Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Diisopropylphosphitocobalamin–acetone–water (1/3.48/7.56)

Susan M. Chemaly,[a]* Helder M. Marques[b] and Christopher B. Perry[b]

[a]Department of Pharmacy and Pharmacology, School of Therapeutic Sciences, University of the Witwatersrand, PO Wits, Johannesburg 2050, South Africa, and [b]Molecular Sciences Institute, School of Chemistry, University of the Witwatersrand, PO Wits, Johannesburg 2050, South Africa
Correspondence e-mail: chemalysm@therapy.wits.ac.za

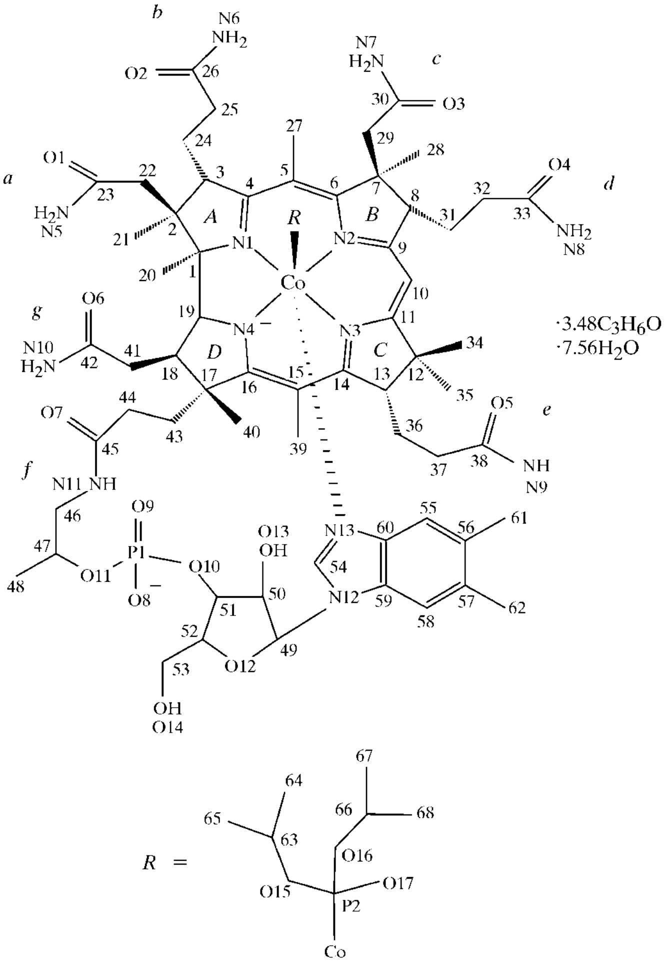
Received 20 November 2003
Accepted 6 January 2004
Online 31 January 2004

The diisopropylphosphite ligand in the title diisopropylphosphitocobalamin compound, $[Co(C_{68}H_{102}N_{13}O_{17}P_2)]\cdot 3.48C_3H_6O\cdot 7.56H_2O$, coordinates to the Co^{III} atom *via* its P atom. The crystal structure is isomorphous with that of other cobalamins that adopt packing type II [Gruber, Jogl, Klintschar & Kratky (1998). *Vitamin B_{12} and B_{12} Proteins*, edited by Kräutler, Arigoni & Golding, pp. 335–347. New York: Wiley–VCH], with a Co—P bond length [2.227 (1) Å] similar to that found in other phosphitocobalamins. The structural *trans* influence in cobalamins is discussed.

Comment

Cobalamins (Cbls; vitamin B_{12} derivatives; Fig. 1) contain a cobalt(III) ion that is coordinated to four N atoms from a delocalized corrin ring (in the equatorial plane) and one axial N atom from a 5,6-dimethylbenzimidazole ligand; the other axial ligand, *R* (in the upper or β-position), is variable, *e.g.* CN^- in vitamin B_{12} itself. The *trans* influence in these compounds refers to the Co—N bond length *trans* to *R*, *viz.* Co—N_{ax} (Glusker, 1982; Kratky & Kräutler, 1999). The X-ray crystal structures of dimethylphosphitoCbl, $[PO(OCH_3)_2\text{-}Cbl]$, hereafter DiMePC, and fluoromethylphosphitoCbl, $[PO(OCH_3)(F)Cbl]$, hereafter FMePC, have been reported previously (Kopf, 1986; Bieganowski *et al.*, 1980, 1981). We have determined the X-ray crystal structure of diisopropylphosphitoCbl, $[P(O)(O^iPr)_2Cbl]$, (I) (Fig. 1), in order to compare the structural *trans* influence of the $P[OCH(CH_3)_2]_2O^-$ ligand with that of the $P(OCH_3)_2O^-$ ion (in DiMePc) and to ascertain the effect of the sterically large $P[OCH(CH_3)_2]_2O^-$ ligand on anionic phosphitoCbls.

Compound (I) is isomorphous with the other cobalamins having packing type II (Gruber *et al.*, 1998). The ligand coordinates to the Co^{III} atom *via* atom P2, in agreement with the effect of the quadrupole moment of ^{59}Co on the ^{31}P NMR spectrum of (I) (Chemaly, 1991*a*). DiMePC and FMePC have been shown by electrophoresis to have a negative charge on the phosphite ligand (Bieganowski & Friedrich, 1980). It is assumed that this situation also occurs in (I), with the charge of +3 on the Co atom balanced by single negative charges on the corrin ring, the phosphite ligand and the phosphate group.



(I)

The bond lengths and angles of the diisopropylphosphite ligand are listed in Table 1. The geometry around atom P2 of the diisopropylphosphite ligand is close to trigonal pyramidal. The O15—P2—O16 bond angle is smaller than the O15/O16—P2—O17 bond angles, consistent with the presence of a negative charge on atom O17. Compared with the P2—O15/O16 bond lengths, the P2—O17 bond is short, suggesting that, notwithstanding the negative charge on atom O17, this bond has some double-bond character. These bond lengths and angles are similar to those of the $P(OCH_3)_2O^-$ ligand *trans* to N7-bonded 3-benzyladenine in a previously reported cobaloxime complex (Toscano *et al.*, 1981), but the P2—O and O—C bonds in (I) are slightly longer, and the P2—O—C bond angles are slightly smaller.

The ^1H NMR spectrum of (I) shows that the four CH_3 groups in the ligand are all in different environments (Chemaly, 1991*a*), and this fact is verified by the X-ray crystal structure. A bulky axial ligand in the β-position does not have

DOI: 10.1107/S0108270104000344

freedom of rotation about its bond to the Co^{III} atom; rotation is hindered by the steric sentinel substituents above the plane of the corrin ring [the C34 and C40 methyl groups, and the acetamide methylene groups of the *a* side chain (C22) and of the *c* side chain (C29) (Glusker, 1982)]. The diisopropylphosphite ligand exhibits many close contacts with the corrin ring, with 26 intramolecular distances shorter than 4 Å (three shorter than 3 Å). There are nearly twice as many close contacts in (I) as in DiMePC, presumably because the steric bulk of the isopropyl group is greater than that of the methyl group.

In contrast to DiMePC, which has packing type I (Gruber *et al.*, 1998) and in which intramolecular hydrogen bonding is observed between the amide group of the *c* side chain and one of the O atoms of the ligand (Kopf, 1986), the ligand in (I) does not form any hydrogen bonds, as the *c* side chain of the corrin ring points away from the ligand. The extensive network of intermolecular hydrogen bonds is very similar to that observed for SCNCbl and SeCNCbl (Garau *et al.*, 2003), which also have packing type II.

Table 2 shows the bond lengths and angles of the coordination sphere of Co^{III} and the pK_a value of the 5,6-dimethylbenzimidazole base for (I), DiMePC and FMePC. The Co—P bond length in (I) is similar to the Co—P bond length in DiMePC and also to the Co—P bond length for the cobaloxime containing the dimethylphosphite ligand (2.229 Å; Toscano *et al.*, 1981). Within the limits of experimental precision, the Co—N$_{ax}$ bond length in (I) is the same as the Co—N$_{ax}$ bond length in DiMePC, and hence the structural *trans* influence is similar. It is possible that the Co—P bond is slightly elongated as a result of steric strain in (I) and that this elongation compensates for the slightly greater inductive effect of the isopropyl group. FMePC has a shorter Co—N$_{ax}$ bond length than DiMePC and (I) because of the high electronegativity of the F atom. The P—Co—N$_{ax}$ bond angle in (I) is similar to those in DiMePC and FMePC. Both the structural *trans* influence and the thermodynamic *trans* influence [influence on the equilibrium constants of the ligand *trans* to *R*, *e.g.* pK_a for the 5,6-dimethylbenzimidazole base (Pratt, 1972)] increase with increasing σ-donor ability. The Co—N$_{ax}$ bond length in (I) is similar to the Co—N$_{ax}$ bond in methylcobalamin (2.162 Å; Randaccio *et al.*, 2000). Thus, the diisopropylphosphite ligand has a structural *trans* influence similar to that of methyl, confirming that diisopropylphosphite (as expected) is a good σ-donor ligand. It has been shown (Chemaly *et al.*, 1987; Chemaly, 1991*b*) that the thermodynamic *trans* influence order for anionic phosphite ligands in Cbls (pK_a values for protonation of the 5,6-dimethylbenzimidazole base) is R = P(OCH$_3$)$_2$O$^-$ < P(OCH$_2$CH$_3$)$_2$O$^-$ < P[OCH(CH$_3$)$_2$]$_2$O$^-$ and that this order is due to both electronic and steric influences of phosphite ligands. Thus, the thermodynamic *trans* influence is consistent with the structural *trans* influence.

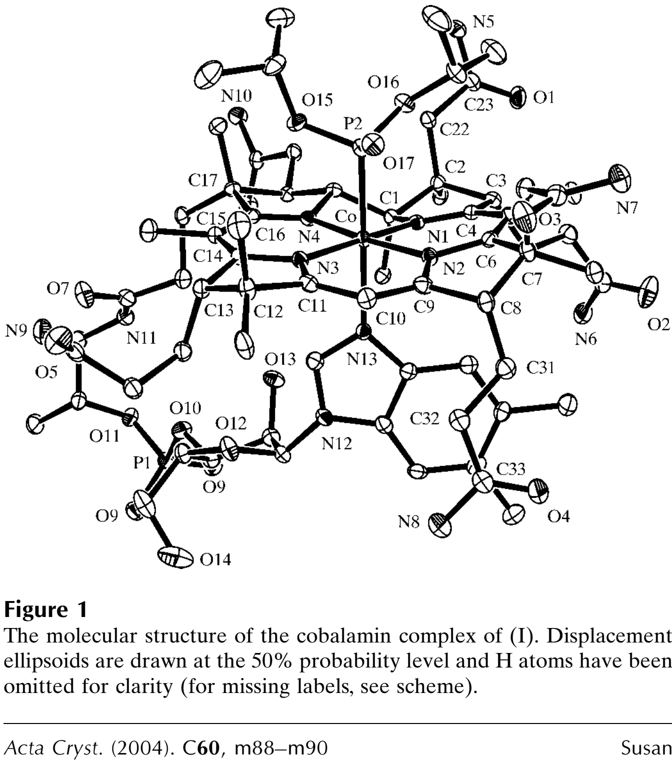


Figure 1
The molecular structure of the cobalamin complex of (I). Displacement ellipsoids are drawn at the 50% probability level and H atoms have been omitted for clarity (for missing labels, see scheme).

Experimental

Compound (I) was prepared and characterized as described previously (Chemaly, 1991*a*). Crystals suitable for X-ray analysis were grown by dissolving (I) (20 mg) in deionized water (0.30 ml) in a small glass vial and allowing acetone vapour to diffuse into the aqueous solution in a cold room (277 K). Crystals appeared after approximately one month. The selected crystal was removed from the mother liquor and mounted immediately in a stream of liquid nitrogen at 123 K.

Crystal data

[Co(C$_{68}$H$_{102}$N$_{13}$O$_{17}$P$_2$)]·3.48C$_3$H$_6$O·7.56H$_2$O
M_r = 1832.83
Orthorhombic, $P2_12_12_1$
a = 15.889 (5) Å
b = 22.070 (7) Å
c = 25.941 (8) Å
V = 9097 (5) Å^3
Z = 4
D_x = 1.338 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 1013 reflections
θ = 2.2–25.5°
μ = 0.31 mm^{-1}
T = 123 (2) K
Rectangular, red
0.38 × 0.14 × 0.12 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.892, T_{max} = 0.964
54 647 measured reflections
19 561 independent reflections
15 746 reflections with $I > 2\sigma(I)$
R_{int} = 0.047
θ_{max} = 27°
$h = -20 \rightarrow 20$
$k = -19 \rightarrow 28$
$l = -31 \rightarrow 33$

Refinement

Refinement on F^2
$R(F)$ = 0.041
$wR(F^2)$ = 0.095
S = 1.03
19 561 reflections
1144 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0468P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.82 e Å^{-3}
$\Delta\rho_{min}$ = −0.38 e Å^{-3}
Absolute structure: Flack (1983), 8794 Friedel pairs
Flack parameter = −0.003 (9)

Table 1
Selected geometric parameters (Å, °).

C63—O15	1.464 (3)	C66—C67	1.519 (4)
C63—C65	1.506 (4)	P2—O17	1.4823 (18)
C63—C64	1.513 (4)	P2—O15	1.6064 (19)
C66—O16	1.464 (3)	P2—O16	1.6213 (19)
C66—C68	1.502 (4)		

O15—C63—C65	107.5 (2)	O17—P2—O16	110.95 (10)
O15—C63—C64	108.9 (2)	O15—P2—O16	101.06 (10)
O16—C66—C68	107.2 (2)	C63—O15—P2	119.91 (16)
O16—C66—C67	111.0 (2)	C66—O16—P2	122.44 (16)
O17—P2—O15	113.11 (10)		

Table 2
Bond lengths (Å) of the coordination sphere of $\mathrm{Co^{III}}$ and pK_a values of the 5,6-dimethylbenzimidazole base for (I), DiMePC and FMePC.

Ligand	Co—P2	Co—$\mathrm{N_{ax}}$	P2—Co—$\mathrm{N_{ax}}$	pK_a
$\mathrm{P[OCH(CH_3)_2]_2O^-}$	2.2269 (10)	2.189 (2)	170.16 (6)	3.12†
$\mathrm{P(OCH_3)_2O^-}$‡	2.21 (2)	2.20 (1)	171	2.29§
$\mathrm{P(OCH_3)(F)O^-}$‡	2.18 (4)	2.09 (2)	174	1.6¶

† Chemaly (1991*b*). ‡ Kopf (1986). § Chemaly *et al.* (1987). ¶ Bieganowski & Friedrich (1980).

H atoms were positioned geometrically and allowed to refine on their respective parent atoms, with $U_{\rm iso}$(H) values of $1.2U_{\rm eq}$(C) [$1.5U_{\rm eq}$(C) for methyl groups]. The structure contains six ordered water and three ordered acetone molecules. In addition, there are three disordered water molecules (site occupancy 0.52) sharing a site with an acetone molecule (site occupancy 0.48). A FLAT restraint was used to ensure that the disordered acetone molecule remained planar. No elemental analyses have been carried out, as these have been found to be unreliable with respect to the water content. The occupancies of the acetone molecule and three water molecules sharing a site sum to unity, with the atomic displacement parameters still behaving reasonably well.

Data collection: *SMART-NT* (Bruker, 1998); cell refinement: *SMART-NT*; data reduction: *SAINT-Plus* (Bruker, 1999); program(s) used to solve structure: *SHELXTL* (Bruker, 1999); program(s) used to refine structure: *SHELXTL*; molecular graphics: *ORTEP*-3 *for Windows* (Farrugia, 1997); software used to prepare material for publication: *SHELXTL*.

This work was supported by the University Research Committee of the University of the Witwatersrand (SMC) and the National Research Foundation, Pretoria (HMM).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GA1038). Services for accessing these data are described at the back of the journal.

References

Bieganowski, R. & Friedrich, W. (1980). *Naturforscher*, **35b**, 1335–1340.

Bieganowski, R., Friedrich, W., Kopf, J. & von Deuten, K. (1980). Sixth European Crystallographic Meeting, Barcelona, Spain, Abstract 5-A-32.

Bieganowski, R., Kopf, J., Hinrichs, W. & von Deuten, K. (1981). *Acta Cryst.* A**37**, C-235.

Bruker (1998). *SMART-NT*. Version 5.050. Bruker AXS Inc., Madison, Wisconsin, USA.

Bruker (1999). *SAINT-Plus* (Version 6.02) and *SHELXTL* (Version 5.1). Bruker AXS Inc., Madison, Wisconsin, USA.

Chemaly, S. M. (1991*a*). *J. Inorg. Biochem.* **44**, 1–15.

Chemaly, S. M. (1991*b*). *J. Inorg. Biochem.* **44**, 17–25.

Chemaly, S. M., Betterton, E. A. & Pratt, J. M. (1987). *J. Chem. Soc. Dalton Trans.* pp. 761–767.

Farrugia, J. L. (1997). *J. Appl. Cryst.* **30**, 565.

Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.

Garau, G., Geremia, S., Marzilli, L. G., Nardin, G., Randaccio, L. & Tauzher, G. (2003). *Acta Cryst.* B**59**, 51–59.

Glusker, J. P. (1982). *B_{12}*, Vol. 1, edited by D. Dolphin, pp. 23–107. New York: Wiley–Interscience.

Gruber, K., Jogl, G., Klintschar, G. & Kratky, C. (1998). *Vitamin B_{12} and B_{12} Proteins*, edited by B. Kräutler, D. Arigoni & B. T. Golding, pp. 335–347. New York: Wiley–VCH.

Kopf, J. (1986). Habilitationschrift, University of Hamburg, Germany.

Kratky, C. & Kräutler, B. (1999). *Chemistry and Biochemistry of B_{12}*, edited by R. Banerjee, pp. 9–41. New York: Wiley–Interscience.

Pratt, J. M. (1972). In *Inorganic Chemistry of Vitamin B_{12}*. London: Academic Press.

Randaccio, L., Furlan, M., Geremia, S., Šlouf, M., Srnova, I. & Toffoli, D. (2000). *Inorg. Chem.* **39**, 3403–3413.

Sheldrick, G. M. (1996). *SADABS*. Version 2.03. University of Göttingen, Germany.

Toscano, P. J., Chiang, C. C., Kistenmacher, T. J. & Marzilli, L. G. (1981). *Inorg. Chem.* **20**, 1513–1519.