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Replacement of the Cobalt Center of Vitamin B$_{12}$ by Nickel: Nibalamin and Nibyric Acid Prepared from Metal-Free B$_{12}$ Ligands

Hydrogenobalamin and Hydrogenobyric Acid

Christoph Kieninger, Klaus Wurst, Maren Podewitz, Maria Stanley, Evelyne Deery, Andrew D. Lawrence, Klaus R. Liedl, Martin J. Warren,* and Bernhard Kräutler*

Dedicated to Professor Albert Eschenmoser on the occasion of his 95th birthday

Abstract: The (formal) replacement of Co in cobalamin (Cbl) by Ni$^{II}$ generates nibalamin (Nibl), a new transition-metal analogue of vitamin B$_{12}$. Described here is Niby, synthesized by incorporation of a Ni$^{II}$ ion into the metal-free B$_{12}$ ligand hydrogenobalamin (Hby). The related Ni$^{II}$ corrin nibyric acid (Niby) was similarly synthesized from Hby, the metal-free cobyric acid ligand. The solution structures of Hbl and Niby and Nibl, were characterized by spectroscopic studies. Hbl features two inner protons bound at N2 and N4 of the corrin ligand, as discovered in Hby. X-ray analysis of Niby shows the structural adaptation of the corrin ligand to Ni$^{II}$ ions and the coordination behavior of Ni$^{II}$. The diamagnetic Niby and Nibl, and corresponding isoelectronic Co$^{II}$ corrins, were deduced to be isostructural. Nibl is a structural mimic of four-coordinate base-off Cbls, as verified by its ability to act as a strong inhibitor of bacterial adenosyltransferase.

Introduction

Biologically active vitamin B$_{12}$ derivatives exclusively utilize cobalt as their specific transition metal center, which is bound and activated exquisitely by a helical corrin macrocycle. The metal-free corrin ligand of vitamin B$_{12}$, hydrogenobyric acid (Hby), has recently been made available as a consequence of engineered B$_{12}$ biosynthesis in E. coli. The availability of Hby has provided an unparalleled opportunity for the effective synthesis of metal-free and transition metal analogues of the natural cobalt-corrinoids a previously intractable challenge in bioinorganic and B$_{12}$ chemistry. We have recently used Hby for the synthesis of the corresponding zinc-cobyrinic acid (Zaby) and the Zn analogue of vitamin B$_{12}$, zincobalamin (Zabl), of interest as luminescent structural B$_{12}$ mimics.

Herein, we report on the first nickel-complexes of natural corrin ligands, including nibalamin (Nibl). We also describe the syntheses of crystalline nibyric acid (Niby), the novel Ni$^{II}$ complex of Hby, and hydrogenobalamin (Hbl), the metal-free complete B$_{12}$ ligand (see Scheme 1 and Scheme 2). Koppenhagen and co-workers, back in the 1970s, reported the isolation of Hbl from a Chromatium strain supplemented with 5,6-dimethylbenz-imidazole (DMB). They were able to characterize Hbl by UV/Vis-spectroscopy and demonstrated that it could be converted into vitamin B$_{12}$ by insertion of cobalt, and later reported its mass spectrum.

A Ni$^{II}$-corrin, the NiCor (see Scheme 1), was prepared in the Eschenmoser labs as the first synthetic corrin, making use of the Ni$^{II}$ ion as a “template” for the assembly of the corrin macro-ring. NiCor also became the object of the first X-ray crystallographic investigation of the structure of a non-cobalt corrin. Four coordinate Ni$^{II}$ complexes prefer to adopt a planar geometry and therefore are more structurally related to the corresponding Co$^{II}$ complexes. Indeed, recently, there has been a resurgence in the quest for close Ni analogues of the B$_{12}$ cofactors.[10] The planar ligand set of Nibl potentially represents a structural B$_{12}$ mimic that is inert to the organometallic transformations typical of B$_{12}$-dependent enzymes, as suggested by its expected coordination chemistry and structural properties.

Specific interest in Nibl, the Ni$^{II}$ analogue of vitamin B$_{12}$ and of other cobalamins (Cbls) (see Scheme 1), is thus a consequence not only of its chemistry, but also of its possible use as a molecular probe in B$_{12}$ biology and biomedicine, helpful for the investigation of cobalamin-dependent processes and their physiological effects. [11]
Results and Discussion

Nibyric acid (Niby) was prepared by dissolving 1.40 mg (1.6 μmol) of crystalline hydrogenobyric acid (Hby) in 3.5 mL of deoxygenated 0.5 M aqueous NiII acetate, pH 6, with stirring at 90°C for 75 min. Separation on a short reverse phase column, evaporation and crystallization from aqueous acetonitrile yielded 0.90 mg (0.97 μmol, 61%) of Niby, which was isolated as yellow crystals (see Scheme 2, Exptl. Part and Supporting Information (SI)). The UV/Vis absorption spectrum of an aqueous solution of Niby displayed bands at 464 nm (shoulder), 448 nm and 334 nm (Figure 1), and exhibited similar gross features to those observed in an absorption spectrum of the Ni-corrin NiCor (but with a slightly red-shifted maxima) [6,6a]. The solution structure of the diamagnetic NiII-corrin Niby (molecular formula C45H64N10O8Ni, for HR mass spectra see SI, Figure S3) was analyzed by NMR spectroscopy, providing assignment of all 52 non-exchangeable H atoms and 44 C atoms (see SI, Figure S4 and Table S1). A 500 MHz 1H NMR spectrum of Niby in D2O displayed five high field singlets for the six methyl groups, a singlet of HC10 at 6.30 ppm, as well as several signals at intermediate field for HC19, HC3, HC8 and HC13 (see Figure 2). The data from homonuclear and heteronuclear correlations confirmed the stereostructure of Niby (see SI, Figure S5).

Figure 1. Absorption spectra of aqueous solutions of metal-free B12 ligands Hby and Hbl and of their NiII-complexes Niby and Nibl at 298 K. Top: UV/Vis-absorption spectra of Hby (ε = 31.5 μM, pH 5, black trace) and Niby (ε = 34.5 μM, unbuffered, red trace). Bottom: UV/Vis-absorption of Hbl (pH 5, black trace) and of Nibl (unbuffered, red trace).

Figure 2. 500 MHz 1H NMR spectrum of Niby in D2O (ε = 1.9 mm, 298 K); the water signal after presaturation is marked by an X.

Scheme 1. Structural formulae of cobalt, zinc, nickel and metal-free corrinoids. Left: cobalamins with “base-on” structures: vitamin B12 (R = CN, CNCbl), coenzyme B12 (R = 5'-deoxyadenosyl, AdoCbl), methylcobalamin (R = CH3, MeCbl), cob(II)alamin (R = e, CblII). Center, top: the NiII-corrin nibyrate (Niby), hydrogenobyric acid (Hby), cobIII-cobyrinic acid (CbyIII) and zincoxobyrinic acid (Znby), where CoII and ZnII carry an unspecified axial ligand (e.g., solvent molecule). Center, bottom: Eschenmoser’s synthetic racemic NiII-corrin NiCorII Right: nibalamin (Nibl), four-coordinate “base off” cob(II)alamin (4-c-CblII) and cob(II)alamin (CblII).

Scheme 2. Preparation of the NiII-corrins Niby and Nibl from Hby. i) 0.5 M Ni(OAc)2, pH 6, 1 h, 90°C, Ar. ii) 3 equiv B12 nucleotide moiety, HOBt, EDC*HCl, H2O, 0°C, 4 d, iii) 0.5 M Ni(OAc)2, pH 6, 1 h, 90°C, Ar (see the SI for details).
The complete metal-free ligand of the cobalamins, hydrogenobalamin (Hbl), was assembled by attaching the B_{12} nucleotide moiety\(^{[11,12]}\) to the propionate moiety of Hby at 0°C through application of the carbodiimide method (Scheme 2).\(^{[14,15]}\) In brief, an aqueous solution of 9.12 mg (10.4 μmol) of Hby and of 14.71 mg (33.4 μmol) of the B_{12}-nucleotide was treated with 9.4 moleq of HOBt and degassed. To the frozen reaction mixture 4.4 moleq of EDC·HCl were added under Ar. Upon subsequent warm-up of the reaction mixture to 0°C, 16 moleq EDC·HCl were added and stirring was continued for 4 d (see SI). Work-up, using RP18-chromatographic purification, precipitation with MeCN and drying, furnished 11.3 mg (8.89 % yield) of Hbl as an orange powder. An aqueous solution of Hbl at pH 5 exhibited UV/Vis absorption maximum at 525 nm of the α-band of Hbl and the fluorescence emission maximum at 554 nm (SI, Figure S8 and S9) similar to those of Hby.\(^{[3]}\) The UV/Vis absorption maximum at 525 nm of the α-band of Hbl and the fluorescence emission maximum at 554 nm (SI, Figure S10) located the first excited singlet state of Hbl at \(E^0\) near 221 kJ mol\(^{-1}\), marginally lower than for Hby.\(^{[3]}\) The structure of Hbl (molecular formula C\(_{62}\)H\(_{90}\)N\(_{13}\)O\(_{14}\)P, see HR-MS data in SI, Figure S11) in H\(_2\)O was characterized by NMR spectroscopy (600 MHz \(^1\)H NMR spectrum in SI, Figure S12), providing assignment of 89 H atoms and of all 62 C atoms (see SI, Table S2). The two “inner” H atoms gave rise to singlets at \(\delta = 12.32\) and \(\delta = 12.57\) ppm, which were assigned to H(N4) and H(N2), respectively, indicating a minor up-field shift of both of them when compared to Hby.\(^{[3]}\) The methyl group singlet of H\(_3\)C\(_1\) at \(\delta = 0.81\) ppm occurred at 0.47 ppm to higher field, compared to Hby, suggesting a temporary residence of the heteroaromatic DMB unit of Hbl near to its corrin moiety, a conclusion that was further supported by weak inter-residual correlations in the \(^1\)H,\(^1\)H ROESY spectra (see SI, Figure S13). However, the signals of the DMB moiety (HN2 at \(\delta = 8.35\) ppm, HN4 at \(\delta = 7.31\) ppm, HCN7 at \(\delta = 7.30\) ppm) were found at similar chemical shift values to those of the free B\(_{12}\) nucleotide,\(^{[12]}\) effectively incompatible with a time-averaged positioning of the DMB part close to the corrin chromophore, as found for zincoabalin (Zahl)\(^{[5]}\) and for typical “base-on” Co\(^{II}\)Chb\(^{[14]}\).

The Ni\(^{II}\)-corrin nibalamin (Nibl) was prepared by heating a deoxygenated aqueous solution of Hbl and Ni(OAc)\(_2\) for 1 h at 90°C (Scheme 2), furnishing Nibl in 77% yield as a yellow powder. An unbuffered aqueous solution of Nibl exhibited a UV/Vis spectrum that is incompatible with coordination by the DMB base and nearly indistinguishable (at > 300 nm) from the spectrum of the free B\(_{12}\) nucleotide,\(^{[12]}\) effectively incompatible with a time-averaged positioning of the DMB moiety and the 

The absorption maxima of Nibl occurred at characteristically longer wavelengths when compared to the spectrum of the recently described vitamin B\(_{12}\)-derived 5,6-dihydroxy-5,6-dihydroni-

The nickel corrin Niby was crystallized from aqueous acetonitrile, furnishing yellow single crystals (P\(_{2}\)1\(_{1}\)2\(_1\)/m) suitable for X-ray analysis (see Figure 4). The incorporation of a Ni\(^{II}\) ion into the corrin macrocycle of the metal-free Hby increased the effective symmetry of the corrin ligand as revealed by a comparison of the crystal structures of Niby and

**Figure 3.** 500 MHz \(^1\)H NMR spectrum of Nibl in D\(_2\)O (\(\epsilon = 1.4\) mm, 298 K); residual water signal after presaturation marked by an X.

**Figure 4.** Crystal structure of Niby. Left. Crystallographic model of Niby in two projections; Right. Graphs representing the corrin core with display of N-Ni bond lengths (top) and the coordination geometry around Ni\(^{II}\) center, highlighting the arrangement of the four inner corrin N atoms in a flattened tetrahedron around the Ni\(^{II}\) center (middle and bottom).
of Hby (see SI for details). Coordination of the Ni$^{II}$-ion largely equalizes the lengths of the two diagonals, where the N2-N4 diagonal of Niby exceeds its N1-N3 counterpart by only $\Delta d = 0.047 \, \text{Å}$, far less than in Hby ($\Delta d = 0.297 \, \text{Å}$)\textsuperscript{[3]} or in Znby ($\Delta d = 0.197 \, \text{Å}$)\textsuperscript{[3]}. The somewhat longer N2-N4 diagonals in the metal corrins Niby and Znby appear to reflect the preferred mode of the conformational adaptation of the coordination hole of the flexible, unsymmetrical corrin ligand to bound metal ions. The radial size of the coordination hole also shrunk upon Ni$^{II}$ coordination as the average length of the N1-N3 and N2-N4 diagonals of Hby ($d = 3.82 \, \text{Å}$) was reduced to $d = 3.71 \, \text{Å}$ in the complex Niby. Hence, the coordination of the Ni$^{II}$ ion in Niby contracts the corrin ligand and makes it more symmetrical. This latter effect is also expressed by the regularly alternating bond lengths of the corrin $\pi$-system in Niby, observations that are compatible with the model Ni-corrin CCor\textsuperscript{[9]}. The four-coordinate Ni$^{II}$ ion sits very close to the plane of the four inner corrin N atoms, comparable to the situation in the Ni$^{II}$-corrin CCor\textsuperscript{[9]} and in typical Co$^{III}$-corrins,\textsuperscript{[16a]} but contrasting somewhat with the out of plane distance of 0.048 Å of the five-coordinate Co$^{II}$ center of heptamethylcob(II)yrinate perchlorate (Cbin$^{II}$)\textsuperscript{[17]} (SI, Table S5). As expected,\textsuperscript{[9,18]} the metal–N bonds in Niby (average Ni–N bond length = 1.86 Å) are shorter than those found in the Co$^{II}$ analogue Cbin$^{II}$ and in the Co$^{III}$-corrin coenzyme B$_{12}$ (AdoCbl), where average (Co$^{II}$-N) and (Co$^{III}$-N) bond lengths of 1.89 Å\textsuperscript{[19]} and of 1.90 Å,\textsuperscript{[20]} respectively, were observed.

The coordination of the Ni$^{II}$ ion barely affects the conformational properties of the metal-free corrin ligand (Figures 5,6). Only a slight reduction of the helicity, $h$ (Figure 7), of the inner corrin N atoms from $h = 12.9^\circ$ in Hby to $h = 10.1^\circ$ is seen in Niby. Indeed, the effect of the binding of the Ni$^{II}$ ion on the corrin helicity is comparable to the situation in the enzyme-bound four-coordinate cob(II)alamin (4c-Cbl$^{II}$ (ACA)) of the adenosyltransferase ACA,\textsuperscript{[23]} for which $h = 8^\circ$.\textsuperscript{[15]} In contrast, in five-coordinate Co$^{III}$-corrins the corrin helicity is significantly smaller, for example, $h = 6.1^\circ$ in the Co$^{III}$-corrin Cbin$^{II}$, and in typical Co$^{III}$-corrins planarization of the corrin ligand is still more pronounced, leading, for example, to $h = 3.5^\circ$ in AdoCbl.\textsuperscript{[3]}

The observed lower drive of the four-coordinate $d^8$ Ni$^{III}$ ion to planarize the corrin macrocycle is similarly reflected by its own coordination geometry, which deviates strongly in Niby from the coplanar arrangement of the coordinating ligand atoms in typical four-coordinate low-spin Ni$^{III}$ complexes.\textsuperscript{[19,10,18]} In Niby a remarkably large interplanar angle $\phi$ (Figure 7) at Ni$^{III}$ ($\phi = 11.1^\circ$) results from extensive directional conformational adaptation of the Ni$^{III}$ center to the geometric requirements imposed by the helical corrin ligand (see Figure 6 and SI). $\phi$ is significantly larger in Niby than in Co$^{III}$-corrins, which exhibit $\phi$’s around 5° or less,\textsuperscript{[3]} and is comparable to the situation in five-coordinate Co$^{III}$-corrins Cbl$^{II}$ ($\phi = 12^\circ$) and Cbin$^{II}$ ($\phi = 7.6^\circ$).

The corrin helicity $h$ and the inter-planar angle $\phi$ (Figure 7), were introduced recently as two complementary parameters characterizing inner conformational effects of the mutual structural adaptation of the corrin macrocycle and of the coordination geometry at the bound metal ion.\textsuperscript{[3]} The so called corrin fold of the helical corrin macrocycle,\textsuperscript{[22]} a classic parameter characterizing the nonplanar corrin ring in Cbls and in other “complete” cobamides (Figure 7), was not used in this current study. Conceived as a measure of the major conformational adaptation of the corrin ring to the cobalt coordination of the (bulky) DMB moiety in “base-on” Cbls, it runs roughly along the Co-C10 (east-west) axis.\textsuperscript{[22]} However, in four- and five-coordinate metal-corrins lacking the DMB unit, like Cbin$^{II}$, Niby and Znby, the calculated corrin-fold is dominated by the effects of the corrin helicity and the intersection between the two relevant planes adheres to a north-south direction (see SI Table S5 and Figure S22).

DFT calculations were carried out to test further the proposed close structural similarity between Ni$^{II}$-corrins and their analogues with four-coordinate cobalt centers (see Figure 8 and SI for further details). In order to minimize the relevance of peripheral H-bonds between the amide functions in the implicit solvent calculations, the five-coordinate lip-
ophilic heptamethyl-cob(II)yrinate perchlorate (CbinII)\[^{[17]}\] was used as a starting model. Calculations of the structures of the related unknown corphins heptamethyl-nibyrinate (Nibin), four-coordinate heptamethyl-cob(II)yrinate (4c-Cob\(^{\text{II}}\)in) and heptamethyl-cob(II)yrinate (Cob\(^{\text{II}}\)in) were carried out. They indicate extensive structural similarities, but the N1-N3 diagonal was calculated to be shorter than its N2-N4 by roughly 0.01–0.02 Å, which is also in good qualitative agreement with the crystallographic data for Nibin and CbinII\[^{[17]}\]. All 4-coordinate metal centers (Ni\(^{\text{II}}\), Co\(^{\text{I}}\) and Co\(^{\text{II}}\)) were calculated to be located virtually in the best plane through the four corrin N-atoms. The latter is arranged in a helix with a calculated value of \(h\) slightly decreasing from Nibin (7.6°) to Cob\(^{\text{II}}\)in to 4c-Cob\(^{\text{II}}\)in (6.6°), and induced an interplanar angle \(\phi\) that slightly decreased in the same order (from 8.4° to 7.5°). The calculations for five-coordinate Cbin\(^{\text{II}}\) also reproduced, qualitatively, the still smaller value for \(h\) (5.4°), a larger value for \(\phi\) (11.3°) and a significant displacement of the Co\(^{\text{II}}\) center towards the axial \(\beta\)-ligand (calculated as 0.112 Å).

The deduced utility of Nibl as a specific new structural mimic of four-coordinate base-off Cbls was initially tested in binding studies of Nibl to an adenosyltransferase enzyme (ATP-Corrinoid adenosyltransferase), which catalyzes the biosynthetic construction of AdoCbl by Co\(^{\text{II}}\)-adenosylation of bound Cbl\(^{\text{I}}\). Such bacterial\[^{[23]}\] and human adenosyltransferases\[^{[24]}\] for example, BtuR\[^{[23a]}\], CobA\[^{[23b]}\], ACA\[^{[21]}\] and CblB\[^{[24]}\] have been shown to facilitate the adenosylation process by first inducing the corrin substrate to adopt a four-coordinate structure, thus raising the redox potential of the Co\(^{\text{II}}\)/Co\(^{\text{I}}\) couple by around 250 mV\[^{[23,24]}\] thereby allowing the physiologically difficult reduction. We, thus, investigated the effect of Nibl on the adenosylation process by incubating the Brucella melitensis BtuR\[^{[23a]}\] and the structural Cbl mimic Nibl in the presence of an excess of Cbl\(^{\text{I}}\) (see SI, Figures S27–S29). As expected, Nibl itself was not a substrate for the enzyme and was not adenosylated. However, the presence of Nibl within the incubation did effectively inhibit the adenosyltransferase, reducing the activity of the enzyme by 38% at a concentration of 1 μM, and by 60% at 5 μM (Figure S29). Thus, the four-coordinate Ni\(^{\text{II}}\) center of Nibl affords it the ability to bind within the active site of the adenosyltransferase and to prevent the productive binding of the natural substrate Cbl.

**Conclusion**

Herein, we have described the first Ni\(^{\text{II}}\) analogues of natural cobalt corrins vitamin B\(_{12}\) (CNCHbl) and cobyric acid (Chy). The new Ni-corrins Nibl and Niby display the same basic structural features and lack of coordinative activity as synthetic model Ni\(^{\text{II}}\)-corrins, such as NiCor\[^{[1a,6a,c]}\]. The Ni\(^{\text{II}}\) corrins are known to be exceptionally stable in regard to the chemical removal of their metal center\[^{[25]}\] and to exhibit no affinity for axially coordinating ligands\[^{[1a,6c,7]}\]. This latter feature has been rationalized by the extraordinary stabilization of the low-spin d\(^{8}\) configuration by the ligand field of the ring-contracted corrin ligand\[^{[1a,9]}\]. As shown here, the natural corrin ligand undergoes only a small contraction of its coordination hole by about 0.03 to 0.04 Å to accommodate the low-spin Ni\(^{\text{II}}\) ion. Indeed, the 15-membered inner perimeter provided by the natural corrin macrocycle, selected for binding low-spin cobalt ions, also binds Ni\(^{\text{II}}\) consistently in comparison to the four-coordinate Co\(^{\text{II}}\)-corrin 4c-Cob\(^{\text{II}}\)in and 5-coordinate Cbin\(^{\text{II}}\). The N1-N3 diagonal was calculated to be shorter than its N2-N4 by roughly 0.01–0.02 Å, which is also in good qualitative agreement with the crystallographic data for Nibin and Cbin\(^{\text{II}}\).
its low-spin state. In contrast, in the porphyrinoid $\text{B}_{12}$-related nickel complex coenzyme $F_{550}$[1a,18,26] the 16-membered porphyrinoid macrocycle is a key player in the active, specific adjustment of the spin state and coordinative activity of the nickel center to its function in the enzyme catalyzed methane formation.[27] Indeed, the discovery of coenzyme $F_{550}$ provoked an entirely new look at the structural effect of the tetrapyrrolic macrocycle on the coordination chemistry of bound first-row transition metals.[18]

A common feature of the valence shell of the low spin states of the transition metal ions $\text{Ni}^{II}$, $\text{Co}^{III}$, $\text{Co}^{II}$ and $\text{Co}^{I}$ is their unoccupied $d_{x^2-y^2}$ orbital, a key factor responsible for their strong sigma bonding interactions with the four inner corrin N atoms, leading to similar radial characteristics of their corrin complexes. A differing number of valence shell electrons in $\text{Ni}^{II}$, $\text{Co}^{III}$, $\text{Co}^{II}$ and $\text{Co}^{I}$-corrins is transduced primarily into characteristically different reactivity of the metal centers in the axial direction, strongly affecting their potential binding sites there. Consequently, $\text{Ni}^{II}$-corrins are to be considered particularly well-suited structural mimics of corresponding isoelectronic $\text{Co}^{I}$-corrins, the critical intermediates in heterolytic organometallic transitions in $\text{B}_{12}$-dependent enzymes.[28] Crystallographic insights and DFT-based structure calculations also indicate a structural similarity between $\text{Ni}^{II}$-corrins and the exceptional four-coordinate $\text{Co}^{II}$-corrins. This result contrasts strikingly with the mutually different structures of the typical five-coordinate $\text{Co}^{III}$-corrins and their $\text{Zn}^{II}$-analogues[11] with similarly sized metal ions[29] that differ by the number of electrons in the valence shell.[30]

The structural analysis of the Nibyrinates predicts that the constitutively robust $\text{Nbl}$ would likely be an excellent redox-resistant structural mimic for the elusive cob(I)alamin ($\text{Cbl}^{I}$), a highly reactive redox-active intermediate[30] that is found in $\text{B}_{12}$-dependent methyl group transferases, such as methionine synthase,[26a] as well as in the biosynthesis of $\text{AdoCbl}$ from $\text{Chbl}^{I}$ (via $\text{Chb}^{I}$) by $\text{Cbl}$-adenosyltransferases.[23,24] $\text{Nbl}$ may, likewise, act as a good structural mimic of the recently described natural four-coordinate $\text{Co}^{III}$-corrins, proposed as key intermediates in the enzymatic transformations catalyzed by the vitamin $\text{B}_{12}$-tailoring enzyme $\text{CblC}^{III}$[31] in corrinoid dehalogenases[29] or as substrates for the reduction to $\text{Co}^{II}$-species in enzymatic cobalt alklylation.[14,33] Indeed, as verified here, $\text{Nbl}$ is a very effective inhibitor of the bacterial $\text{Cbl}$-adenosyltransferase $\text{BtuR}$.

We have developed a rational and direct synthetic path from hydrogentcobalamin (H$\text{bbl}$) via hydrogenobalamin ($\text{Hbl}$) to nibalamin ($\text{Nbl}$), a novel transition-metal analogue of the $\text{Cbl}$s. Our recent studies with the $\text{Rh}^{II}$ analogue $\text{AdoRhbl}$ of $\text{AdoCbl}^{II}$,[32] with the $\text{Zn}^{II}$ analogue $\text{Zbl}$ of $\text{Chbl}^{II}$,[33] and now the $\text{Ni}^{II}$ analogue $\text{Nbl}$ of $\text{Chbl}$,[34] have furnished a valuable suite of cobalamin mimics for use in the study of $\text{B}_{12}$-dependent enzymatic processes,[18a,26,30,34,35] and in $\text{B}_{12}$-dependent biological regulation.[36] Well-characterized and adequately accessible transition metal analogues (M$\text{etbls}$) of the $\text{Cbl}$s provide a promising small-compound platform that may contribute significantly to the ongoing quest for innovative $\text{B}_{12}$-based biological and biomedical applications.[13,36] Along these lines, some $\text{Methbs}$ may find applications as effective antivitamins $\text{B}_{12}$.[34,111] The availability of selected $\text{Methbs}$ and of related metal corrins (MetCor) will also allow more detailed experimental investigations into the chemical relevance of the coordination of transition metal ions by the uniquely skewed, strongly helical and unsymmetric natural corrin ligands.[3] Such studies will endow a more informed understanding of the specific evolutionary selection of cobalt rather than any other transition metal[1] for the task of complex organometallic catalysis achieved by the $\text{B}_{12}$ cofactors.

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**Conflict of interest**

The authors declare no conflict of interest.

**Keywords:** cobalamins - porphyrinoids - transition metals - crystal structures - vitamins

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Nibalamin (Nbl), the novel Ni\textsuperscript{II} analogue of vitamin B\textsubscript{12}, was synthesized from the metal-free B\textsubscript{12} ligand hydrogenobalamin, prepared from biosynthetic hydrogenobyric acid (Hby). An X-ray crystal analysis of nibyric acid, the Ni\textsuperscript{II} complex of Hby, revealed the first structural details of a nickel complex of a natural corrin ligand. Nbl is a structural mimic of the corresponding four-coordinate cobalamins, which are of interest in biological investigations.