C(1)C(4)C(3)	−145	−145	N(2)C(5)C(8)C(7)	152
Dihedral Angles, Deg				
PtN(1)N(2)-PtN(1)Cl(1)	0.3			
PtN(1)N(2)-PtN(2)Cl(2)	1.5			

[a] Pt was given no weight in this calculation.

(16) Most programs used for initial data treatment were from the XRAY package (Stewart, J. M. "The XRAY 76 System", Technical Report TR-446; Computer Science Center: University of Maryland, College Park, MD, 1976). Structure solution and most least-squares refinement used SHELX (Sheldrick, G. M. "SHELX, Program for Crystal Structure Determination"; University of Cambridge: Cambridge, England, 1976). Final refinements and differences used the internally written Fourier and full-matrix least-squares programs SYMFOU and CUDLS written by J. S. Rutherford and J. S. Stephens, respectively. The least-squares planes were calculated by using NRC-22 (Pippy, M. E.; Ahmed, F. A. "NRC-22"; National Research Council of Canada, Ottawa, Canada). The diagrams were prepared by using ORTEP II (Johnson, C. K. "ORTEP II", Report ORNL-5138; Oak Ridge National Laboratory: Oak Ridge, TN, 1976). All calculations were carried out on CDC-6400 and CYBER 170/730 computers.

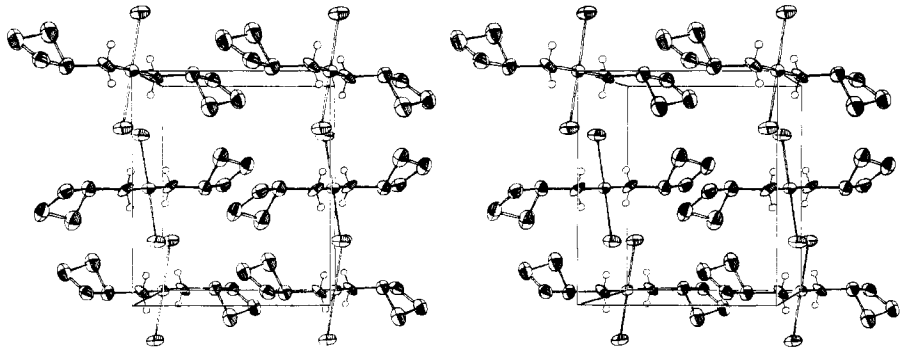

Figure 4. Packing of *trans*-dichlorobis(cyclobutylamine-*N*)platinum(II) within the unit cell. *a* and *b* are parallel to the top and side of the page, respectively, and the view is down *c**.

Table VI. Powder Data and Calculated *d* Spacings for *cis*- and *trans*-$PtCl_2(C_4H_7NH_2)_2$

trans[a]					cis[b]				
	d spacing					*d* spacing			
hkl	calcd[c]	obsd	I_{obsd}[d]	I_{cryst}[d]	*hkl*	calcd[c]	obsd	I_{obsd}[d]	I_{cryst}[d]
100	7.69	7.6-7.8	77	85	020	10.23	9.9-10.4	100	100
01$\bar{1}$	6.30	6.2-6.4	95	92	002	5.17	5.05-5.2	47	32
11$\bar{1}$	5.12	5.1-5.2	26	34	022	4.61	4.5-4.6	20	32
111	4.66	4.6-4.7	100	100	130	4.22	4.1-4.2	18	17
002	4.27	4.3	10	33	042	3.63	3.6	7	20
120	3.99	3.97-3.99	43	19	062	2.85	2.84-2.85	9	15
200	3.85	3.83-3.86	36	58	132	2.82			10
10$\bar{2}$	3.54	3.54-3.56	25	62	024	2.50	2.5	9	7
21$\bar{1}$	3.43	3.42-3.44	30	35					
211	3.15	3.16-3.17	16	24					
20$\bar{2}$	3.07	3.06-3.07	18	38					
031	2.92	2.90-2.92	19	24					
131	2.69	2.68-2.70	40	39					
22$\bar{2}$	2.56	2.56	6	6					
31$\bar{1}$	2.46	2.46	5	12					
213	2.37	2.37	24	35					
040	2.33	2.32-2.33	27	46					
140	2.23	2.24	18	44					
004	2.14	2.14	10	25					
10$\bar{4}$	2.13			37					
302	2.09	2.08-2.09	10	14					
20$\bar{4}$	1.98	1.99-2.01	21	29					
142	1.95	1.93-1.94	13	17					
242	1.76	1.75-1.76	15	22					
044	1.57	1.57-1.58	6	14					
14$\bar{4}$	1.57			18					
24$\bar{4}$	1.51	1.51	13	13					
144	1.51			12					

[a] The observed data for the trans compound (d_{obsd}, I_{obsd}) were recorded for a powdered sample of the material obtained from recrystallization in acetone. [b] The observed data for the cis compound (d_{obsd}, I_{obsd}) were recorded for the yellow powder obtained from the reaction of cyclobutylamine with K_2PtCl_4 and before any recrystallization had been attempted (see Experimental Section). [c] The *d* spacings were calculated from the single-crystal unit cell parameters. [d] I_{obsd} represents the measured intensity from the powder photographs recorded with use of Cu Kα radiation and scaled to $I_{max} = 100$. I_{cryst} is the intensity of the single-crystal reflection recorded with use of using Mo Kα radiation and scaled to $I_{max} = 100$.

range of distances observed previously.[5] The N–C distances are also insignificantly different and normal for an N–C single bond.[17] Distances and angles within the cyclobutylamine ring agree well with published values.[18-27] The dihedral angles between the C(1)C(2)C(4) [C(5)C(6)C(8)] and C(2)C(3)C(4) [C(6)C(7)C(8)] in the cyclobutylamine rings are 150° [153°] for the cis and 145° for the trans complex. The values for the cis compound do not lie far from the average for cyclobutane structures (157°),[18-27] but the angle for the trans compound is slightly lower than the bottom of the range (149 (2)–168.1 (2)°). Values from previous structures are evenly distributed within the range suggesting relatively easy folding of the ring, and we assume the angles observed here are determined primarily by packing forces.

The packing of the molecules within the unit cells is shown in Figures 3 and 4. In the cis complex, the molecules lie in chains along the *c* direction roughly at $y = 1/4$. The glide plane causes the square planes of adjacent molecules to be twisted

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about 90° with respect to each other. This arrangement maximizes both dipole–dipole interactions between the molecules and hydrogen bonding between Cl(1)····N(2)^{i} and Cl(1)···N(1)^{ii}. Packing in the *a* direction is determined primarily by hydrocarbon ring contacts and hydrogen bonds, Cl(2)···N(1)^{iii}. In the *b* direction, contact is between the hydrocarbon rings. The packing of this compound is noteworthy in that it is one in which the $PtX_2(amine)_2$ molecules are not packed such that the ligand atom square planes of pairs of molecules are stacked one above the other to give a 3.4–3.5 Å Pt–Pt distance. This pair arrangement is very common, as we have noted previously.[6]

Molecules of the trans compound lie with the ligand atom plane almost in the *bc* plane with the Pt–Cl axis roughly along *b* and the Pt–N axis roughly along *c*. Hydrogen bonding (Cl···H(1)^{iv}, Cl···H(2)^{ii}) gives a two-dimensional network. Contact in the *a* direction is between the hydrocarbon rings.

The preparation of a trans complex from a procedure which was supposed to give the cis complex gave rise to some interesting problems, particularly as this effect has been observed before.[4,6,7,9] It is particularly important since the same procedures had been used to prepare samples of cis amine platinum complexes used in animal tests in which it was shown that cis complexes were active against cancers, whereas trans complexes were not. Three obvious possibilities exist: (1) The cis preparation procedure actually gives the trans complex. (2) The *cis* preparation procedure gives a mixture of cis and trans complexes, but in the recrystallization procedure the trans complex is less soluble and crystallizes first, or the trans crystals are better formed and are automatically selected by the crystallographer for study. (3) The cis procedure gives the correct isomer, but, in the process of recrystallization, the cis complex is converted to the trans. (3) The cis procedure gives the correct isomer, but, in the process of recrystallization, the cis complex is converted to the trans.

Explanation 1 seems unlikely. Trans complexes prepared by conventional procedures were physiologically inactive whereas the compounds from the cis preparations show good physiological acitivity.[1,2] This could only occur if the conventional trans preparation gave a product other than the trans complex. Explanation 2 is possible. If this were the case, then there are important implications. It would mean that the cis complex used in animal tests was diluted with the inactive trans complex and thus the cis complex would have greater physiological activity than was reported. Explanation 3 is also possible, but is surprising considering the mild conditions of recrystallization. As we shall show, however, this is the correct explanation.

The single-crystal X-ray structure characterization of both the cis and trans isomers of the cyclobutylamine complex allowed the calculation of powder patterns for each complex and comparison with X-ray diffraction powder patterns of the products obtained at various stages of the preparative procedure. The results obtained at two important stages are presented in Table VI. These stages were after the crude product had been isolated with use of the literature procedure and before any attempt was made to recrystallize the product, and second after the crude product was reprecipitated from a boiling acetone solution used in recrystallization. The results are unambiguous in showing that the cis complex is the product of the preparative procedure, but the process of recrystallization from acetone has converted the cis to the trans isomer. Such an interconversion has been suggested before in dimethyl sulfoxide on the basis of infrared results.[28] Recrystallization from dimethylformamide, however, did not cause the cis isomer to convert to the trans.

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Table VII. Vibrational Frequencies for *cis*- and *trans*-$PtCl_2(C_7H_7NH_2)_2$

cis-$PtCl_2(C_4H_7NH_2)_2$				*trans*-$PtCl_2(C_4H_7NH_2)_2$			
infrared		Raman		infrared		Raman	
wavenumber, cm^{-1}	I	wavenumber, cm^{-1}	I	wavenumber cm^{-1}	I	wavenumber, cm^{-1}	I
				3260	vs		
~3200 br	vs	3213	1.6	3222	vs		
3130	sh	3197	1.8	3145	vs		
2994	sh	2994	sh	2994	sh		
2981	vs	2976	3.6	2985	vs		
		2968	sh				
2951	vs	2962	3.3	2945	vs		
2938	sh	2942	3.3				
2899	m	2910	3.9	2900	sh		
2874	s			2878	s		
1662	w	1603	0.6				
1586	s	1582	0.9	1591 br	s		
1562 br	vs						
1468	m	1461	0.6	1462	w		
1447	m			1450	m		
1440	m	1442	2.5	1438	m		
1415	sh	1407	0.8				
1396	s			1395	s		
1318	w	1309	0.9	1296	m	1290[a]	1.5
1286	m	1280	4.1	1273	w	1271	1.7
1245	s			1241	s		
1235	s	1231	2.0	1229	sh		
1222	sh	1222	2.5	1219	s	1210	1.8
1190	w	1195	0.7				
		1186	0.7	1188	m		
1162	m			1153	s		
1114	sh	1120	0.6				
1104	s	1109	0.6	1110	s		
		1098	0.9				
		1085	3.7				
		1077	sh				
1028	w	1020	1.2	1020	w		
				966	m		
956	sh	951	6.0	956	m	951	5.2
946	s	940	2.8			938	2.0
897 br	m	904	5.5	900	m	901	3.9
790	sh			797	w		
776	m			775	w		
747	w			750	w		
728	m						
637	m	634	1.7			631	1.8
627	w	623	1.2	622	m		
588	sh	590	3.4				
577	m	577	0.9	580	m	578	3.2
416	m	412	1.3	432	m		
311 br	s	312	10.0	333 br	m	329	10.0
		277	sh				
274 br	w	270	3.4	288 br	m	289	2.2
		232	1.3			226	1.8
		210	1.1				
		183	2.9			169	1.8
		128	1.8			130	1.1
		113	1.4			115	4.1
		97	0.9				
		75	1.2			79	4.6

[a] The Raman spectrum could not be obtained more than 1300 cm^{-1} from the exciting line because of an increasingly intense fluorescence background.

We have recorded the vibrational spectra (both infrared and Raman). The spectra are sufficiently different to allow identification of the two compounds, but, because of coincidences of bands in the Pt–Cl stretch region, they would not allow one a priori to distinguish between the two compounds. The ν_{Pt-Cl} stretches, both symmetric and asymmetric, would be expected to cause absorption in the 300–400-cm^{-1} region of the spectrum. Both modes should be active in the infrared and Raman spectra for the cis complex, while only the asymmetric mode should be active in the infrared and the symmetric

mode in the Raman for the trans complex. Only one band is observed in both the infrared and Raman spectra for both compounds. In addition, the wave numbers of the bands are almost the same in the infrared and Raman spectra although the trans bands are ~ 20 cm^{-1} above those of the cis. We think there are two reasons for this. First, although the symmetric and asymmetric bands in $PtCl_2L_2$ usually are well resolved, being up to 25 cm^{-1} apart, they may be as little as 8 cm^{-1} apart[29] and on a geometrical basis should have the same wavenumber.[30] The separation can be related to ligand field strength.[31] We suggest that for the trans compound, this difference is reduced to 4 ± 2 cm^{-1}. Second, the resolution of the bands for the cis compound is not good. The width at half-height for the infrared band is 30 cm^{-1} and for the Raman band is 13 cm^{-1}. On the assumption of a similar separation of the symmetric and asymmetric modes, 5–10 cm^{-1}, it is reasonable that no resolution of the bands has taken place. Thus, although band position allows identification of the compounds, counting numbers of bands does not, in this case, allow differentiation.

We conclude that although literature procedures for the preparation of *cis*-$PtCl_2(amine)_2$ do give the desired products, the process of recrystallization may cause cis to trans interconversion. This interconversion is clearly easier than had previously been assumed. Thus procedures for purifying *cis*-$PtCl_2(amine)_2$ complexes for animal tests should be monitored carefully to make sure that cis–trans interconversion has not taken place. Further, infrared–Raman spectroscopy is not, in itself, a completely unambiguous method of differentiating cis and trans isomers.

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Supplementary Material Available: Listings of structure factor amplitudes (10 pages). Ordering information is given on any current masthead page.

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Oxidation of Phenacetin and Related Amides to Their Hydroxamic Acids. Crystal Structures of the Dioxomolybdenum(VI) Hydroxamates Derived from Phenacetin and Acetanilide

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An existing method of oxidation involving oxodiperoxo(hexamethylphosphoramide)molybdenum(VI) has been adapted for the direct conversion of phenacetin and related amides to their respective hydroxamic acids. The hydroxamic acids are initially isolated as their stable dioxomolybdenum(VI) salts, in which form they can conveniently be stored and from which they are readily liberated by ligand displacement. The hydroxamic acids are of interest as the suspected toxic metabolites of several related drugs. The Mo(VI) derivatives of two analgesics, phenacetin and acetanilide, have been characterized by single-crystal X-ray diffraction. The ligand environment about the Mo atom is a markedly distorted octahedron in each case, with the dioxo O atoms bonded cis to each other, while trans to these bonds the hydroxamate Mo–O bonds are elongated. There is no conjugation between the phenyl rings and the hydroxamic acid group. Crystal data: MoO_2L_2, space group $P2_1/c$, $Z = 4$, $a = 12.350$ (6) Å, $b = 17.477$ (3) Å, $c = 10.309$ (7) Å, $\beta = 95.25$ (3) °, $V = 2216$ Å^3, $R = 5.0\%$, 2738 reflections; $MoO_2L'_2$, space group *Pbca*, $Z = 8$, $a = 13.137$ (3) Å, $b = 11.620$ (3) Å, $c = 22.820$ (5) Å, $V = 3483$ Å^3, $R = 4.7\%$, 1549 reflections. L and L′ represent the hydroxamate anions derived from phenacetin and acetanilide, respectively.

Introduction

The oxidation of amides to the corresponding hydroxamic acids is a recognized pathway for the metabolism of certain *N*-acyl aromatic amines.[1] Phenacetin, Figure 1, a widely used analgesic and antipyretic, is metabolized in the liver, a major route being deethylation to acetaldehyde and acetaminophen.[2] Similarly, the metabolism of acetanilide involves rapid hydroxylation to acetaminophen, through which the analgesic and antipyretic effects are chiefly exerted.[2] N-Oxidation of phenacetin has been proposed to account for the appearance of hydroquinone and acetamide as minor urinary metabolites of this drug.[3] Further, the N-hydroxylation of phenacetin has been suggested to be the cause of acute nephrotoxicity of this molecule and related derivatives.[4]

The relationship between large doses and renal failure in man is widely accepted although the exact mechanism of this process has not been determined.[5] It has been shown that there is a correlation between the toxicity of phenacetin and related derivatives and pretreatment with compounds known to stimulate the cytochrome P-450 mixed-oxidase system.[6] This also suggests that amide oxidation products may be key intermediates in the toxic pathways open to phenacetin and related molecules.

The testing of the postulate that the hydroxamic acids are the toxic intermediates is greatly hampered by the lack of a ready supply of these acids. The syntheses are difficult, and storage presents further problems, due to rapid decomposition.

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