Cyanide-Bridged Vitamin B_{12}–Cisplatin Conjugates

Stefan Mundwiler, Bernhard Spingler, Philipp Kurz, Susanne Kunze, and Roger Alberto*[a]

Abstract: *cis*-$[PtCl(OH_2)(NH_3)_2]^+$, the monoactivated form of cisplatin, reacts with the cyano ligand of cobalt in vitamin B_{12} (cyanocobalamin) to form a Co–C≡N–Pt conjugate (**1**). Compound **1** is prepared in good yield directly in aqueous solution. The remaining chloride ligand of Pt^{II} is labile. It hydrolyzes slowly in aqueous solution and can be exchanged by stronger coordinating ligands, such as 9-methylguanine or 2′-deoxyguanosine, to yield vitamin B_{12}–nucleobase conjugates. X-ray structures of the vitamin B_{12}–cisplatin conjugate **1** as well as of the product with coordinated 9-methylguanine (**2**) are presented. The coordination geometry at Pt^{II} is almost perfectly square-planar. The structure of the cobalamin compound remains essentially unchanged when compared with the original B_{12} structure. The guanine moiety of compound **2** binds in a 45° angle to the cisplatin molecule and interacts with neighboring molecules by means of π stacking and hydrogen bonds.

Keywords: bioinorganic chemistry · bridging ligands · cobalamins · nucleobases · platinum

Introduction

In inorganic medicinal chemistry, cisplatin, *cis*-$[PtCl_2(NH_3)_2]$, and some of its derivatives are well established anticancer drugs.[1] They are potent, therapeutic pharmaceuticals but are also toxic to normal, healthy cells. The relatively large doses administered to a patient cause severe side effects. Enhanced selectivity by targeting cancer cells would be beneficial for the therapeutic index and the life quality of the patient. Site-specific uptake can be achieved by combining biologically active molecules with a chelating moiety for Pt^{II}. Some attempts have been described but, so far, have not shown the expected improvements.[2] A bioactive molecule that merits more attention is cyanocobalamin (vitamin B_{12}).[3,4] Fast-proliferating cancer cells are high B_{12} consumers. This very high demand makes B_{12} a potential "Trojan horse" for delivering therapeutic agents.[5,6,7,8]

Combining B_{12} and Pt^{II} compounds has been the subject of earlier studies. Wilson et al. described a B_{12} derivative with a diamino chelator covalently attached to the corrin ring yielding a cobinamide-$[N_2PtCl_2]$ unit.[9] This conjugate was expected to transport cisplatin into cancer cells by specific surface receptors for the cobalamin–*trans*-cobalamin protein complex. A more direct way is the use of native B_{12} as a ligand. Some metal complexes, for example, $[PdCl_4]^{2-}$ or a mixture of Pt^{II} and Pt^{IV} species, react quite strongly with cobalamins and demethylate methylcobalamin to aquo- or chlorocobalamin.[10,11] Interaction of the activated form of cisplatin, *cis*-$[Pt(NH_3)_2(OH_2)_2]^{2+}$, with alkyl cobalamins is milder. *cis*-$[Pt(NH_3)_2(OH_2)_2]^{2+}$ binds to N^3 of the dimethylbenzimidazole unit in the B_{12}-backloop, yielding an alkylcobalamin base-off form. It also binds to adenosylcobalamin at the N^7 or N^1 position of the nucleoside ligand.[12] As it is known that the least sensitive position in B_{12} for recognition by the B_{12} transport proteins is the β ligand, we aimed at introducing the *cis*-$\{Pt(NH_3)_2\}^{2+}$ moiety at this site.[13,14] In vitamin B_{12}, this ligand is a cyanide group. The cyanide is an artifact of the isolation process and is enzymatically replaced by an adenosyl or methyl group in the cell.[15,16,17] In addition to being a transporter for Pt^{II}, derivatized cyanides could, therefore, act as inhibitors for the enzymes involved in the alkylating reactions or act as inhibitors for gene regulation (riboswitches).[18] Although cyanide bridges between two metal centers belong to the most common motifs in inorganic chemistry, the cyanide ligand in vitamin B_{12} has not yet been exploited for derivatization; the only cyanide-bridged platinum–B_{12} species that has been described is the adduct of tetracyanoplatinate(II) to hydroxycobalamin.[19] We recently reported the coordination of Re^I and Tc^I com-

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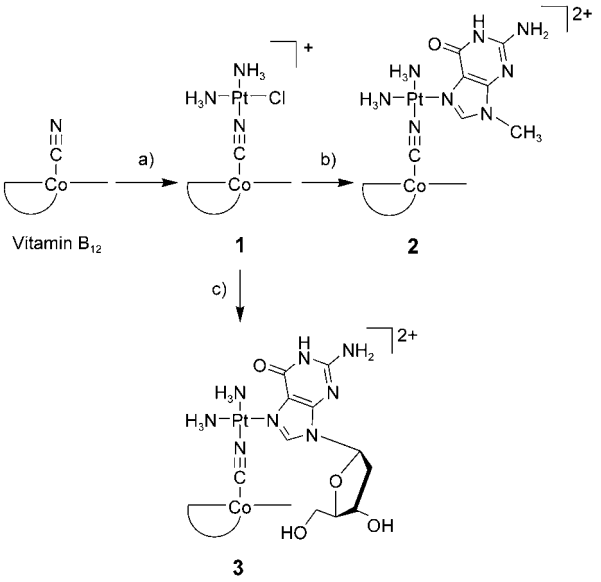
plexes directly to the cyanide in vitamin B_{12} and anticipated that other robust complexes would behave similarly.[20] We have now studied the direct interaction of monoactivated cisplatin with cyanocobalamin (vitamin B_{12}) to use B_{12} as a ligand and a targeting molecule for Pt^{II} at the same time (Scheme 1).



Scheme 1. Formation of conjugate **1** by reaction of monoactivated cisplatin with vitamin B_{12} and subsequent coordination of 9′-methylguanine or 2′-deoxyguanosine to Pt^{II} to give the conjugates **2** or **3**, respectively. Reagents and conditions: a) *cis*-$[PtCl(NH_3)_2(OH_2)]^+$, water, 16 h at 50 °C, 72 %; b) 9-methylguanine, 4 days at 50 °C, 79 %; c) 2′-deoxyguanosine, water, 4 days at 50 °C, 67 %.

Results and Discussion

The B_{12}–cisplatin conjugate **1** can be prepared in good yield by the reaction of vitamin B_{12} with *cis*-$[PtCl(NH_3)_2(OH_2)]^+$, the monoactivated form of cisplatin. It could be expected from previous work that the *cis*-$[PtCl(NH_3)_2(OH_2)]^+$ species would coordinate preferentially to displaced benzimidazole. We found a straightforward and almost exclusive coordination to the cyano group in B_{12}, resulting in a heterodinuclear complex, with {Co–C≡N–Pt} as a central, structural unit. The progress of the reaction was monitored by HPLC. The traces recorded during the reaction exhibited the formation of one single species in quantitative yield. The UV/Vis spectrum was almost identical to the one of native vitamin B_{12}. This confirms that benzimidazole is not displaced from the cobalt center. IR spectroscopy showed a ν_{CN} band at 2199 cm^{-1}, which is 55 cm^{-1} higher than that in vitamin B_{12}. Such shifts to higher energies are characteristic for bridging cyanides.[21] The ^{195}Pt NMR spectrum gave a broad peak at −2340 ppm, which is in the region where signals of cisplatin complexes bound to one purine base with one remaining chloride ligand are usually found.[22] The electrochemical properties of **1** are quite different from those of vitamin B_{12}. We found a partially reversible reduction wave at −515 mV (versus $Ag^+/AgCl$), which is at a significantly more positive potential than vitamin B_{12} (−670 mV). The increased oxidation power of the Co^{III} center is understood to be a consequence of the electron-withdrawing properties of the Pt^{II} center, competing for the electrons localized in the cyanide bridge.

It was possible to grow X-ray quality crystals of **1** to elucidate its structure. Surprisingly, it crystallized in the space group *P*1 and not, as is usual for cobalamin structures, in $P2_12_12_1$. Two monocationic B_{12}–platinum conjugates (**1**) and only one trifluoroacetate group could be found in the asymmetric unit. The cobalamin structure is essentially identical to that of native vitamin B_{12}. The platinum center is almost perfectly square-planar, with angles ranging from 89° to 92° (Figure 1). The bond lengths of the bridging cyanide and

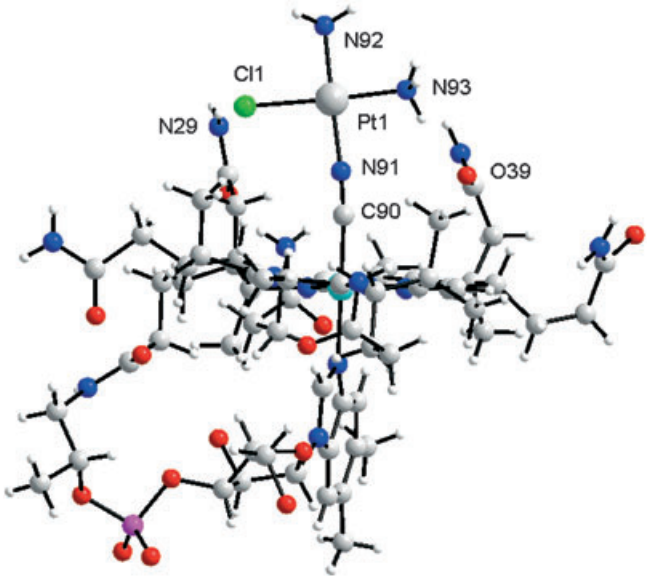


Figure 1. Depiction of one of the two cations found in the crystal structure of **1**.

from the cobalt atom to the cyanide carbon atom, in particular, are not significantly different to the corresponding values for vitamin B_{12} or an {Fe–CN–Pt} model complex.[23] There are two hydrogen bonds formed with the cisplatin moiety: one between the chloride ligand and N29, the nitrogen atom of the *a*-acetamide side chain of cobalamin, the other between N93, the amine ligand *trans* to the chloride, and O39, the oxygen atom of the *c*-acetamide side chain of cobalamin. The bond angles along the bridge are very close to 180° (Figure 2), unlike in the case of the Fe-CN-Pt angle.[23]

Knowledge about some basic physicochemical properties, such as stability in water and human serum or interaction with nucleobases and other ligands, is crucial to estimate the versatility of such new B_{12}–cisplatin complexes for application in biology. Compound **1** is stable in water and saline. After one day at room temperature, no release of *cis*-[PtCl-

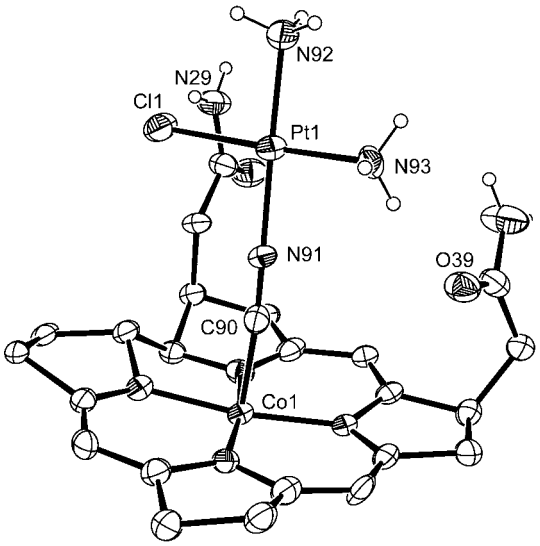


Figure 2. ORTEP presentation of a close-up of the corrin ring and the cisplatin moiety of **1**. Selected bond lengths [Å] and angles [°]: Co1–C90 1.879(9), C90–N91 1.17(1), N91–Pt1 1.953(7), Pt1–Cl1 2.300(3), Pt1–N92 2.000(8), Pt1–N93 1.982(9), N29–Cl1 3.40(1), O39–N93 2.96(1); N91-C90-Co1 174.2(9), C90-N91-Pt1 173.4(9).

$(NH_3)_2(OH_2)]^+$ or *cis*-$[PtCl(NH_3)_2(NC)]$ species could be observed, confirming the kinetic and thermodynamic stability of **1**. The chloride ligand was, however, slowly exchanged by water. Measurements with a Cl^--sensitive electrode showed about a 10% release of Cl^- ions after one day and about 65% after four days. This labile coordination site determines the behavior towards bovine serum albumin. Whereas native vitamin B_{12} and **3** (see below) did not show significant interaction with the same proteins in aqueous phosphate buffer solution, the weakly bound chloride ligand in **1** was exchanged for potential coordinating sites from the protein. After two and six days, 34% and 47%, respectively, of **1**, freshly dissolved in phosphate buffer solution, associated with the protein. Protein binding most likely occurs by ligand exchange on the platinum with competing coordinating sites in the side chains of the amino acid molecules, either by direct exchange of the chloride ligand or by the aqua species.

The main target for cisplatin is DNA, with the platinum atom coordinating preferentially to N^7 of two adjacent guanosine units. Although it is not expected that a B_{12}–cisplatin conjugate would enter the cell nucleus, it is known that adenosylcobalamin plays an important role in mitochondria and, as riboswitch, in gene regulation.[18] It was therefore of interest to determine whether **1** retains its ability to bind to nucleobases. For this reason, the reactivity of **1** towards 9-methylguanine, representing the basic coordinating unit encountered in DNA or RNA, and towards 2′-deoxyguanosine, a more complete model comprising the sugar unit of DNA bases, was investigated. Other monodentate ligands are, of course, also of interest. In particular, we anticipate that Pt^{II} can mediate the conjugation of, for example, a cytotoxic agent in B_{12} by Pt^{II} binding, a strategy that represents another attractive aspect of the chemistry presented herein.

Complex **1** reacted slowly under mild conditions in aqueous solution with 9-methylguanine to form **2** quantitatively (Scheme 1). NMR analysis of the product indicated the formation of a 1:1 adduct of **1** and 9-methylguanine. The downfield part of the ^{1}H NMR spectrum shows the characteristic five signals of B_{12} and a singlet for the H^8 proton of guanine (Figure 3). None of the signals have shifted significantly.

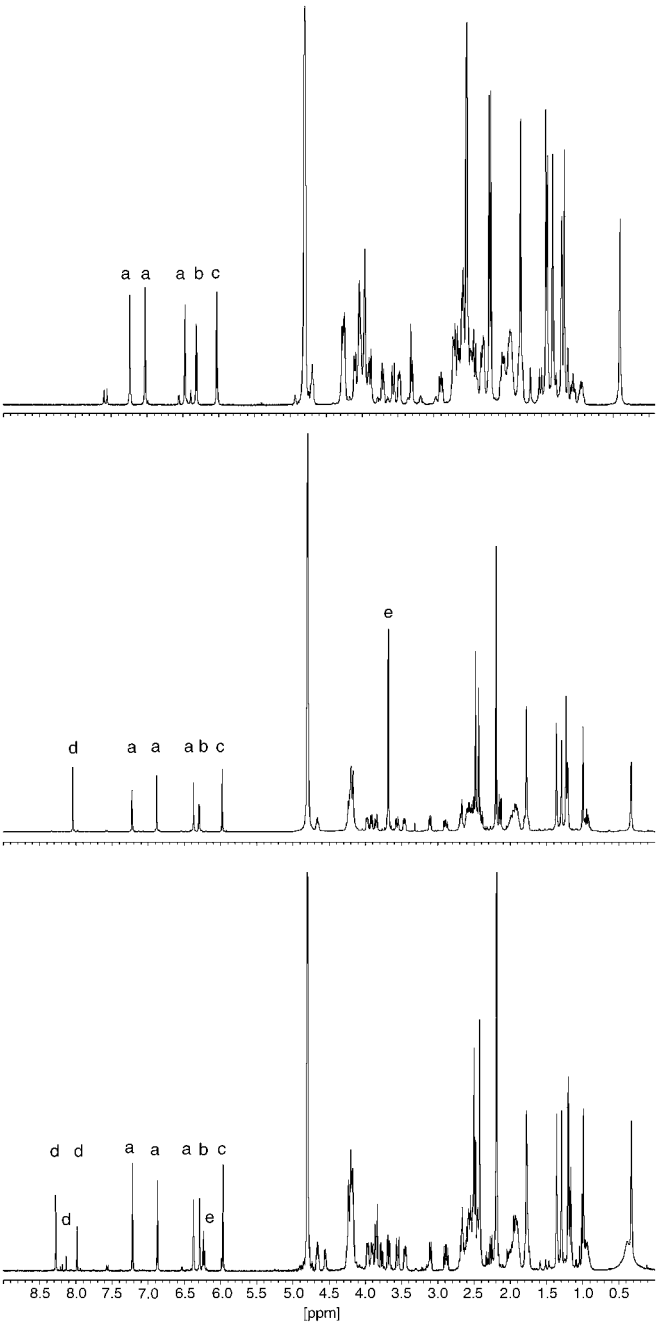


Figure 3. ^{1}H NMR (500 MHz, D_2O) of **1** (top), **2** (middle), and **3** (bottom). Signal legend: a = benzimidazole signals of the cobalamin unit; b = ribose H^1 of the cobalamin unit; c = corrin H^{10} of the cobalamin unit; d = guanine H^8; e = CH_3 group of the guanine unit and ribose H^1 of the 2′-dG unit.

The guanine H^8 proton shows an NOE signal to the peak of the methyl group of 9-methylguanine at 3.7 ppm.

The structure of **2** has been confirmed by single-crystal X-ray analysis (Figure 4). The asymmetric unit contains one

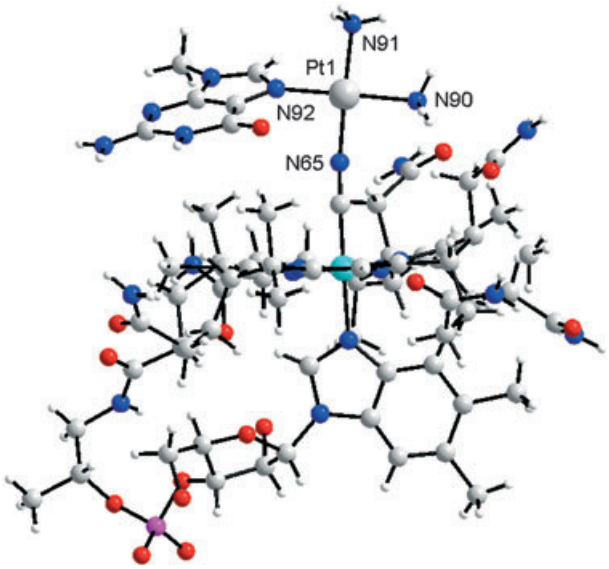


Figure 4. Depiction of the cation found in the crystal structure of **2**.

molecule of **2**, 8.5 molecules of water, and two molecules of methanol. The counterions could not be detected. Coordination of 9-methylguanine to the platinum atom does not induce drastic changes in the Co–C≡N–Pt unit; only a significant, slight shortening of the Co–C bond and a significant, slight lengthening of the Pt–N bond *trans* to the methylguanine are observed (Figure 5). The torsion angle between the guanine plane and the square-planar platinum moiety is 45(1)°. The amide groups on the corrin ring do not show any hydrogen-bond interaction with the platinum unit any more and are instead turned outwards.

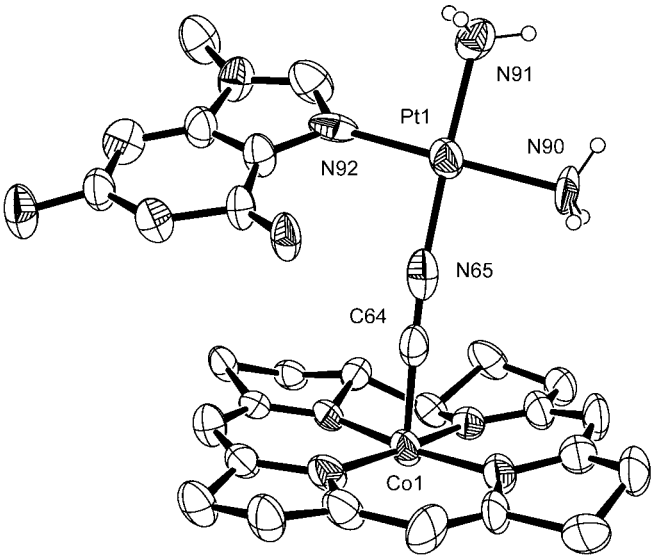


Figure 5. ORTEP presentation of a close-up of the corrin ring and the cisplatin moiety of **2**. Selected bond lengths [Å] and angles [°]: Co1–C64 1.80(2), C64–N65 1.21(2), Pt1–N65 1.978(18), Pt1–N92 1.996(15), Pt1–N91 2.013(12), Pt1–N90 2.077(12); N65-C64-Co1 173.4(14), C64-N65-Pt1 175.1(14).

As in the case of **1**, **2** did not crystallize in the typical cobalamin space group ($P2_12_12_1$) but, this time, in $P2_12_12$. This is probably due to the numerous interactions of the cisplatin-methylguanine moiety with three different neighboring molecules of **2** (Figure 6). The two molecules of **2** (labeled #1 and #3 in Figure 6) that are related to each other by the

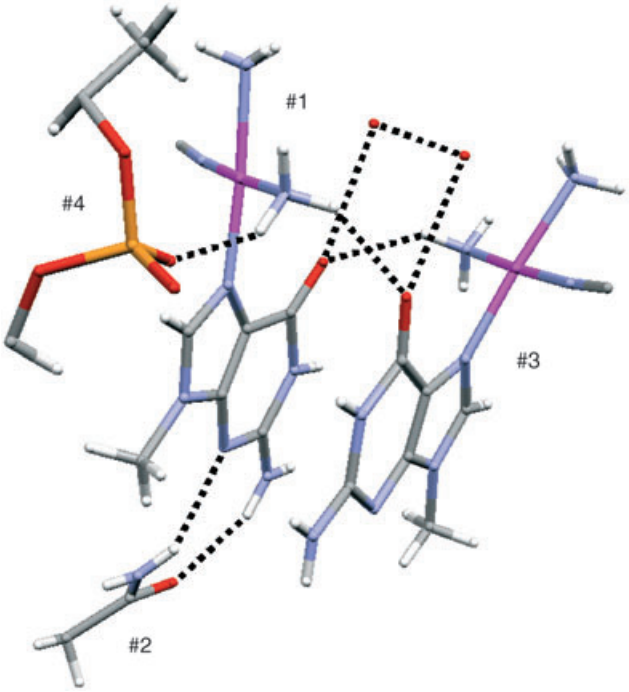


Figure 6. Interactions between molecules in the crystal packing of **2**. Symmetry operations needed to generate the fragments surrounding #1, #2: $x, y, z+1$; #3: $-x+1, -y, z$; #4: $-x+1/2, y+1/2, -z+1$. See text for more detailed explanation of hydrogen bonds (dashed lines).

twofold axis interact by π stacking of the guanine bases. This interaction is enforced by hydrogen bonds between the O^6 carbonyl oxygen atoms of the guanine units and one of the amine ligands of the opposing molecule as well as between the two opposing O^6 carbonyl oxygen atoms, through two water molecules. The same amine ligand also binds to the phosphate group of a third molecule (#4 in Figure 6) of **2**, and an amide group of a corrin side chain of a fourth molecule (#2 in Figure 6) of **2** forms a dual hydrogen bond to N^2 and N^3 of the methylguanine unit. The dashed lines, shown in Figure 6, between the two oxygen atoms of the water molecules and between the O^6 carbonyl oxygen atoms and the water molecules represent the corresponding hydrogen bridges, rationalized from the mutual distances but not localized in the X-ray structure analysis.

In parallel to the preparation of **2**, the reaction of **1** with 2′-deoxyguanosine (2′-dG) gave the conjugate **3** in very good yield. The reaction was relatively slow with an approximate second-order rate constant of about 0.2–0.3 $M^{-1}s^{-1}$ at 38 °C determined under pseudo-first-order conditions (disappearance of **1**). In contrast to product **2**, the H^8 resonance of the coordinated 2′-dG was split into three signals, a main product integrating for 0.65 and two isomers, or side-products, integrating for 0.1 and 0.25 protons (Figure 3). The ^{1}H NMR signals of the main product with the H^8 resonance at about 8.3 ppm confirmed the formation of **3,** because an NOE signal with the peak of $H^{1'}$ of the deoxyribose unit of 2′-deoxyguanosine could be observed at about 6.25 ppm.

Prolonged stirring of an aqueous solution of **3** increased the relative amount of the compound with the H^8 signal at 8.1 ppm from 0.25 to 0.5, indicating a decomposition product of **3**. An additional sign of decomposition was the absence of a resonance for the proton at the 1′-position of the ribose in 2′-deoxyguanosine and the absence of any NOE interaction of this H^8 resonance. We anticipate that the ribose moiety is cleaved from the purine base, but this assumption needs further confirmation. The ^{195}Pt NMR spectrum showed a broad peak at −2475 ppm, in the range of DNA-bound cisplatin.[22]

Compounds **2** and **3** can be considered as models for a monobound cisplatin-to-DNA analogue. Compound **3** showed only very weak interaction with bovine serum albumin, thus confirming the formation of a very stable base-to-platinum coordination. Chemical competition reactions gave a similar picture: stirring an aqueous solution of **3** with a tenfold excess of imidazole for one day did not show the release of 2′-deoxyguanosine or the formation of any new Pt^{II} complex. Obviously, one can not expect from this chemical behavior that cisplatin is simply released from **1** to start its well-known interaction with DNA. However, one must consider that the platinum moiety could be cleaved from vitamin B_{12} intracellularly by reducing agents or enzymes involved in the reduction of cobalamins, such as cobalamin reductase, methionine synthase reductase, or adenosyl transferase, just as cyanide and other known axial ligands are.[15,16,17]

Further studies are currently underway to elucidate the cytotoxicity and in vivo behavior of these conjugates. It is, of course, of special interest to determine whether the platinum complex will be cleaved from the cobalamin or if it reacts as an entity with B_{12}-dependent enzymes or DNA.

Conclusion

Vitamin B_{12} (cyanocobalamin) can act as a ligand for cisplatin by the formation of a cyanide-bridged species (**1**). The platinum(II) unit neither influences the structure nor the spectroscopic properties of B_{12} significantly, but facilitates the electrochemical reduction of the cobalt center. The remaining chloride ligand in **1** is labile and can be exchanged by stronger coordinating ligands, such as guanine derivatives. The vitamin B_{12}–cisplatin–methylguanine conjugate **2** and compound **3** can be regarded as simple models of a vitamin B_{12}–cisplatin–DNA adduct. Adduct **3** shows unexpected instability of the deoxyribose unit of 2′-dG, which merits closer examination.[24]

Experimental Section

General procedures: All chemicals were purchased from Fluka, Buchs (Switzerland). Chemicals were of reagent grade and used without further purification. HPLC analyses were performed on a Merck-Hitachi L-7000 system equipped with a diode array UV/Vis spectrometer and Macherey Nagel Nucleosil C-18ec RP columns (5 μm particle size, 100 Å pore size, 250×3 mm). HPLC solvents were 0.1% aqueous trifluoroacetic acid (A) and methanol (B). Preparative HPLC separations were performed on a Varian Prostar system equipped with two Prostar 215 pumps, a Prostar 320 UV/Vis detector, and Macherey Nagel Nucleosil C-18ec RP columns (7 μm particle size, 100 Å pore size, 250×20 mm, 13 mL min^{-1} flow rate, and 250×40 mm, 40 mL min^{-1} flow rate). MALDI-TOF mass spectra were measured on a Voyager-DE PRO with α-cyano-4-hydroxycinnamic acid as matrix. UV/Vis spectra were recorded on a Varian Cary 50 spectrometer. IR spectra were recorded on a Perkin–Elmer Spectrum BX spectrometer with the samples in compressed KBr pellets. NMR spectra were recorded on a Bruker DRX 500 MHz spectrometer. The chemical shifts are reported relative to TMS using the residual solvent protons as internal reference. Cyclic voltammetry (CV) was carried out on a Metrohm 757 VA Computrace system with a glassy carbon working electrode, a glassy carbon counter electrode, and a Ag^+/AgCl reference electrode. Compound **1** was measured as a solution (1 mM) in tetrabutylammonium hexafluorophosphate in methanol (0.1 M), the sweep rate for CV being 0.1 Vs^{-1}.

Vitamin B_{12}–cisplatin adduct 1: A mixture of *cis*-diaminedichloroplatin(II) (66.4 mg, 0.221 mmol) and silver nitrate (37.6 mg, 0.221 mmol) in water (6 mL) was stirred at 35 °C for 2 h. The precipitate was removed by centrifugation and washed with water (4 mL). The solutions were added to cyanocobalamin (300 mg, 0.221 mmol), and the resulting solution was stirred at 50 °C for 16 h. HPLC analysis exhibited full conversion of the cobalamin. The solvent was removed in vacuo, and the crude product was purified by preparative HPLC (gradient: linear from 100% A to 20% B in 5 min, then linear to 65% B in 40 min). Lyophilization of the product fraction gave **1** as a red powder. Yield: 259.8 mg (72.6%); ^{1}H NMR (500 MHz, D_2O): see Figure 3a; ^{31}P NMR (121 MHz, D_2O): $\delta = -0.38$ ppm; ^{195}Pt NMR (107 MHz, D_2O): $\delta = -2340$ ppm; IR: $\tilde{\nu} = 2199$ cm^{-1} (CN); UV/Vis (H_2O): λ (logε) = 279.9 (4.1), 361.9 (4.4), 519.9 (3.8), 550.9 nm (3.8 mol $L^{-1}cm^{-1}$); MALDI-TOF MS: *m/z*: 1607 $[M-Cl+Na]^+$, 1591 $[M-Cl-NH_3+Na]^+$, 1571 $[M-Cl-2NH_3+Na]^+$; CV: $E_{1/2} = -515$ mV versus Ag^+/AgCl, ca. 50% reversible.

Vitamin B_{12}–cisplatin–methylguanine adduct 2: A solution of **1** (37.4 mg, 23.1 μmol) and 9-methylguanine (4.2 mg, 25 μmol) in water (2 mL) was stirred at 50 °C. After four days, HPLC analysis showed almost complete conversion of the starting materials. The solvent was removed in vacuo, and the crude product was purified by preparative HPLC (gradient: 20% B for 10 min, then linear from 20% B to 40% B in 20 min). Lyophilization of the product fraction gave **2** as a red powder. Yield: 32.0 mg (79%); ^{1}H NMR (500 MHz, D_2O): see Figure 3b; ^{31}P NMR (202 MHz, D_2O): $\delta = 0.73$ ppm; UV/Vis (H_2O): λ (logε) = 279.0 (4.1), 361.9 (4.1), 520.0 (3.6), 548.0 nm (3.6 mol $L^{-1}cm^{-1}$); MALDI-TOF MS: *m/z*: 1736 $[M-CH_3]^+$, 1715 $[M-NH_3-CH_3]^+$.

Vitamin B_{12}–cisplatin–2′deoxyguanosine adduct 3: A solution of **1** (58.5 mg, 36.1 μmol) and 2′-deoxyguanosine (11.6 mg, 43.3 μmol) in water (5 mL) was stirred at 30 °C. After four days, HPLC analysis showed almost complete conversion of the starting materials. The solvent was removed in vacuo, and the crude product was purified by preparative HPLC (gradient: linear from 25% B to 65% B in 30 min). Lyophilization of the product fraction gave **3** as a red powder. Yield: 45.3 mg (67.7%);

^{1}H NMR (500 MHz, D_2O): see Figure 3c; ^{31}P NMR (202 MHz, D_2O): $\delta =$ 0.71 (94), 0.21 ppm (6%); ^{195}Pt NMR (107 MHz, [D_4]methanol): $\delta =$ −2475 ppm (line width ca. 1.5 kHz); UV/Vis (H_2O): λ (logε) = 278.0 (4.2), 361.9 (4.2), 521.0 (3.7), 546.0 nm (3.7 mol L^{-1} cm^{-1}); MALDI-TOF MS: *m/z*: 1723 [*M*−ribose−2NH_3+Na]$^+$.

Chloride release of compound 1: Release of chloride ions from compound **1** was measured potentiometrically with a chloride sensitive electrode (Metrohm 6.0502.120), by using an Ag^+/AgCl reference electrode and a Metrohm 713 pH meter. All measurements were done in aqueous potassium hexafluorophosphate (10 mM) to keep the ion strength constant. Calibration curves were done with sodium chloride solutions (0.005–5 mM), and compound **1** was kept at room temperature as a 0.55 mM solution and measured after 20 min, 1 day, and 4 days. The following chloride concentrations were measured: 0.01 mM after 20 min, 0.06 mM after 1 day, 0.36 mM after 4 days, 0.37 mM after 7 days.

Binding of vitamin B_{12}, 1, and 3 to bovine serum albumin: Bovine serum albumin (13 mg, 0.2 μmol) was dissolved in phosphate buffer (pH 7.4, 0.1 M, 1.0 mL). Aliquots of the freshly dissolved cobalamin derivatives (0.2 μmol) were added, and the solutions were stirred at room temperature. Binding to the albumin was measured by HPLC with detection at 360 nm. The following amounts of protein-bound cobalamin were found: vitamin B_{12}: no binding after 6 days; **1**: 4.8% after 4 h, 34.3% after 2 days, 47.2% after 6 days; **3**: 1.3% after 4 h, 1.6% after 2 days, 1.9% after 6 days (most likely binding of an impurity).

Imidazole challenge: An aqueous solution of **3** (0.5 mM) and imidazole (5.0 mM) was stirred at room temperature. After 1 day, HPLC analysis exhibited less than 1% of free 2′-dG. After 4 days, about 4% of 2′-dG as well as unknown cobalamin-free products in the same range were detected. Additionally, after this time about 50% of the starting material **3** had converted to the product in which the ribose is presumably cleaved.

Crystallographic details: Crystals of **1** and **2** were obtained by vapor diffusion of acetone into an aqueous solution of **1** or **2**. Suitable crystals for X-ray diffraction were covered with Paratone N oil, mounted on top of a glass fiber, and immediately transferred to a Stoe IPDS diffractometer. Data was collected at 183(2) K using graphite-monochromated Mo radiation (0.71073 Å). Data was corrected for Lorentz and polarization effects, as well as for absorption. Structures were solved with direct methods by using SIR97[25] and were refined by full-matrix least-squares methods on F^2 with SHELXL-97.[26] In compound **1**, apart from the two cationic B_{12} derivatives in the asymmetric unit, one trifluoroacetate (from the preparative HPLC purification), 18 water, three methanol, and two acetone molecules were found. The second anion could not be located, most likely due to disorder. Appropriate restraints were applied. In compound **2**, additional 8.5 water and two methanol molecules were found. The two anions could not be located, most likely due to disorder. Appropriate restraints and constraints were applied. The crystal data and refinement parameters of compounds **1** and **2** are summarized in Table 1. CCDC-261001 (for **1**) and CCDC-261002 (for **2**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. ORTEP plots were drawn with the program ORTEP-3 for Windows at a probability of 30%.[27]

Table 1. Crystal data and structure refinement[a] for **1** and **2**.

	1	**2**
formula	$C_{137}H_{184}Cl_2Co_2F_3N_{32}O_{56}P_2Pt_2$	$C_{71}H_{133}CoN_{21}O_{25.50}PPt$
M_r	3873.04	1979.97
T [K]	183(2)	183(2)
λ [Å]	0.71073	0.71073
crystal system	triclinic	orthorhombic
space group	$P1$	$P2_12_12$
a [Å]	16.9434(17)	27.2778(17)
b [Å]	17.3115(15)	24.9345(6)
c [Å]	18.0814(17)	14.0940(14)
α [°]	111.999(10)	90
β [°]	99.721(11)	90
γ [°]	90.580(11)	90
V [Å^3]	4831.2(8)	9586.2(11)
Z	1	4
ρ_{calcd} [Mg m^{-3}]	1.331	1.380
μ [mm^{-1}]	1.741	1.727
F(000)	1979	4160
crystal size [mm^3]	0.34 × 0.14 × 0.10	0.16 × 0.13 × 0.07
θ range [°]	2.31–28.05	2.08–22.51
index ranges	$-22 \leqq h \leqq 22$	$-29 \leqq h \leqq 29$
	$-22 \leqq k \leqq 22$	$-26 \leqq k \leqq 26$
	$-23 \leqq l \leqq 23$	$-15 \leqq l \leqq 15$
reflns collected	46915	52291
independent reflns	38480 [R(int) = 0.0685]	12552 [R(int) = 0.0906]
completeness [%]	92.0 (to θ = 28.05°)	99.8 (to θ = 22.51°)
max/min transmission	0.8545/0.7101	0.8892/0.7708
data/restraints/parameters	38480/61/1937	12552/25/997
goodness-of-fit on F^2	0.914	0.944
final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0720, $wR2$ = 0.1731	$R1$ = 0.0762, $wR2$ = 0.1941
R indices (all data)	$R1$ = 0.1138, $wR2$ = 0.1925	$R1$ = 0.1135, $wR2$ = 0.2110
absolute structure parameter	−0.015(5)	0.015(12)
largest diff. peak/hole [e Å^{-3}]	1.141/−1.967	1.246/−0.513

[a] Both compounds were refined by the method of full-matrix least-squares on F^2.

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