Zinc Substitution of Cobalt in Vitamin B\textsubscript{12}: Zincobyric acid and Zincobalamin as Luminescent Structural B\textsubscript{12}-Mimics

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Dedicated to Professor Dieter Jahn on the occasion of his 60th birthday

Abstract: Replacing the central cobalt ion of vitamin B\textsubscript{12} by other metals has been a long-held aspiration within the B\textsubscript{12}-field. Herein, we describe the synthesis from hydrogenobyric acid of zincobyric acid (Znby) and zincobalamin (Znbl), the Zn-analogues of the natural cobalt-corrinoids cobyric acid and vitamin B\textsubscript{12}, respectively. The solution structures of Znby and Znbl were studied by NMR-spectroscopy. Single crystals of Znby were produced, providing the first X-ray crystallographic structure of a zinc corrin. The structures of Znby and of computationally generated Znbl were found to resemble the corresponding Co\textsuperscript{2+}-corrins, making such Zn-corrins potentially useful for investigations of B\textsubscript{12}-dependent processes. The singlet excited state of Znby had a short life-time, limited by rapid intersystem crossing to the triplet state. Znby allowed the unprecedented observation of a corrin triplet (E\textsubscript{T} = 190 kJ mol\textsuperscript{-1}) and was found to be an excellent photo-sensitizer for \(^1\)O\textsubscript{2} (Φ\textsubscript{3} = 0.70).

The biological use of cobalt as the specific transition metal center in natural B\textsubscript{12}-cofactors and the interaction between cobalt and the corrin ligand raise intriguing questions concerning the origins of its natural selection.\textsuperscript{[1]} Engineered B\textsubscript{12}-biosynthesis\textsuperscript{[2]} has opened up a preparative route to hydrogenobyric acid (Hby).\textsuperscript{[3]} The metal-free corrin ligand of vitamin B\textsubscript{12}, providing an excellent opportunity for the synthesis of transition-metal analogues of the natural cobalt-corrinoids.\textsuperscript{[4]} Zn\textsuperscript{2+}-analogues of natural corrinoids have hardly been explored\textsuperscript{[5,6]} but are attractive, as Zn- and low-spin Co\textsuperscript{II}-centers exhibit similar structural properties in small complexes and in metalloproteins.\textsuperscript{[9]}

Fischli and Eschenmoser reported the synthesis and characterization of the first Zn-corrin (ZnCor), when exploring the synthesis and chemistry of corrins in model studies towards the total synthesis of vitamin B\textsubscript{12}.\textsuperscript{[4]a,6} Indeed, in the Eschenmoser\textsuperscript{[7]} and Woodward labs\textsuperscript{[8]} a 5,15-nor-zincobyric acid was an intermediate of the B\textsubscript{12}-synthesis. UV/VIS-spectroscopically characterized samples of zincobalamin (Znbl) and zincobyric acid (Znby), the Zn-analogues of vitamin B\textsubscript{12} (CNChl) and cobyric acid (Chy) (Scheme 1), were first reported by Koppenhagen and Pfifflner.\textsuperscript{[9]}

Herein, we delineate an effective synthesis of Znby and of Znbl, starting from crystalline Hby.\textsuperscript{[3]}describe the pertinent spectroscopic and structural properties of these luminescent

\[\text{Scheme 1. Formulae of metal-free, cobalt- and zinc-corrinoids. Left:} \]

General formula of the cobalamin vitamin B\textsubscript{12} (R = CN, CNChl), coenzyme B\textsubscript{12} (R = 5’-deoxyadenosyl, AdoChl), cob(II)alamin (R = e\textsubscript{−}, Chl\textsuperscript{−})

Center: Formula of hydrogenobyric acid (Hby), Co\textsuperscript{2+}-cobyrinate (Chy\textsuperscript{2−}) and zincobyrate (Znby), where the axial solvent ligands for both the Zn\textsuperscript{2+} and Co\textsuperscript{II} have been omitted. Right: formula of zincobalamin (Znbl) in its “base-on-” form.

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B$_{12}$-derivatives and report a kinetic study of the binding of Zn$^{II}$-ions to Hby. Znby was prepared at room temperature in 83% yield from Hby$^{[a]}$ and Zn$^{II}$acetate (see Scheme 2 and the Supporting Information). Zn$^{II}$-ions bound to Hby readily under these conditions (Supporting Information, Figure S4), and over 20 times faster than Co$^{II}$-ions. Znby was resistant to removal of the Zn$^{II}$-ion in acidic aqueous solution, and Hby could not be efficiently (re)generated from Znby.

The UV/Vis spectrum of Znby in aqueous buffer, pH 5, displayed absorption maxima at 335 nm, 493 nm, and 518 nm$^{[9a]}$ (see Figure 1) and showed similar basic features as those recorded for ZnCo$^{[a]}$ and for a 5,15-nor-zincobyrinate$^{[7,8]}$ but with maxima at roughly 20 nm longer wavelengths. The aqueous solution of Znby fluoresced with a maximum emission at 552 nm.

The solution structure of Znby (molecular formula C$_9$H$_{24}$N$_{16}$O$_2$Zn, see Supporting Information, Figure S3) was characterized by NMR spectroscopy, providing assignment of 52 H-atoms and of all C-atoms (Supporting Information, Table S1). A 500 MHz $^1$H-NMR spectrum of Znby in D$_2$O (Figure 2a) featured eight methyl singlets, the singlet of HC10 at 5.51 ppm, and signals for HC19, HC3, HC8, and HC13 at intermediate field.

Covalent attachment of the B$_{12}$-nucleotide moiety$^{[1a,10]}$ to Znby was achieved using a recently developed carboximide method$^{[3a,11]}$. In brief, from 5.0 mg (4.8 µmol) of Znby 4.8 mg of Znbl (3.6 µmol, 75%) were obtained, after chromatography and crystallization from aqueous acetonitrile (Scheme 2). An aqueous solution of Znbl exhibited a UV/Vis spectrum as previously reported$^{[9b]}$ (Figure 1). The absorption maxima of the $\alpha$, $\beta$-bands in the UV/Vis spectrum of Znbl occurred at 528 and 502 nm, suggesting intramolecular coordination of the nucleotide base.$^{[46]}$ A fluorescence spectrum of Znbl showed an emission with a maximum at 560 nm, that is, about 8 nm longer wavelength than in the spectrum of Znby (Figure 1). The structure of Znbl (molecular formula C$_{12}$H$_{25}$N$_{16}$O$_3$PZn, see Supporting Information, Figure S5) was established by NMR spectroscopy (Figure 2 and Supporting Information, Table S2), providing assignment of 73 H-atoms and all C-atoms. The high-field shifts of the signals of H$_2$C1A (by about 0.5 ppm to $\delta = 0.65$ ppm) and of HN2 and HC7N of the DMF-moiety, by about 0.8 ppm to $\delta = 7.55$ ppm and $\delta = 6.72$ ppm, respectively, indicated a “base-on” form, as in Co$^{III}$cobalamins$^{[12]}$ and in Co$^{III}$cobalamin (Chbl$^{[a]}$). The intramolecular Zn-coordination of the DMB-base was analyzed further using $^1$H,$^3$H-ROESY spectroscopy (see Supporting Information, Figure S3), characterizing Znbl as a roughly isostructural analogue of Chbl$^{[13]}$.

Znby furnished orange-red single crystals from aqueous acetonitrile ($P2_1,2_1,2_1$), suitable for X-ray crystal structure analysis (Figure 3 and Supporting Information, Table S3). The Zn$^{II}$-center is coordinated in an approximate pyramidal fashion, where the axial ligand is attached to the “top” (or $\beta$) face of the corrin-bound Zn-ion, lifting it by 0.624 Å from the best plane through the inner corrin N-atoms (Figure 3). However, in the crystal the individual Znby-molecules were part of a coordinative Znby polymer, generated by repetitive intermolecular axial Zn$^{II}$-coordination by the carboxylate function of a neighboring Znby molecule (see the Supporting Information).

A comparison of the crystal structures of Znby and Hby$^{[3]}$ (Figure 4 and Supporting Information, Table S4) indicates a minor increase only in the radial size of the coordination hole on Zn-binding. The average lengths of the N1–N3 and N2–N4 diagonals in Hby ($d = 3.82$ Å) and in Znby ($d = 3.84$ Å) are similar. Coordination of Zn$^{II}$ leads to a reduction of the corrin “helicity” $h$ from $h = 12.9^\circ$ in Hby$^{[13]}$ to $h = 8.0^\circ$ in

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**Scheme 2.** Preparation of Znby and Znbl from Hby. i) 2 mg Hby in 2.3 mL aq. 0.5 mM Zn(OAc)$_2$ at pH 6, 80 min, room temperature; ii) 5 mg Znby, 3.3 meq B$_{12}$-nucleotide moiety, 20 meq HOBt and 23 meq EDC-HCl in 1.9 mL H$_2$O, 4 h, 0°C (see the Supporting Information for details).

**Figure 1.** Absorption and fluorescence spectra of Znby and Znbl at 298 K. Left: UV/Vis absorption (black trace), CD (red trace), and fluorescence emission (blue trace) of Znby in H$_2$O. Right: UV/Vis absorption (black trace), CD (red trace), and fluorescence emission (blue trace) of Znbl in 10 mM Na-phosphate buffer, pH 5 (see the Supporting Information for details).

**Figure 2.** 500 MHz $^1$H-NMR spectra of Znby and Znbl (in D$_2$O, 298 K). Top: Znby ($\delta = 1.1$ ppm). Bottom: Znbl ($\delta = 7.2$ ppm); residual water signal after pre-saturation marked by an X.
Znby (Supporting Information, Table S4). The major effects of the formal replacement of the penta-coordinate Co\(^{III}\)-center in a vitamin B\(_{12}\) derivative by a Zn\(^{II}\)-ion are seen in a structural comparison of Znby and Co\(^{II}\)-heptamethyl-cobyrinate perchlorate (Chin\(^{II}\))\(^{[14]}\) (Figure 4 and Supporting Information, Table S4). The Zn–N bonds in Znby (average length = 2.03 Å) are longer than those found in Chin\(^{II}\) (average Co–N bond length = 1.90 Å). Likewise, the axial displacement of the metal-ion from the mean plane through the four corrin N-atoms in the Zn-corrinate Znby (0.624 Å) is palpably greater than that of the Co\(^{II}\)-center of Chin\(^{II}\) (0.048 Å). In Znby and Chin\(^{II}\), an axial ligand is bound at the β-face with a long metal-oxygen bond, and the four corrin N-atoms are displaced slightly from a planar to a squashed tetrahedral arrangement (Supporting Information, Table S4). However, whereas the core of the corrin ligand is made nearly C2-symmetrical by the coordination of a Co\(^{III}\)-center, in Znby the N2–N4 diagonal remains remarkably longer than its N1–N3 counterpart, with Δd = 0.186 Å. Hence, about 60 % of Δd = 0.297 Å in Hby are retained in the corrin ligand of Znby. This feature of Znby reflects a preferred mode of the conformational adaptation of the coordination hole of the flexible, unsymmetrical corrin ligand to the 5-coordinate closed-shell Zn-ion. The “helicity” h(Znby) = 8.0° is in line with a small directional effect of Zn\(^{II}\), compared to Co\(^{III}\) or Co\(^{II}\)-binding, where h = 6.1° in Chin\(^{II}\) and h = 4.1° in CNChl\(^{[3]}\). In Znby, the corrin ligand adapts to the skewed pyramidal arrangement around the Zn\(^{II}\)-center by an unprecedented conformational “doming” of the corrin ligand (Figure 4). Consequently, the corrin-based inter-planar angle ϕ\(^{[3]}\) of the coordination polyhedron at the Zn-center ϕ(Znby) = 50.2° far exceeds ϕ(Chin\(^{II}\)) = 7.6° and ϕ(CNChl) = 4.6°\(^{[3]}\).

The fluorescence of Znby in EtOH at 296 K showed an emission maximum at 548 nm and an energy of the lowest singlet excited state of Znby of 225 kJ mol\(^{-1}\), close to the value observed with the metal-free Hby (E\(^S\) = 223 kJ mol\(^{-1}\))\(^{[13]}\). Hence, the closed shell Zn-ions do not appear to significantly perturb the π,π*-transitions of the corrin ligand. However, the fluorescence of Znby (fluorescence lifetime τ\(_{fl}\) < 0.4 nsec) decayed about an order of magnitude more rapidly at 23°C than that of Hby (τ\(_{fl}\) = 3.3 nsec), exhibiting a correspondingly lower quantum yield Φ\(_{fl}\) = 0.025 (for Hby Φ\(_{fl}\) = 0.18). The short fluorescence lifetime of photo-excited Znby at 296 K is due to the efficient singlet-triplet intersystem crossing with an estimated rate of more than 2 x 10\(^6\) sec\(^{-1}\), boosted by the coordination of the Zn-ion.\(^{[5]}\) At 77 K the solution of Znby in EtOH displayed an absorption maximum at 523 nm, and emitted both fluorescence (λ\(_{max}\) = 538 nm) and phosphorescence (first maximum at 628 nm, Figure 5, see the Supporting Information for details). Hence, at 77 K the lowest triplet state of Znby occurred at E\(^T\) = 190 kJ mol\(^{-1}\), furnishing the first such benchmark value for a natural corrin ligand. The phosphorescence of photo-excited Znby decayed with a lifetime of 13 ± 1 msec at 77 K. Znby sensitized the formation of O\(_2\) with a quantum yield Φ\(_{q}\) = 0.70. The Zn-corrin ZaCor\(^{[8]}\) emitted fluorescence with a maximum at 573 nm (Φ\(_{fl}\) = 0.09) at room temperature in EtOH and was an efficient triplet sensitizer in the legendary photo-induced A/D-secocorrin to corrin cycloisomerization.\(^{[4a,7,16]}\)

Table S4). The Zn–N bonds in Znby (average length = 2.03 Å) are longer than those found in Chin\(^{II}\) (average Co–N bond length = 1.90 Å). Likewise, the axial displacement of the metal-ion from the mean plane through the four corrin N-atoms in the Zn-corrinate Znby (0.624 Å) is palpably greater than that of the Co\(^{II}\)-center of Chin\(^{II}\) (0.048 Å). In Znby and Chin\(^{II}\), an axial ligand is bound at the β-face with a long metal-oxygen bond, and the four corrin N-atoms are displaced slightly from a planar to a squashed tetrahedral arrangement (Supporting Information, Table S4). However, whereas the core of the corrin ligand is made nearly C2-symmetrical by the
To shed further light on the structure of Znby, the gas-phase structure of the hypothetical 4-coordinate analogue Znby(4) was calculated, using DFT, from the crystal structures of Hby, as well as of the heptamethyl ester Chin(8), the latter providing computational Znby models in which the polar side chain functions are replaced by methyl ester groups (for details, see the Supporting Information). Ligation of an acetate ligand at the “upper” (β) or at the “lower” (α) side of the latter Znby(4) structure, furnished models of Znby and of its coordination isomer Znby(α). The calculated structure of Znby closely reflected the observed crystallographic structural peculiarities of Znby, such as the longer N2–N4 diagonal (A_d_α = 0.22 Å), the long Zn–N-bonds (Zn–N_a = 2.06 Å), the out-of-plane position of the 5-coordinate Zn-ion (0.65 Å), and the doming of the corrin ligand. In Znby(α), the calculations generated a model with comparably long Zn–N-bonds (Zn–N_a = 2.06 Å), an N2–N4 diagonal shorter than N1–N3 (A_d_α = −0.10 Å), a profound out-of-plane position of the 5-coordinate Zn-ion (−0.62 Å) and an “inverted” doming of the corrin ligand. A structure of Znbl was calculated (Figure 6) starting from a previously optimized gas-phase structure of Chl(10). It showed a pronounced out-of-plane movement of the 5-coordinate Zn-ion (−0.46 Å), exceeding that of Co(10) in Chl(10) (−0.13 Å), but compensated in part by the slightly shorter Zn–N_DMAB bond (2.07 Å) in Znbl than the Co–N_DMAB bond (2.11 Å) in Chl(10). The structure of Znbl showed a downward movement of the DMBA-base, compared to Chl(10), but was similar in its overall architecture. Hence, Znbl can be considered as a good structural mimic of the non-luminescent Chl(10).

As an isostructural analogue of some Chls that is inactive in the organometallic processes typical of B12-dependent enzymes, Znbl may represent an “antivitamin B12”[27] and be a useful fluorescent molecular probe in B12-biology and biomedicine.[28,29] The structure analysis of Znby has indicated that the closed shell d^10-iron of Zn(10) lacks the precise fit of the similarly sized low-spin Co^-centers (d^-ions),[29] where an empty d^-5^-orbital provides an excellent electronic complement for the four corrin N-atoms.[29] Hence, the basic fit of low spin Co^- and diamagnetic Co^-ions to the ring size of the corrin ligand[30,31] is not extended to the 5-coordinate Zn^-ion. A similar (but less pronounced) difference is seen in Zn^- and Co^-porphyrins, where porphyrin “doming” and axial displacement of 5-coordinate Zn^-centers towards the axial ligand exceed the effect of the 5-coordinate Co^-ions.[21]

The lack of out-of-plane displacement of the 5-coordinate Co^-centers in Co^-corrins appears to be a consequence of the partially occupied valence shell of this electronically adaptable d^-ion. Indeed, the 15-membered equatorial perimeter of the “ring contracted” corrin ring is able to accommodate the size of both low-spin Co^- and diamagnetic Co^-ions, which have the capacity to fit their electronic configuration to favorable interactions with the ligand.[30,14,15] In contrast, when binding a 5-coordinate closed shell d^10 Zn^-ion, the corrin ligand undergoes doming and further conformational relaxations. In spite of the structural differences between Znby and Chl(10), as well as those deduced for Znbl and Chl(10), the redox-inactive Zn-complexes of natural corrins may be useful as luminescent (inactive) mimics of corresponding B12-derivatives.

The work reported here describes a rational avenue to the construction and characterization of Znbl, promising to be useful in biological and biomedical experiments. Significantly, the engineering of bacterial strains for the production Hby[3] has unlocked the gateway to the direct generation of a range of other Methls and Methys, the transition-metal analogues of the Chls and Chys, respectively. The helical, un-symmetric natural corrin-ligand is a unique binding partner for transition-metal ions, providing an exciting opportunity to construct a diverse range of metal analogues of vitamin B12, investigate their structural behavior, examine their reactivity, and to test biological effects.

**Experimental Section**

Crystallographic Data. X-ray crystal data of Znby have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under the reference number CCDC 1921462.

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**Conflict of interest**

The authors declare no conflict of interest.

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