Metal Complexes of Benzodiazepines. Part 1. Synthesis, Crystal Structure, and Characterization in Solid and Solution of *trans*-Dichloro(7,8-dichloro-2,3-dihydro-2,2,4-trimethyl-1*H*-1,5-benzodiazepine)(tri-n-propylphosphine)-palladium(II) *

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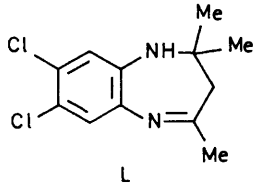
The complex, $[PdCl_2L(PPr^n_3)]$, which to our knowledge is the first example of a metal complex of 1,5-benzodiazepines, is easily obtained by cleavage of the bridged complex $[Pd_2Cl_4(PPr^n_3)_2]$ with 7,8-dichloro-2,3-dihydro-2,2,4-trimethyl-1*H*-1,5-benzodiazepine (L) in CH_2Cl_2. Proton and ^{13}C n.m.r. spectra in $CDCl_3$ of the complex suggest that the ligand is co-ordinated through N(5). Single-crystal analysis confirms that the benzodiazepine is indeed co-ordinated through this nitrogen atom and the geometry around palladium is square planar with the two chlorides *trans* to each other. Co-ordination affects bond distances and angles without changing the boat conformation of the ligand.

Benzodiazepines are interesting compounds because of their pharmacological properties.[1] Many members of this family are, in fact, nowadays widely used as tranquilizing and anticonvulsant agents. Although the first benzodiazepine was introduced as a drug nearly 30 years ago[2] the research in this area is still very active and is directed toward the synthesis of compounds of enhanced pharmacological activity. The complexation of benzodiazepines with metals, through the nitrogen atoms of the diazepine ring, can alter their properties as drugs by changing the stereochemistry and the electronic properties. In this sense the study of the interactions of benzodiazepines with metals can provide useful information in elucidating the relation between structure and pharmacological activity of this series of compounds. Nonetheless up to date very few complexes of benzodiazepines have been characterized unambiguously. In addition all these studies refer to 1,4-benzodiazepines.[3] We have recently started to study the interaction between benzodiazepines and metals by using a series of 1,5-benzodiazepines previously investigated by some of us,[4] mainly with reference to their synthesis and stereochemistry.

In this paper we report the properties in solid and solution of the complex *trans*-$[PdCl_2L(PPr^n_3)]$ where L represents 7,8-dichloro-2,3-dihydro-2,2,4-trimethyl-1*H*-1,5-benzodiazepine.[4f,5] The substance, which is to our knowledge the first example of a metal complex of 1,5-benzodiazepines, has been obtained by cleavage of the bridged complex $[Pd_2Cl_4(PPr^n_3)_2]$ with the ligand and has been characterized in $CDCl_3$ solution by ^1H and ^{13}C n.m.r. spectroscopy and in the solid by *X*-ray diffraction.

Experimental

The complex was prepared by cleavage of the chloro-bridged complex $[Pd_2Cl_4(PPr^n_3)_2]$[6] in dichloromethane. To this end $[Pd_2Cl_4(PPr^n_3)_2]$ was dissolved in the minimum amount of solvent and the benzodiazepine added in a ratio of 1:2. The solution was left under magnetic stirring for 0.5 h and then an equal volume of hexane was added. Slow evaporation of the solvent gave the complex in the form of yellow crystals suitable for *X*-ray analysis.



L

The preparation of 7,8-dichloro-2,3-dihydro-2,2,4-trimethyl-1*H*-1,5-benzodiazepine has already been reported.[5] All the solvents used were of spectroscopic grade.

Conductivity measurements were performed with a Radiometer CDM 3 conductivity bridge. The electronic spectra were recorded by means of a model 8452A Hewlett-Packard diode-array spectrophotometer, n.m.r. spectra on a Varian FT 80 instrument.

X-Ray Data Collection and Structure Refinement.—Diffraction data were collected on an Enraf-Nonius CAD4 four-circle diffractometer using graphite-monochromated Mo-K_α (λ = 0.710 63 Å) radiation. Accurate unit-cell dimensions and crystal-orientation matrices were obtained from least-squares refinement of 2θ, ω, χ, and ψ values of 25 strong reflections in the range $13 < 2\theta < 18°$. The compound crystallizes in the monoclinic space group $P2_1/n$, with a = 11.829(2), b = 18.654(3), c = 13.542(2) Å, β = 110.79(4)°, U = 2 793.6 Å^3, Z = 4, and D_c = 1.414 g cm^{-3}, M = 594.71, $F(000)$ = 1216. During the course of the intensity-data collection the crystal showed no loss in intensity. Lorentz and polarization corrections were applied to the intensity data. An empirical absorption correction (μ = 11.1 cm^{-1}) based on a set of ψ scans was applied. Relative transmission coefficients ranged from 0.960 to 1.00 (average 0.975). The structure was solved by using standard Patterson methods, successive least-squares refinements and Fourier difference maps. Anisotropic thermal

* *Supplementary data available:* see Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1990, Issue 1, pp. xix—xxii.

Table 1. Peak maxima in the electronic absorption spectra of the complex $[PdCl_2L(PPr^n_3)]$ in various solvents

Solvent	$\lambda_{max.}$/nm (10^{-3} ε/dm^3 mol^{-1} cm^{-1})		
CH_2Cl_2	332 (5.3),	276 (11),	232 (35)
Me_2SO	334 (4.1)		
$HCONMe_2$	340 (3.2)		
MeOH	338 (4.0),	224 (45)	

Table 2. N.m.r. parameters for 7,8-dichloro-2,3-dihydro-2,2,4-trimethyl-1*H*-1,5-benzodiazepine (L) and its complex *trans*-$[PdCl_2L(PPr^n_3)]$ in $CDCl_3$[a]

	Free ligand	Complex
H(1)	2.98 (br, s)	2.70 (br, s)
H(3)	2.27 (s)	2.29 (s)
H(6)	7.25 (s)	8.40 (s)
H(9)	6.84 (s)	6.88 (s)
2-Me_2	1.33 (s)	1.30 (s)
4-Me	2.35 (s)	3.00 (s)
$CH_2CH_2CH_3$		1.10 (t)
$CH_2CH_2CH_3$		1.78 (m)
C(2)	68.17	68.99
C(3)	45.14	46.84
C(4)	172.24	180.93
C(5a)	140.08	139.05
C(6)	128.59	129.24
C(7)	128.54[b]	128.29[b]
C(8)	132.09[b]	130.57[b]
C(9)	123.40	123.76
C(9a)	137.44	138.30
2-Me_2	30.40	30.32
4-Me	29.72	31.02
$CH_2CH_2CH_3$		16.65 (d)
$CH_2CH_2CH_3$		17.07 (d)
$CH_2CH_2CH_3$		25.47 (d)

[a] The ^1H (80 MHz) and ^{13}C (20 MHz) n.m.r. chemical shifts (δ) are reported with $SiMe_4$ as internal standard. The ^{13}C resonances of PPr^n_3 with all proton coupling removed are split into doublets by coupling with ^{31}P. [b] These attributions are interchangeable.

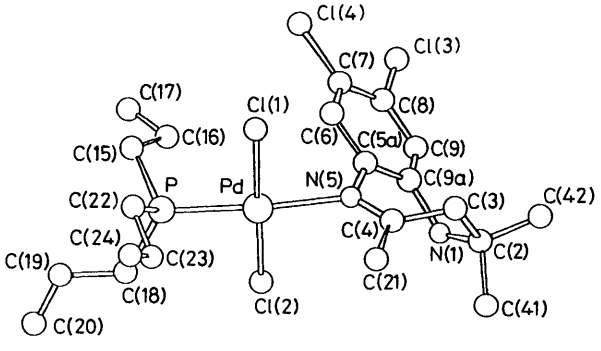


Figure 1. Molecular structure and numbering scheme for *trans*-$[PdCl_2L(PPr^n_3)]$

parameters were introduced for all non-hydrogen atoms. Hydrogen atoms were added at calculated positions and included in the structure-factor calculations with a common thermal parameter (U = 0.07 Å^2).

Of 4 450 independent reflections, measured with an ω—2θ scan technique in the range $3 < 2\theta < 50°$, 3 777 having $I > 3\sigma(I)$ were used to refine 281 parameters to final residuals of R = 0.031 and R' = 0.033. The weighting scheme used in the last refinement cycles was $w = 1.223/[\sigma^2(F_o) + 0.000\,355\,1F_o^2]$. Scattering factors for non-hydrogen atoms were taken from ref. 7 and for hydrogen atoms from ref. 8. Anomalous dispersion

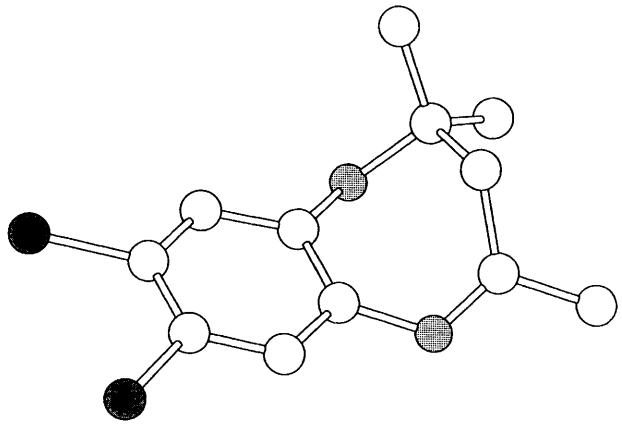


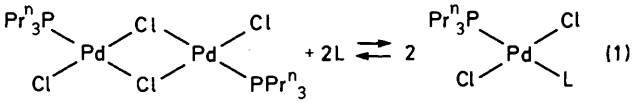
Figure 2. View of the benzodiazepine framework

corrections for Pd, Cl, and P atoms were taken from ref. 9. All calculations were performed with SHELX 76[10] and PARST[11] programs on the IBM 3090/120S computer at the Centro di Calcolo dell' Università di Messina.

Additional material available from the Cambridge Crystallographic Data Centre comprises H-atom co-ordinates and thermal parameters.

Results and Discussion

On addition of the benzodiazepine ligand to a CH_2Cl_2 solution of the complex in a ratio of 2:1 an immediate reaction takes place according to equation (1). The reaction product, which



can be obtained in an almost quantitative yield as a yellow crystalline solid by addition of diethyl ether to the solution, analyses for $C_{21}H_{35}N_2Cl_4PPd$. It is soluble and stable in most common organic solvents. Conductivity measurements in CH_2Cl_2, MeOH, dimethylformamide, Me_2SO, and $MeNO_2$ show that this complex is essentially a non-electrolyte. The electronic spectrum in CH_2Cl_2, characterized by two maxima at 232 and 332 nm, the one at lower wavelength having the higher intensity, closely resembles that of the free ligand ($\lambda_{max.}$ 232 and 328 nm). The absorption maxima and molar absorptivities in several solvents are listed in Table 1.

Proton and ^{13}C n.m.r. spectra both of the complex and of the free ligand have been recorded in $CDCl_3$. The parameters (Table 2) show that only the electronic environment of the nitrogen atom in position 5 of the ligand is substantially affected by co-ordination. Only the proton chemical shifts of 4-Me and H(6) are significantly different for the free and co-ordinated ligand. Likewise only the C(4) resonance of the co-ordinated ligand is substantially deshielded (to 180.93 p.p.m.) with respect to the free ligand. This strongly suggests that co-ordination to palladium occurs through N(5) of the ligand.

In order to gain conclusive evidence on the bonding mode of the ligand and to obtain structural information on the complex molecule we have performed a single-crystal determination of the substance. The crystal consists of a packing of monomeric molecules separated by normal van der Waals interaction. Final atomic co-ordinates are listed in Table 3, selected bond lengths and angles in Table 4. A view of the molecule and a representation of the benzodiazepine framework are shown respectively in Figures 1 and 2. The $[PdCl_2L(PPr^n_3)]$

Table 3. Fractional non-hydrogen co-ordinates for the complex $[PdCl_2L(PPr^n_3)]$

Atom	*x*	*y*	*z*
Pd	0.298 73(3)	−0.095 63(1)	0.709 97(2)
Cl(1)	0.117 0(1)	−0.155 94(6)	0.666 89(9)
Cl(2)	0.477 0(1)	−0.034 53(7)	0.749 27(9)
Cl(3)	0.464 0(1)	−0.233 05(7)	0.303 5(1)
Cl(4)	0.337 3(1)	−0.305 16(6)	0.450 8(1)
N(5)	0.246 7(3)	−0.055 3(2)	0.552 9(2)
C(4)	0.187 3(3)	0.002 1(2)	0.519 0(3)
C(21)	0.147 1(4)	0.047 3(2)	0.591 5(4)
C(3)	0.150 5(3)	0.024 4(2)	0.405 2(3)
C(2)	0.252 5(4)	0.057 8(2)	0.376 3(3)
N(1)	0.360 4(3)	0.011 1(2)	0.418 8(3)
C(41)	0.287 9(5)	0.131 2(3)	0.426 6(5)
C(42)	0.212 5(5)	0.063 1(4)	0.257 8(4)
C(9a)	0.346 7(3)	−0.063 4(2)	0.420 9(3)
C(9)	0.400 1(4)	−0.108 2(2)	0.366 1(3)
C(8)	0.397 6(4)	−0.181 1(2)	0.374 4(3)
C(7)	0.342 5(4)	−0.212 8(2)	0.438 0(3)
C(6)	0.290 9(4)	−0.170 0(2)	0.494 0(3)
C(5a)	0.292 1(3)	−0.096 1(2)	0.485 9(3)
P	0.360 7(1)	−0.148 60(6)	0.868 39(8)
C(15)	0.391 7(6)	−0.242 6(2)	0.850 3(4)
C(16)	0.485 2(6)	−0.251 1(3)	0.787 5(7)
C(17)	0.508 5(7)	−0.325 0(5)	0.770 7(7)
C(18)	0.498 7(4)	−0.114 3(2)	0.965 9(3)
C(19)	0.537 4(6)	−0.150 2(3)	1.073 2(4)
C(20)	0.655 4(6)	−0.124 1(4)	0.146 4(4)
C(22)	0.249 8(5)	−0.146 7(4)	0.933 5(4)
C(23)	0.216 0(8)	−0.073 6(6)	0.957 8(7)
C(24)	0.133(1)	−0.072(1)	1.007(1)

molecule displays a *trans* square-planar co-ordination around palladium. Nevertheless, the least-squares plane through the four atoms of the co-ordination sphere shows a lack of planarity with N(5) and P deviation by 0.064(7) and 0.059(3) Å, respectively; Cl(1) and Cl(2) are −0.061(3) and −0.062(3) Å on the opposite side, indicating a slight distortion towards the tetrahedral configuration around the metal atom which is −0.057(1) Å out of this plane. The two *trans* Pd–Cl(1) and Pd–Cl(2) bond distances, 2.310(1) and 2.287(1) Å respectively, although different, are in good agreement with values found in related compounds.[12,13] Such a difference may be determined by steric rather than electronic factors. The Cl(1)–Pd–Cl(2) bond angle deviates slightly from linearity being 178.75(5)°. The Pd–P distance of 2.236(1) Å is equal, within the estimated standard deviations (e.s.d.s), to that found in *trans*-$[PdCl_2(pap)(PPr^n_3)]$[13] (pap = pyridine-4-carbaldehyde phenylhydrazone) and similar to that found in *trans*-$[PdCl_2(ampy)(PEt_3)]$[14] (ampy = 2-amino-3-methylpyridine). In PPr^n_3 the structural features are as usual, including the large thermal parameters of the propyl chains. The ligand is co-ordinated to the palladium atom *via* its nitrogen atom N(5). The Pd–N(5) bond distance of 2.131(3) Å is relatively long (because of the large *trans* influence of PPr^n_3) and comparable with the value of 2.115(6) Å found in *trans*-$[PdCl_2(pap)(PPr^n_3)]$ but lower than that found in the *trans*-$[PdCl_2(ampy)(PEt_3)]$ [2.155(5) Å]. The P–Pd–N(5) angle deviates from linearity, being 173.75(9)°, in order to minimize repulsive contacts of Cl(1) and Cl(2) with the bulkier phosphine and benzodiazepine ligands [Cl(2) · · · C(18) 3.217, Cl(1) · · · C(6) 3.634 Å]. The seven-membered ring conformation of the co-ordinated ligand can be described approximately as a boat-shaped structure. The boat can be described in terms of the angles between the central plane, N(1)C(2)C(4)N(5) (where a large twist is present as can be seen from the corresponding torsion angle of 17.3°) and the

Table 4. Bond distances (Å) and angles (°)

Pd–Cl(1)	2.310(1)	Pd–Cl(2)	2.287(1)
Pd–N(5)	2.131(3)	Pd–P	2.236(1)
Cl(3)–C(8)	1.735(5)	Cl(4)–C(7)	1.734(4)
N(5)–C(4)	1.273(5)	N(5)–C(5a)	1.428(5)
C(4)–C(21)	1.495(7)	C(4)–C(3)	1.504(6)
C(3)–C(2)	1.527(7)	C(2)–N(1)	1.483(5)
C(2)–C(41)	1.521(6)	C(2)–C(42)	1.506(7)
N(1)–C(9a)	1.401(5)	C(9a)–C(9)	1.407(6)
C(9a)–C(5a)	1.403(6)	C(9)–C(8)	1.366(6)
C(8)–C(7)	1.385(7)	C(7)–C(6)	1.383(6)
C(6)–C(5a)	1.383(5)	P–C(15)	1.825(5)
P–C(18)	1.813(4)	P–C(22)	1.822(7)
C(15)–C(16)	1.62(1)	C(16)–C(17)	1.44(1)
C(18)–C(19)	1.515(7)	C(19)–C(20)	1.478(8)
C(22)–C(23)	1.49(1)	C(23)–C(24)	1.37(2)
N(5)–Pd–P	173.75(9)	Cl(2)–Pd–P	92.06(5)
Cl(2)–Pd–N(5)	88.38(9)	Cl(1)–Pd–P	89.19(5)
Cl(1)–Pd–N(5)	90.40(9)	Cl(1)–Pd–Cl(2)	178.75(5)
Pd–N(5)–C(5a)	113.9(2)	Pd–N(4)–C(4)	125.8(3)
C(4)–N(5)–C(5a)	120.2(3)	N(5)–C(4)–C(3)	121.6(3)
N(5)–C(4)–C(21)	120.0(4)	C(21)–C(4)–C(3)	118.3(3)
C(4)–C(3)–C(2)	114.1(3)	C(3)–C(2)–C(42)	108.7(4)
C(3)–C(2)–C(41)	111.7(4)	C(3)–C(2)–N(1)	108.1(3)
C(41)–C(2)–C(42)	110.6(4)	N(1)–C(2)–C(42)	110.7(4)
N(1)–C(2)–C(41)	107.0(4)	C(2)–N(1)–C(9a)	120.1(3)
N(1)–C(9a)–C(5a)	121.8(3)	N(1)–C(9a)–C(9)	120.1(3)
C(9)–C(9a)–C(5a)	117.8(3)	C(9a)–C(9)–C(8)	121.4(4)
Cl(3)–C(8)–C(9)	118.9(3)	C(9)–C(8)–C(7)	120.4(4)
Cl(3)–C(8)–C(7)	120.7(3)	Cl(4)–C(7)–C(8)	121.8(3)
C(8)–C(7)–C(6)	119.4(4)	Cl(4)–C(7)–C(6)	118.7(3)
C(7)–C(6)–C(5a)	120.9(4)	C(9a)–C(5a)–C(6)	120.2(3)
N(5)–C(5a)–C(6)	117.7(3)	N(5)–C(5a)–C(9a)	121.8(3)
Pd–P–C(22)	114.1(2)	Pd–P–C(18)	116.5(2)
Pd–P–C(15)	108.0(2)	C(18)–P–C(22)	104.9(2)
C(15)–P–C(22)	107.3(3)	C(15)–P–C(18)	105.3(2)
P–C(15)–C(16)	111.8(3)	C(15)–C(16)–C(17)	112.4(6)
P–C(18)–C(19)	115.5(4)	C(18)–C(19)–C(20)	112.9(5)
P–C(22)–C(23)	114.8(6)	C(22)–C(23)–C(24)	115.0(10)

stern and bow planes, consisting of atoms N(1), C(9a), C(5a), N(5) and C(2), C(3), C(4). The bow and stern angles with the central plane are 51.1 and 46.4°. While the first one is in the range found for free or co-ordinated benzodiazepine,[3f,15] the second is the highest reported at present. Such a conformation brings the C(3), bow atom into close contact with the stern atoms [C(3) · · · C(9a) 2.787; C(3) · · · C(5a) 2.785 Å] while the dihedral angle between the least-squares plane of the co-ordination sphere of the palladium atom and that of the aromatic ring C(5a)–C(9a) is 94.4°. The C(4)–N(5) formal double bond, 1.273(5), as well as the other structural features in this portion of molecule do not differ significantly from standard values. In conclusion, as reported for other complexes[3] of 1,4-benzodiazepines, co-ordination results in distortion of the ligand without, however, changing its boat conformation.

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