AN UNUSUAL *cis*-DICHLORO[17-(CYCLOBUTYLMETHYL)-3-METHOXYMORPHINAN-14-OL-*N*,*O*]PALLADIUM(II) COMPLEX

Alexandr JEGOROV[a,*], Hana PETŘÍČKOVÁ[b1], Bohumil KRATOCHVÍL[b2] and Ivana CÍSAŘOVÁ[c]

[a] *IVAX Pharmaceuticals, Research Unit, Branišovská 31, 370 05 České Budějovice, Czech Republic; e-mail: alexandr_jegorov@ivax-cz.com*

[b] *Department of Solid State Chemistry, Institute of Chemical Technology, Prague, Technická 5, 166 28 Prague 6, Czech Republic; e-mail:* [1] *hana.petrickova@zentiva.cz,* [2] *bohumil.kratochvil@vscht.cz*

[c] *Department of Inorganic Chemistry, Faculty of Science, Charles University, Hlavova 8, 128 43 Prague 2, Czech Republic; e-mail: cisarova@nature.cuni.cz*

Received November 11, 2005
Accepted February 11, 2006

Dedicated to Professor Jaroslav Podlaha on the occasion of his 70th birthday.

Synthesis and crystal structure of *cis*-dichloro[17-(cyclobutylmethyl)-3-methoxymorphinan-14-ol-*N*,*O*]palladium(II) methanol solvate is reported. The title complex crystallises in the triclinic *P*1 space group and is remarkable both by the number of independent molecules in the unit cell and the coordination sphere of palladium(II) formed by tertiary alcohol, tertiary amine and two chlorine atoms.

Keywords: Morphinan; Opioids; Palladium complexes; Alkaloids; Hemilabile complex; X-ray diffraction.

Hemilabile ligands have attracted much attention in the past thirty years because they were effectively utilised in coordination chemistry and homogenous catalysis[1]. The basic principle of hemilabile ligands is that they contain both strongly and weakly binding groups that coordinate to metal center and then a weaker bond is broken and offers thus a suitable place in the coordination sphere for coordination of substrate or intermediates. In fact, the concept of hemilable ligands stems from original Pearson's hard soft acid base (HSAB) principle[2]. Ligands were classified as type A (hard) or type B (soft) depending on whether they formed more stable complexes with type A (hard) or type B (soft) metals, Table I.

Palladium(II), the complex of which is described here, is classified as a typical type B (soft) metal. With a ligand having two donor atoms, three

doi:10.1135/cccc20060434

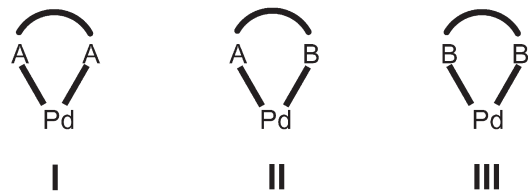
possible combinations exist (in addition to coordination by one donor only) (Scheme 1).

Whereas type III is typical of palladium(II) complexes, e.g., with bisphosphine ligands, type II represents the case of hemilabile ligand with B-donor typically a phosphine, and the A-donor, usually amine or some oxygen donor. The type I is not frequently found due to the expected low stability constant. Jana Podlahová and Jaroslav Podlaha have contributed significantly to the concept of "hemilabile" ligands not only by the synthesis of many ligands and their complexes[3–5] with appropriate metals of the Periodic Table and also by education of many students and breeding of a number of successful followers. Thus the above mentioned summary is particularly important for the understanding why the authors decided to prepare the complex of type I in order to pay tribute to Jana Podlahová and Jaroslav Podlaha.

The aim of the work was to prepare the palladium(II) complex with a morphinan alkaloid. If the coordination ability of such ligand whould be proved, it might represent, e.g., a readily accessible chiral ligand for homogeneous catalysis. The presence of strongly basic tertiary amino group, phenolic OH group, or occasionally some other O-donor group classify morphinan alkaloids as typical "hard" bases. However, the number of their coordination complexes isolated in pure state, is very limited. In contrast to

TABLE I
Classification of ligands

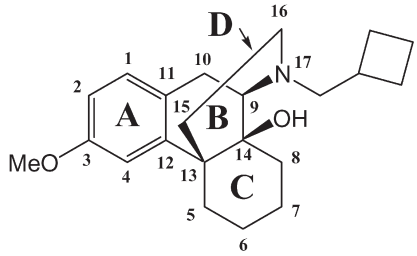
Tendency to complex with Type A (hard) metals	Tendency to complex with Type B (soft) metals
N >> P > As > Sb	N << P > As >Sb
O >> S > Se > Te	O << S < Se ~ Te
F > Cl > Br > I	F < Cl < Br < I



SCHEME 1

expectation, simple *N*-coordinated or phenolate complexes of "hard" metals have apparently never been described. On the other hand, ethynylcodeine complexes of Co (ref.[6]), η^2-platinum complex of morphine, and some η^3-allyl or η^4-diene complexes of various morphinans with Pd, Pt, Cr, Fe, or Mo have been reported[7–10]. Coordination ability of the free electron pair of nitrogen was demonstrated in Rh(I) complex with a *P*,*N*-coordinated phosphite derivative of codeine[11].

(–)-17-(Cyclobutylmethyl)-3-methoxymorphinan-14-ol (**1**) used in this work is the intermediate of an synthesis of butorphanol ((–)-17-(cyclobutylmethyl)morphinan-3,14-diol), a potent opioid agonist-antagonist. Butorphanol has been found to be effective in the management of postoperative pain, migraine, postepisiotomy pain and musculoskeletal trauma[12,13]. In terms of coordination chemistry, **1** possesses a vicinal tertiary alcohol–tertiary amine arrangement (Scheme 2).



SCHEME 2

EXPERIMENTAL

Preparation of Crystals

Single crystals of *cis*-dichloro[17-(cyclobutylmethyl)-3-methoxymorphinan-14-ol-*N*,*O*]palladium(II) complex (**2**) suitable for X-ray diffraction measurements were obtained by slow evaporation of a solution prepared by mixing of *trans*-bis(acetonitrile)dichloropalladium(II) (40 mg, 0.115 mmol) in methanol (3 ml) and **1** (50 mg, 0.147 mmol, IVAX Pharmaceuticals) at ambient temperature. Red crystals of the complex are prone to decomposition due to the desolvatation in air.

X-ray Structure Analysis[14–17]

$(C_{22}H_{31}Cl_2NO_2Pd)\cdot 1.44CH_3OH$, M = 564.67, triclinic system, space group $P1$, a = 8.9710(3) Å, b = 13.7460(5) Å, c = 16.0550(6) Å, α = 90.885(2)°, β = 97.432(2)°, γ = 102.813(2)°, V = 1912.3(1) Å^3, Z = 3, D_c = 1.473 g cm^{-3}, μ(MoKα) = 0.963 cm^{-1}, a block shape dark red crystal dimensions 0.4 × 0.34 × 0.26 mm. Data were collected at 150 K on a Nonius KappaCCD diffractometer with graphite-monochromated MoKα radiation (λ = 0.71073 Å). The structure was solved by direct methods and anisotropically refined by full-matrix least-squares on F to final R = 0.065 and R_w = 0.067 using 13 022 independent reflections (θ_{max} = 27.6131°; total

number of collected reflections 35 652; h(–11→11), k(–17→17), l(–20→20)) and 913 parameters with max/min residual density 2.94/–2.26 e Å^{-3}. No absorption and extinction corrections were applied. Hydrogen atoms linked to the carbon atoms were added from the expected geometry and their positions were not refined. Hydrogen atoms H1–H3 linked to the oxygen atoms of complex **2** were found from Fourier difference electron density map and their positions and isotropical thermal displacement parameters were refined. Hydrogen atoms H4–H9 linked to the oxygen atoms of MeOH were found from Fourier difference electron density map and their positions were refined. CCDC 289514 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

RESULTS AND DISCUSSION

In *cis*-dichloro[17-(cyclobutylmethyl)-3-methoxymorphinan-14-ol-*N*,*O*]palladium(II) complex (**2**), ligand **1** as a vicinal aminoalcohol coordinates to the square planar d^8-palladium(II) complex (Fig. 1). It is worth mentioning that the complex crystallises from methanol, which can compete with the

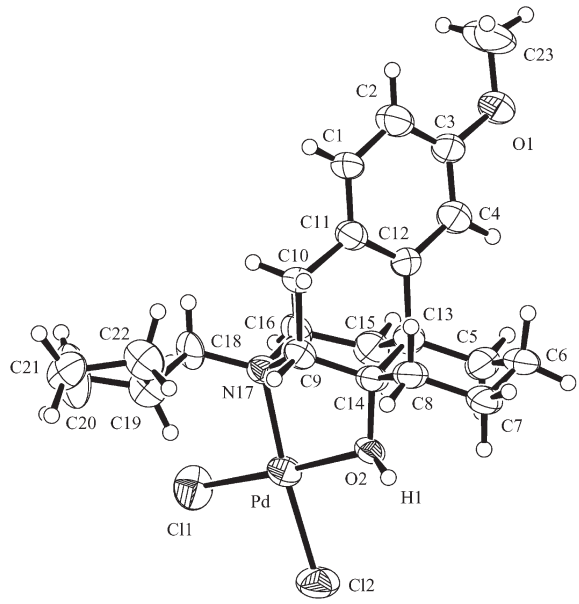


FIG. 1
ORTEP [17] drawing of molecule 1 of *cis*-dichloro[17-(cyclobutylmethyl)-3-methoxymorphinan-14-ol-*N*,*O*]palladium(II) methanol solvate with the numbering system used. Thermal ellipsoids are drawn at the 50% probability level. Hydrogen and solvent atoms were omitted for clarity

coordination of OH group of **1**. Whereas the crystal structures of several 2-aminoalcoholate complexes, such as those of Pt(IV), are known (CCDC database)[18,19], dichloro[1,3-bis(dimethylamino)propan-2-ol-*N*,*O*]nickel(II) was so far the only example of the didentate coordination of vicinal amino-alcohol. In addition, there are also two complexes of Fe(III) and Y(III) where this coordination mode takes part with multidentate ligands[20–22].

The complex **2** is remarkable for three independent molecules in the asymmetric unit cell (Table II). Since the morphinan skeleton is rather rigid, the number of independent molecules in asymmetric unit cell is usually 1 or 2; a higher number is rare[23]. Generally, the conformation of all three molecules in asymmetric unit cell resembles the characteristic T-shape of morphine-related compounds, e.g. ref.[23], with the piperidine ring D and ring C comprising the short arms of the T, and rings A and B forming the stalk of the T (Fig. 1). The aromatic ring A is nearly planar, rings B and C have an envelope conformation, and the piperidine ring D adopts the chair conformation. The three independent molecules differ in the opposite orientation of the 3-methoxy group and in the orientation of the cyclobutylmethyl group.

Usual bond distances were found for Pd–Cl (in the range 2.264(3)–2.312(3) Å) and Pd–N (2.069(8)–2.089(8) Å). There are only two X-ray structures in the CCDC database having the aliphatic alcohol group coordinated to palladium(II)[25,26], where the Pd–O bond distances 2.059 and 2.155 Å

TABLE II
Selected bond and space distances (in Å) and dihedral angles (in °) for complex **2**

Molecule 1		Molecule 2		Molecule 3	
Pd1–N17	2.069(7)	Pd2–N117	2.089(7)	Pd3–N217	2.072(6)
Pd1–O2	2.072(3)	Pd2–O4	2.042(4)	Pd3–O6	2.051(4)
Pd1–Cl1	2.304(2)	Pd2–Cl3	2.312(2)	Pd3–Cl5	2.287(2)
Pd1–Cl2	2.264(2)	Pd2–Cl4	2.276(2)	Pd3–Cl6	2.275(2)
N17···O2	2.755	N117···O4	2.727	N217···O6	2.725
Cl1···Cl2	3.247	Cl3···Cl4	3.293	Cl5···Cl6	3.277
Cl1–Pd1–Cl2	90.59(9)	Cl3–Pd2–Cl4	91.71(8)	Cl5–Pd3–Cl6	91.82(8)
N17–Pd1–O2	83.4(2)	N117–Pd2–O4	82.6(2)	N217–Pd3–O6	82.7(2)
O2–Pd1–Cl2	175.9(2)	O4–Pd2–Cl4	171.2(2)	O6–Pd3–Cl6	174.5(2)
N17–Pd1–Cl1	174.9(2)	N117–Pd2–Cl3	173.6(2)	N217–Pd3–Cl5	172.4(2)

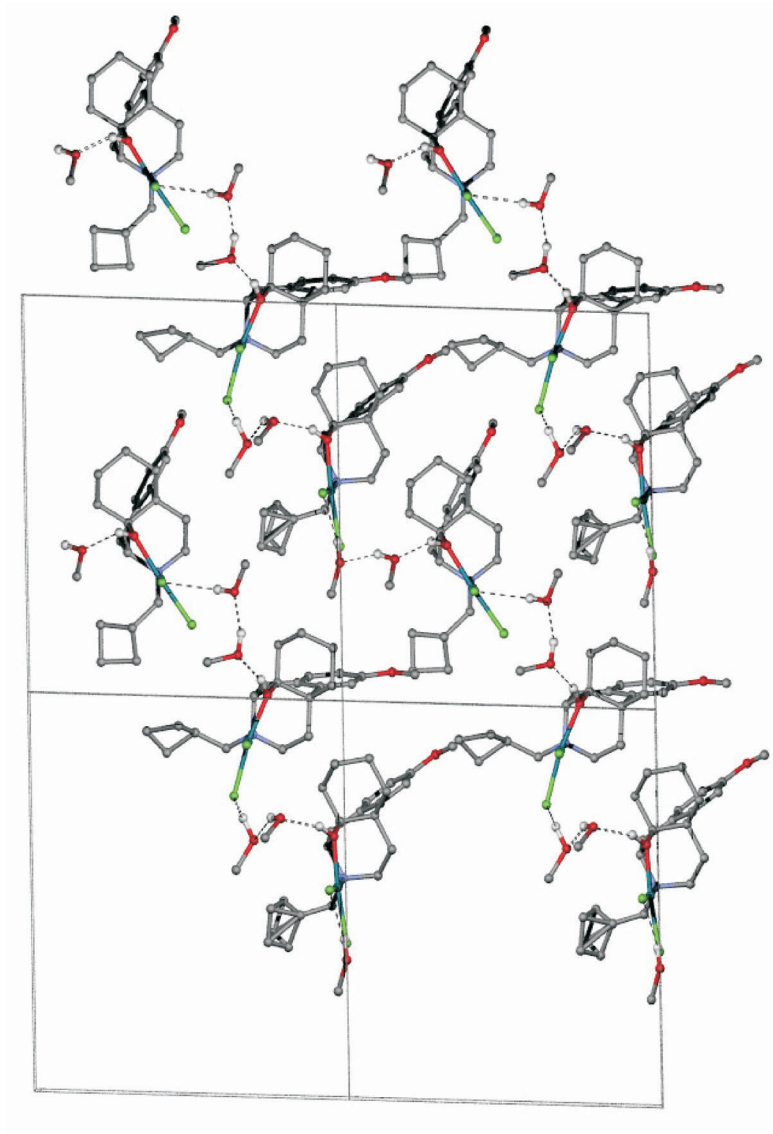


FIG. 2
Molecular packing of *cis*-dichloro[17-(cyclobutylmethyl)-3-methoxymorphinan-14-ol-*N*,*O*]palladium(II) methanol solvate in elementar lattice, viewing the $0 \rightarrow x$ direction

were found. The Pd–O bond distances in **2** (2.042(3)–2.073(5) Å) are slightly longer than those in alcoholate complexes[27,28] (about 2.0 Å). The N–Pd–O angles are unusually low (82.6(2)–83.4(2)°), facilitating the disorder of ideal square planar arrangement. However, a comparison with the complexes having the *cis* O–Pd–N arrangement deposited in CCDC database indicated that this disorder is common and can be found even in complexes, where

TABLE III
Summary of hydrogen bonds found in the crystal system of complex **2**

H-Bonds	Symmetry	D–H, Å	D···A, Å	H···A, Å	D–H···A, Å
O2–H1···O500	*x*, *y*, *z*	0.984(6)	2.615(9)	1.657(6)	162.9(4)
O4–H2···O501	*x*, *y*, *z*	0.971(5)	2.56(1)	1.644(8)	154.3(4)
O6–H3···O504	*x*, *y*, *z*	0.982(7)	2.58(1)	1.60(1)	173.1(5)
O500–H4···O502	*x*, *y*, *z*	0.996(6)	2.669(8)	1.778(6)	147.0(4)
O502–H9···Cl5	*x*, *y*, *z*	1.023(6)	3.072(7)	2.121(3)	153.8(3)
O501–H6···O503	*x*, *y*, *z*	1.003(7)	2.60(1)	1.66(1)	154.2(5)
O503–H5···Cl1	*x*, *y*, *z*	0.98(1)	3.23(1)	2.409(3)	140.0(7)
O504–H8···O505	*x*, *y*, *z*	1.05(1)	2.67(3)	1.68(2)	155(1)
O505–H7···Cl4	*x*, *y*, *z*	0.95(2)	2.70(3)	2.120(3)	118(1)

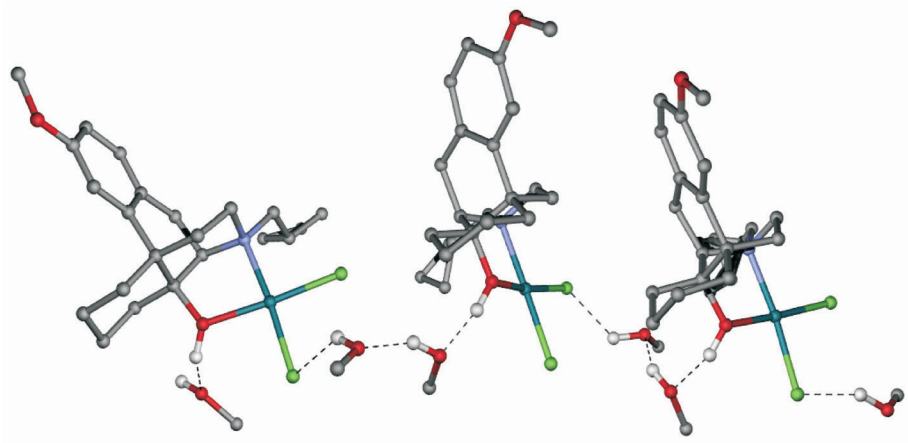


FIG. 3
Hydrogen bond system

nitrogen and oxygen donor atoms of the ligand are separated by more than one single bond; thus, it is not directly dictated by the fixed N–C–C–O geometry.

From the triclinic space group *P*1 it is evident, that the studied system is not well organised. No weak interactions either between three molecules in asymmetric unit and even in the whole crystal structure were observed. Six molecules of methanol solvent were found in the structure; three molecules have occupation 1, two molecules 1/2 and one molecule 1/3. Since the methanol molecules are built in the crystal structure through hydrogen bonds, the presence of methanol molecules in the structure is necessary for its stability (Figs 2 and 3). Table III summarises the hydrogen bonds between molecules of methanol and molecules of complex **2** or between molecules of methanol itself.

cis-Dichloro[17-(cyclobutylmethyl)-3-methoxymorphinan-14-ol-*N*,*O*]palladium(II) complex represents a new type of morphinan coordination complexes. The existence of such complex proved that morphinans are potential chiral ligands for homogeneous catalysis. The title complex is also remarkable for the number of molecules in the unit cell and crystal packing.

This study was partially supported by the research programme MSM 6046137302 of the Ministry of Education, Youth and Sports of the Czech Republic, and the project 204/04/0799 of the Grant Agency of the Czech Republic.

REFERENCES

1. Bader A., Lindner E.: *Coord. Chem. Rev.* **1991**, *108*, 27.
2. Pearson R. G.: *J. Am. Chem. Soc.* **1963**, *85*, 3533.
3. Podlahová J., Kratochvíl B., Podlaha J., Hašek J.: *J. Chem. Soc., Dalton Trans.* **1985**, 2393.
4. Podlaha J., Jegorov A., Buděšínský M., Hanuš V.: *Phosphorus Sulfur* **1988**, *37*, 87.
5. Jegorov A., Podlaha J., Podlahová J., Tureček F.: *J. Chem. Soc., Dalton Trans.* **1990**, 3259.
6. Kajtár M., Kajtár-Miklós J., Giacomelli G., Gaál G., Váradi G., Horváth I. T., Zucchi C., Pályi G.: *Tetrahedron: Asymmetry* **1995**, *6*, 2177.
7. Arzeno H. B., Barton D. H. R., Davies S. G., Lusinchi X., Meunier B. Pascard C.: *Nouv. J. Chim.* **1980**, *4*, 369.
8. Macquet J. P., Beuchamp A. L.: *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1985**, *41*, 860.
9. Kalinin V. N., Belyakova I. L., Derunov V. V., Park J. K., Schmidhammer H.: *Mendeleev Commun.* **1995**, 22.
10. Kalinin V. N., Derunov V. V., Maat L., Park J. K., Schmidhammer H.: *Mendeleev Commun.* **1995**, 222.
11. Gavrilov K. N., Korostylev A. V., Bondarev O. G., Polosuknin A. I., Davankov V. A.: *J. Organomet. Chem.* **1999**, *585*, 290.

12. Gillis J. C., Benfield P., Goa K. L.: *Drugs* **1995**, *50*, 157.
13. Cherny N. I.: *Drugs* **1996**, *51*, 713.
14. Sheldrick G. M.: *SHELXS86. Program for the Solution of Crystal Structures*. University of Göttingen, Göttingen 1986.
15. Altomare A., Burla M. C., Camalli M., Carrozzini G. L., Cascarano G. L., Giacovazzo C., Guagliardi A., Moliterni A. G. G., Polidori G., Rizzi R.: *J. Appl. Crystallogr.* **1999**, *32*, 115.
16. Watkin D. J., Prout C. K., Carruthers R. J., Betteridge P. W., Cooper R. I.: *Crystals*, Vol. 11. Chemical Crystallography Laboratory, University of Oxford, Oxford 2002.
17. Farrugia L. J.: *J. Appl. Crystallogr.* **1997**, *30*, 565.
18. Kuroda R., Neidle S., Ismail I. M., Sadler P. J.: *J. Chem. Soc., Dalton Trans.* **1983**, 823.
19. Galanski M., Zimmermann W., Baumgartner C., Keppler B. K.: *Eur. J. Inorg. Chem.* **2001**, 1145.
20. Hubert-Pfalzgraf L. G., Kessler V. G., Vaissermann J.: *Polyhedron* **1997**, *16*, 4197.
21. Pascaly M., Nazikkol Ç., Schweppe F., Wiedemann A., Zurlinden K., Krebs B.: *Z. Anorg. Allg. Chem.* **2000**, *626*, 50.
22. Chen Q., Chang Y. D., Zubieta J.: *Inorg. Chim. Acta* **1997**, *258*, 257.
23. Chudík M., Jegorov A., Petříčková H., Kratochvíl B., Císařová I.: *Z. Kristallogr.* **2005**, *220*, 1.
24. Jegorov A., Sobotík R., Pakhomova S., Ondráček J., Novotný J., Hušák M., Kratochvíl B.: *Collect. Czech. Chem. Commun.* **1994**, *59*, 1361.
25. Kiers N. H., Feringa B. L., Kooijman H., Spek A. L., van Leeuwen P. W. N. M.: *Chem. Commun.* **1992**, 1169.
26. Bhattacharyya P., Parr J., Slawin A. M. Z.: *J. Chem. Soc., Dalton Trans.* **1998**, 3609.
27. Bouquillon S., du Moulinet d'Hardemare A., Averbuch-Pouchot M.-P., Henin P., Muzart J., Durif A.: *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1999**, *55*, 2028.
28. Fild M., Thöne C., Tötös S.: *Eur. J. Inorg. Chem.* **2004**, 749.