Interactions between Phenothiazine Drugs and Metal Ions. Part 2.† Crystal and Molecular Structure‡ of Protonated Trichloro[2-chloro-10-(3'-dimethylaminopropyl)phenothiazine-*S*]palladium(II), [Pd(cpzH)Cl_3]; Hydrogen-1 and Carbon-13 Nuclear Magnetic Resonance Data for the Chlorpromazine Complexes [M(cpzH)Cl_3](M = Pd or Pt)

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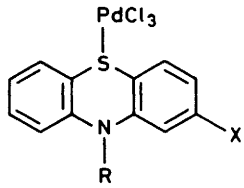
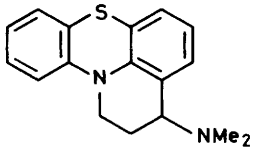
The structure of the chlorpromazine complex [Pd(cpzH)Cl_3] has been elucidated by single-crystal *X*-ray crystallography. Crystals are monoclinic, space group $C2/c$, $Z = 8$, in a unit cell with lattice parameters $a = 29.757(9)$, $b = 9.487(4)$, $c = 16.184(6)$ Å, $\beta = 116.5(1)°$. The structure has been solved using heavy-atom methods and refined by least squares to $R = 0.056$ ($R' = 0.060$) for 1 277 independent reflections collected by counter methods. Chlorpromazine is sulphur-bonded to a $PdCl_3$ unit, the counter ion being a protonated nitrogen on the drug substituent. The side chain adopts an unusual conformation apparently to facilitate both intra- and inter-molecular hydrogen bonding. The n.m.r. data show that this conformation is maintained in the aprotic solvent *NN*-dimethylformamide.

Phenothiazine drugs act on a wide range of receptors in the nervous system and have been found to be versatile anticholinergic and antihistamine compounds.[1] While it is known that the endocyclic sulphur is essential for drug activity,[2] the conformation of the N(10) side chain also appears to play a key role in determining the mode of action.[3]

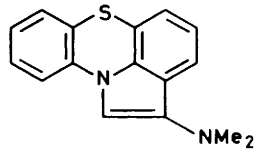
Previously we have been able to investigate the interactions between metal ions and a range of phenothiazine drugs, using spectroscopic and crystallographic techniques.[4] The crystal structure of the promethazine complex [Pd(pmzH)Cl_3] (**1**) shows that the N(10) side chain adopts an unusual 'scorpion' conformation which facilitates the intramolecular hydrogen bonding $N^+H\cdots Cl$. Since it is the protonated form of phenothiazine drugs which is active,[2] such interactions may well also be important in relationship to pharmacological specificity. In this regard it is interesting to note that the protonated ligands (**3**) and (**4**), which cannot adopt a scorpion conformation,[5] are pharmacologically inactive. We report herein the crystal and molecular structure of the chlorpromazine complex [Pd(cpzH)Cl_3] (**2**), together with the solution n.m.r. spectra for this and the analogous platinum complex.



[Pd(pmzH)Cl_3] (**1**), R = $CH_2CH(Me)\overset{+}{N}HMe_2$, X = H
[Pd(cpzH)Cl_3] (**2**), R = $CH_2CH_2CH_2\overset{+}{N}HMe_2$, X = Cl



(**3**)



(**4**)

Results and Discussion

The molecular structure of [Pd(cpzH)Cl_3] is shown in the Figure and many of the structural features are similar to those found in the related promethazine complex (**1**). The most pertinent aspects of the geometry of the two complexes are compared in Table 1. The protonated cpz ligand is found to be sulphur-bonded to palladium such that the $PdCl_3$ unit occupies a pseudo-axial position on the heterocycle. The tilt of the ligand [Pd–S(5)–N(10), 92.9(5)°] is comparable to that found in (**1**) and would seem to reflect the use of sp^3 orbitals by sulphur in its interaction with palladium. The C_6 rings are planar and inclined at 44.5° to each other in a butterfly arrangement. While the overall arrangement of the fused ring system is similar to that found in cpzH·Cl,[6] the conformations adopted by the side chain in the complexed and uncomplexed ligand are quite different. Thus the *trans* arrangement of the N(10)–C(15)–C(16)–C(17) chain present in cpzH·Cl is replaced, upon co-ordination, by a *gauche* conformation such that the N(10)–C(15)–C(16)–C(17) torsion angle is reduced from 179.0° to 62.5°. This arrangement, together with the orientation of the ligand with respect to the $PdCl_3S$ plane gives rise to the scorpion conformation as found in (**1**). However, replacement of the isopropyl chain in (**1**) by a propyl chain in (**2**) results in the quaternary nitrogen, N(18), being further from the $PdCl_3S$ plane [N ··· Cl(2) 3.17 Å in (**1**),

† Part 1 is ref. 4.

‡ *Supplementary data available* (No. SUP 56531, 3 pp.): H-atom co-ordinates, other bond lengths and angles, thermal parameters. See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1986, Issue 1, pp. xvii—xx. Structure factors are available from the editorial office.

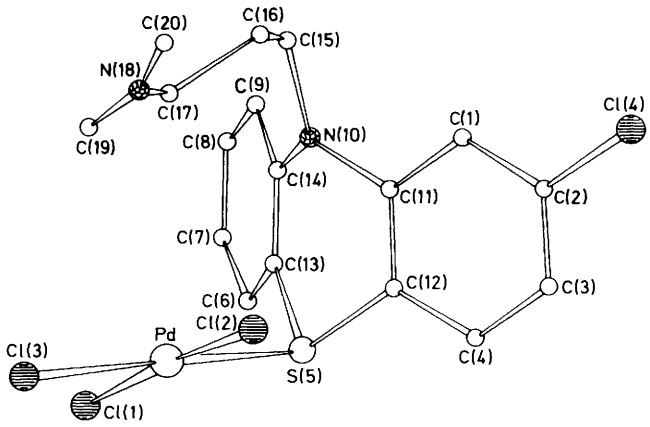


Figure. Molecular structure for $[Pd(cpzH)Cl_3]$, hydrogen atoms have been omitted for clarity

3.74 Å in (**2**)]. While the intramolecular $N^+H \cdots Cl$ interaction is thereby weakened, the molecules are arranged in pairs about centres of symmetry such that N(18) is involved in both intra- and inter-molecular interactions [N(18) · · · Cl(1′) 3.54 Å].

Carbon-13 n.m.r. data for cpzH·Cl and the complexes $[M(cpzH)Cl_3]$ (M = Pd or Pt) are given in Table 2. While the observed ^{195}Pt–^{13}C coupling for C(4) and C(6) confirms the drug to be sulphur-bonded to the MCl_3^- unit, the values for the co-ordination chemical shifts are more difficult to understand. The withdrawal of electron density from the ring system upon complexation would be expected to lead to increased carbonium ion character on the carbon atoms adjacent to sulphur [C(12) and C(13)] and a consequent positive value for δΔ. The large and negative δΔ values observed for the carbons is, at first sight, difficult to rationalise with the suggested mode of co-ordination. However, similarly negative values for δΔ have been observed for the carbons adjacent to nitrogen upon protonation of the heteroatom in pyridine and aniline.[7] Thus the δΔ values found for the complex may be rationalised providing that the electron withdrawal *via* protonation of nitrogen may be considered to be analogous to withdrawal of electrons *via* the ring sulphur upon co-ordination. The presence of back donation between the central metal and sulphur coupled with the further possible delocalisation of electron density throughout the C_6 rings may afford an alternative or contributory explanation.

Hydrogen n.m.r. data for cpzH·Cl and $[Pd(cpzH)Cl_3]$ are summarised in Table 3. It can be seen that all the signals from the side chain move to lower frequency upon co-ordination. The magnitude of the shifts seems to preclude them being associated purely with the change in charge density on N(18) and may, in part, be due to the proximity of the side chain to the $PdCl_3S$ plane. A similar effect has been reported[8] in the complex $[Pd\{C(Bu^t)=CHCH=CCl(Bu^t)\}Cl\{MeSCH_2CH_2SMe\}]$, where a δΔ of 2 p.p.m. for one of the methine protons has been attributed to its proximity to the Pd^{II}. Perhaps the most significant feature of the ^1H n.m.r. spectra are the apparent triplets associated with the C(15) and C(17) protons which, on closer inspection, are due to AA′BB′ coupling rather than a first-order process. The *gauche* and *trans* isomer populations have been calculated[9] and are given in Table 3. It can be seen that in aprotic hydrophilic solvents such as *NN*-dimethylformamide (dmf) and dimethyl sulphoxide (dmso) the conformation of the side chain in cpzH·Cl is quite random. However, upon co-ordination a conformation whereby the N(10)–C(15)–C(16)–C(17) and C(15)–C(16)–C(17)–N(18) groups are *gauche* and *trans* respectively is strongly preferred. It therefore appears that

Table 1. Comparison of structural features for the complexes $[Pd(LH)Cl_3]$ [L = pmz (**1**) or cpz (**2**)]. Estimated standard deviations are given in parentheses

		(**1**)	(**2**)
(*a*)	Bond distances (Å)		
	Pd–Cl(1)	2.292(3)	2.298(3)
	Pd–Cl(2)	2.283(3)	2.295(6)
	Pd–Cl(3)	2.328(2)	2.310(4)
	Pd–S(5)	2.296(2)	2.308(4)
	S(5)–C(12)	1.758(10)	1.708(16)
	S(5)–C(13)	1.771(11)	1.816(22)
	C(1)–C(11)	1.387(15)	1.40(3)
	C(1)–C(2)	1.386(18)	1.43(3)
	C(2)–C(3)	1.400(19)	1.40(3)
	C(3)–C(4)	1.367(18)	1.39(3)
	C(4)–C(12)	1.375(17)	1.42(3)
	C(11)–C(12)	1.418(12)	1.41(3)
	C(6)–C(7)	1.367(18)	1.39(4)
	C(7)–C(8)	1.386(18)	1.38(4)
	C(8)–C(9)	1.372(25)	1.37(3)
	C(9)–C(14)	1.389(15)	1.42(3)
	C(13)–C(14)	1.397(13)	1.35(3)
	C(6)–C(13)	1.397(16)	1.39(3)
	C(11)–N(10)	1.396(15)	1.44(3)
	C(14)–N(10)	1.418(13)	1.40(2)
	N(10)–C(15)	1.515(12)	1.47(2)
(*b*)	Bond angles (°)		
	Cl(1)–Pd–Cl(2)	173.8(1)	175.5(2)
	Cl(1)–Pd–Cl(3)	91.0(1)	88.7(2)
	Cl(1)–Pd–S(5)	86.4(1)	86.3(2)
	Cl(2)–Pd–Cl(3)	90.6(1)	91.6(2)
	Cl(2)–Pd–S(5)	92.2(1)	93.4(2)
	Cl(3)–Pd–S(5)	176.2(1)	175.0(2)
	Pd–S(5)–C(12)	110.9(3)	112.7(4)
	Pd–S(5)–C(13)	106.1(3)	107.0(5)
	C(12)–S(5)–C(13)	97.3(5)	96.6(9)
	S(5)–C(12)–C(4)	118.9(8)	120(1)
	S(5)–C(12)–C(11)	119.8(8)	121(1)
	C(4)–C(12)–C(11)	121.6(10)	119(1)
	C(3)–C(4)–C(12)	120.7(11)	120(1)
	C(2)–C(3)–C(4)	119.5(12)	121(1)
	C(1)–C(2)–C(3)	119.7(11)	120(1)
	C(2)–C(1)–C(11)	120.0(10)	119(1)
	N(10)–C(11)–C(12)	119.7(9)	120(1)
	C(11)–N(10)–C(14)	117.7(7)	117(1)
	C(1)–C(11)–C(12)	116.4(11)	121(1)
	C(11)–N(10)–C(15)	119.3(8)	121(1)
	N(10)–C(14)–C(9)	123.0(8)	122(1)
	N(10)–C(14)–C(13)	119.5(9)	120(1)
	C(9)–C(14)–C(13)	117.6(9)	118(1)
	C(8)–C(9)–C(14)	120.4(10)	119(1)
	C(7)–C(8)–C(9)	121.8(13)	121(1)
	C(6)–C(7)–C(8)	118.8(12)	121(1)
	C(7)–C(6)–C(13)	119.9(10)	117(1)
	C(6)–C(13)–S(5)	119.0(8)	115(1)
	C(6)–C(13)–C(14)	121.4(10)	124(1)
	S(5)–C(13)–C(14)	119.6(8)	121(1)
(*c*)	Planarity of the fused ring system and its orientation with respect to the $PdCl_3S$ plane		
	Tilt (°)		
	Pd–S(5)–N(10)	90.1(3)	92.9(5)
	Twist (°)		
	N(10)–S(5)–Pd–Cl(2) torsion angle	68.5(7)	−73.4(11)
	Inclination of C_6 rings (°)	41.3(11)	44.5(16)

Table 2. Carbon-13 n.m.r. signals (δ/p.p.m.) of cpzH·Cl and the complexes $[M(cpzH)Cl_3]$ (M = Pd or Pt)[a] in $[^2H_6]$dmf

Atom	cpzH·Cl	$[M(cpzH)Cl_3]$	δΔ[b]
C(11)	147.1	147.9	+0.8
C(14)	144.6	145.7	+1.0
C(4)	128.7	133.0[c]	+2.4
C(6)	128.5	132.0[c]	+3.5
C(2)	133.6	136.0	+2.4
C(8)	127.9	130.7	+2.8
C(3)	123.8	123.1	−0.7
C(7)	123.0	122.4	−0.6
C(12)	123.5	114.6	−8.9
C(13)	124.7	116.0	−8.7
C(1)	117.2	117.4	+0.2
C(9)	116.6	117.0	+0.4
C(15)	45.1	44.1	−0.9
C(16)	22.3	23.2	+0.9
C(17)	54.9	56.4	+1.5
C(19)	42.3	43.5	+1.2
C(20)	42.3	43.5	+1.2

[a] The ^{13}C n.m.r. data are for $[Pd(cpzH)Cl_3]$ but, within the limits of experimental error (±0.1 Hz), no difference is observed between the spectra for the Pd and that for the Pt complexes (but see *c*). [b] δΔ is defined as positive if the change in shift is from low to high frequency; thus carbon atoms having increased carbonium ion character show positive δΔ. [c] For M = Pt C(4), C(6) signals have satellites at 133.6, 132.5 and 132.2, 131.5 respectively and are assigned ^{195}Pt–^{13}C coupling of 20.6 and 14.4 Hz.

Table 3. Hydrogen-1 n.m.r. signals (δ/p.p.m.) and conformational analysis of the N(10) side chain

^1H N.m.r. data[a]	C(15)	C(16)	C(17)	C(19), C(20)
cpzH·Cl	4.16t	2.28m	3.35t	2.73s
$[Pd(cpzH)Cl_3]$	4.35t	2.45m	4.02t	3.02s

Conformational analysis[b]

Compound	Fragment	Solvent: $[^2H_6]$dmf *N*	$[^2H_6]$dmf *trans* (%)	$[^2H_6]$dmso[c] *N*	$[^2H_6]$dmso[c] *trans* (%)
cpzH·Cl	C(15)–C(16)	14.7	41	13.9	39
	C(16)–C(17)	15.5	67	15.5	67
$[Pd(cpzH)Cl_3]$	C(15)–C(16)	11.5	0		
	C(16)–C(17)	16.3	81		

[a] s = singlet, m = multiplet, t = triplet (but see text). The signals from the side chain protons were assigned using spin decoupling. The signals from the aryl ring protons were not resolvable. [b] $N = J_{AB} + J_{AB'}$. $[Pd(cpzH)Cl_3]$ decomposes in dmso. [c] Data from E. Ragg, G. Fronza, and R. Monmdelli, *J. Chem. Soc., Perkin Trans. 2*, 1982, 1586.

the scorpion conformation present in the solid state also predominates in solution.

It has been postulated that the activity and mode of action of phenothiazine drugs is strongly related to the conformation adopted by the N(10) side chain, with sedative, anticholinergic and antihistamine properties being postulated for three different side-chain conformations.

The scorpion conformation has been postulated as that responsible for the H_1 antihistamine action of phenothiazine drugs.[10] Although we have previously shown that such a conformation is adopted in the solid state,[4] the present work is the first evidence that such a conformation exists in solution (in aprotic hydrophilic solvents) as well as the solid state. It seems likely that the H_1 antihistamine activity of the phenothiazine drugs is dependent, in part, upon the presence of a suitable side chain at N(10) which is capable of undergoing the conformational changes reported in the present paper.

Table 4. Final atomic parameters for non-hydrogen atoms (× 10^5 for Pd; × 10^4 for other atoms) with estimated standard deviations in parentheses

Atom	*x*	*y*	*z*
Pd	35 921(4)	37 616(16)	−513(9)
Cl(1)	3 557(2)	5 722(5)	752(4)
Cl(2)	3 668(2)	1 902(7)	−887(3)
Cl(3)	2 864(2)	4 516(7)	−1 288(3)
Cl(4)	4 920(3)	−3 044(8)	1 138(5)
S(5)	4 316(2)	3 186(5)	1 251(3)
C(1)	4 356(5)	−1 041(21)	1 405(9)
C(2)	4 763(6)	−1 366(24)	1 193(11)
C(3)	5 030(6)	−270(23)	1 036(11)
C(4)	4 899(6)	1 135(25)	1 058(10)
C(6)	4 262(7)	4 181(22)	2 776(13)
C(7)	4 126(7)	4 101(32)	3 492(15)
C(8)	3 898(7)	2 914(31)	3 616(12)
C(9)	3 793(6)	1 784(24)	3 035(12)
C(11)	4 235(6)	374(18)	1 452(10)
C(12)	4 491(6)	1 472(16)	1 251(8)
C(13)	4 147(6)	3 018(21)	2 195(11)
C(14)	3 912(5)	1 847(19)	2 281(11)
N(10)	3 835(5)	710(16)	1 685(10)
C(15)	3 460(5)	−358(21)	1 602(13)
C(16)	3 151(6)	−874(21)	590(15)
C(17)	2 852(6)	341(21)	−32(13)
N(18)	2 555(9)	−36(25)	−971(14)
C(19)	2 249(8)	1 114(27)	−1 575(13)
C(20)	2 568(12)	−1 306(36)	−1 386(16)

Experimental

The syntheses of the complexes discussed in this work have been described before.[4] Recrystallisation from dmf gave crystals suitable for single-crystal *X*-ray studies.

Crystal Data.—$C_{17}H_{20}Cl_4N_2PdS$, M = 532.6, monoclinic, space group $C2/c$, a = 29.757(9), b = 9.487(4), c = 16.184(6) Å, β = 116.5(1)°, U = 4 088.2 Å^3, λ = 0.710 69 Å, D_m = 1.71, Z = 8, D_c = 1.73 Mg m^{-3}. Crystal dimensions (distances to faces from centre): 0.185 (100, 100) × 0.160 (010, 010) × 0.075 mm (001, 001), μ(Mo-K_α) = 2.30 mm^{-1}.

Data Collection and Processing.—Stoe Stadi 2 two-circle diffractometer, ω axis coincident with *b*, background–ω scan–background mode, graphite-monochromated Mo-K_α radiation; 3 122 unique reflections measured, 1 277 with $I > 3.0\sigma(I)$ and used in *X*-ray analysis, Lorentz and polarisation corrections applied.

Structure Analysis and Refinement.—Patterson and normal heavy-atom procedures. Full-matrix least-squares refinement (two blocks for final, anisotropic cycles) with all non-hydrogen atoms anisotropic and phenyl-type hydrogens in calculated positions with one, overall, refined U_{iso} [0.069(20) Å^2]. The weighting scheme $w = 1.000/[\sigma^2(F_o) + 0.0044(F_o)^2]$, final R and R' values 0.056 and 0.060. Scattering factors were taken from ref. 11. The apparent planarity of N(18) with C(17), C(19), and C(20) and high thermal motion of N(18) in a direction perpendicular to the NC_3 plane indicate N(18) to be disordered. Final atomic parameters for non-hydrogen atoms are given in

Table 4. All calculations were performed on an IBM 4341 computer using the SHELX computing package.[12]

The n.m.r. spectra were recorded as saturated solutions of the compounds in $[^2H_6]$dmf at 20 °C, on a Bruker WH 400 instrument at 400 MHz.

Acknowledgements

We thank the S.E.R.C. for computing facilities, 400-MHz n.m.r. spectra and an equipment grant (to I. W. N.), Dr. B. Peart and Dr. B. E. Mann for helpful discussions, May and Baker and Sandoz plc for gifts of the drugs.

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Received 29*th July* 1985; *Paper* 5/1302