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# Encasing the paramagnetic copper( $\parallel$ )-ion by the ring-contracted corrin ligand of vitamin B<sub>12</sub>†‡

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The d<sup>9</sup>-Cu(11)-corrin cupribyrate (Cuby) was synthesized in 93% crystalline yield by rapid chelation of Cu<sup>2+</sup>-ions by the metal-free corrin-ligand of vitamin B<sub>12</sub>. Single crystals of the EPR-active Cuby allowed for the first X-ray structure determination of a Cu-corrin. SCF-calculations provided insights complementary to the experimental data of Cuby and indicated an out-of-plane displacement of the reduced d<sup>10</sup>-Cu(1)-ion, consistent with the observed reductive activation of Cuby towards loss of its Cu-center.

The ring-contracted natural corrin ligand of the B<sub>12</sub>-derivatives is a uniquely skewed, helical environment<sup>1,2</sup> that binds cobalt-ions very tightly.<sup>3,4</sup> This biosynthetically costly ligand for cobalt<sup>5,6</sup> represents a precisely evolved entatic state module,<sup>2</sup> giving B<sub>12</sub>-cofactors the unique capacity for their exceptional bioorganometallic catalysis.<sup>7–9</sup> The complementary fundamental question, why cobalt? in B<sub>12</sub>-cofactors,<sup>1,3,9,10</sup> has generated the long-standing experimental quest for non-cobalt analogues of the B<sub>12</sub>-derivatives,<sup>11,12</sup> a challenge met by newly developed synthetic approaches.<sup>2,13</sup> We have, thus, prepared Rh(m)-,<sup>13–17</sup> Ni(n)-<sup>18</sup> and Zn(n)-complexes<sup>19</sup> of natural corrin ligands for studies of their structures and reactivity. Here, we report on cupribyrate (**Cuby**) (Scheme 1), the Cu(n)-complex of hydrogenobyric acid (**Hby**),<sup>2</sup> including the first Cu-corrin X-ray crystal structure.

The complexation of metal-free **Hby** with Cu(n)-ions occurred readily at room temperature (RT) in a 0.25 M aqueous solution of Cu(n)-acetate at pH 6 and was practically quantitative within 90 min (see the ESI‡). It did not require the reported strong heating ('brief boiling').<sup>11,20</sup> Crystallization of the raw **Cuby**-isolate from water/acetonitrile mixtures furnished **Cuby** in >93% yield.

The UV/Vis-spectrum (Fig. 1) of an aqueous solution of **Cuby** exhibits a corrin-type and is comparable to the earlier reported spectra of partially characterized Cu( $\mu$ )-corrins.<sup>20,21</sup> UV/Vis- and CD-spectra of **Cuby** show remarkably similar features to the corresponding spectra of the Zn( $\mu$ )-complex<sup>19</sup> of **Hby**, consistent with the dominating role of the corrin chromophore for the spectral signature in the UV- and Vis-range. A HR-ESI mass spectrum of **Cuby** confirmed the calculated molecular formula of C<sub>45</sub>H<sub>64</sub>CuN<sub>10</sub>O<sub>8</sub> (see the ESI,‡ Fig. S1).

Glassy frozen solutions of the paramagnetic Cu( $\pi$ )-corrin **Cuby** in 20% glycerol in H<sub>2</sub>O showed the typical EPR-signature (see Fig. 2, for a spectrum at *T* = 148 K) of a roughly square-planar 4-coordinate Cu( $\pi$ )-N<sub>4</sub>-complex with an index<sup>22,23</sup> g<sup>II</sup>/A<sup>II</sup> = 98.2 cm, assigning an exceptionally low value to the encasement of the Cu( $\pi$ )-ion by the corrin ligand (see the ESI‡ for further details).

The neutral cupribyrate **Cuby** crystallized from an aqueous solution upon addition of acetonitrile. The monoclinic crystals (space group  $P2_1$ ) contain two **Cuby** molecules per unit cell, as well as molecules of water and acetonitrile (ordered near the **Cuby**-carboxylate). The Cu( $\pi$ )-center of the **Cuby** molecule sits only +0.033 Å above the mean plane of the four 'inner' corrin N-atoms, which span an unsymmetrical and nearly planar coordination pattern (see Fig. 3), as reflected by the value of



Scheme 1 Structure-based outline of the synthesis of cupribyrate (Cuby) from hydrogenobyric acid (Hby) (see the ESI $\ddagger$ ) and the structural formula of Co<sub>x</sub>cyano, Co<sub>β</sub>aquo-cobyric acid (Coby).

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 $<sup>\</sup>dagger$  Dedicated to the memory of Albert Eschenmoser on the occasion of his 100th birthday.

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Fig. 1 UV/Vis- and CD-spectra of Cuby (19  $\mu\text{M}$  in 10 mM aqueous phosphate pH 7).



**Fig. 2** EPR-spectrum of a 1.34 mM frozen solution (at T = 148 K) of **Cuby** in H<sub>2</sub>O:glycerol (4:1) and its simulation with key parameters obtained by least square fitting (for details see the ESI,‡ Table S1). The spectra exhibited a significant T-dependence, with a maximum signal intensity of around 200 K and continuous decrease at lower temperatures (see the ESI,‡ Fig. S4).

the geometry index  $\tau_4 = 0.17$ .<sup>24</sup> However, **Cuby** exhibits a less planar arrangement around its 4-coordinate d<sup>9</sup> Cu(II)-center, than in the Ni( $\pi$ )-corrin nibyrate (Niby),<sup>18</sup> which experiences a better fit of its 4-coordinate low-spin d<sup>8</sup> Ni(II)-ion (see the ESI,‡ Table S3). The average Cu-N distance in Cuby amounts to 1.91 Å, merely 0.05 Å longer than in Niby, in which the 0.08 Å smaller low spin d<sup>8</sup>-ion Ni(1)<sup>25</sup> induced a slight contraction.<sup>18</sup> In fact, binding of the d<sup>9</sup> Cu(II)-ion largely retains the architecture of the coordination hole of the metal-free corrin ligand Hby, expanded by two 'inner' protons.<sup>2</sup> In Cuby, the critical angle parameters corrinfold<sup>26</sup> (10.0°) and corrin helicity<sup>2</sup> (12.4°) are also similar to those of the ligand Hby,<sup>2</sup> but remarkably larger than in Niby. Likewise, the angle between the planes N1-Cu-N2 and N3-Cu-N4 (roughly  $13.6^{\circ}$ ) relating to the inner coordination-sphere around the Cu(II)-center (see the ESI,‡ Table S3) is close to the value derived for Hby.<sup>2</sup> Interestingly, the N1-M-N3 pseudo-diagonal in Cuby was roughly 0.07 Å shorter than the N2-M-N4 counterpart, thus



Fig. 3 X-ray crystal structure of **Cuby** in ORTEP-representations. Top: axial view from above ( $\beta$ -side); bottom: approximate in-plane view, revealing the slightly nonplanar 4-fold coordination of the encased Cu( $\parallel$ )-ion.

displaying a larger difference of the distances across these pseudo-diagonals than in **Niby**. This desymmetrization of the corrin core in **Cuby** also goes along the one observed in **Hby** and its Zn(n)-complex,<sup>19</sup> but is insignificant in the Co(n)-corrins Co(n)-cobalamin (**Cbl**<sup>II</sup>)<sup>27</sup> and cob(n)ester<sup>28</sup> and in typical Co(m)-corrins, such as coenzyme B<sub>12</sub> (**AdoCbl**)<sup>29</sup> and vitamin B<sub>12</sub>.<sup>30,31</sup>

Our self-consistent field (SCF) in the gas-phase calculation of cupribyric acid (**HCuby**+), the cationic carboxylate-protonated form of **Cuby**, used the atomic coordinates of the **Cuby** crystal structure. In this model, large artefactual electron density contributions of the carboxylate function of **Cuby** to occupied MOs were lacking, consistent with the experimental absence of such interactions. The so-derived computational



**Fig. 4** Frontier molecular orbitals (FMOs) of the cupribyric acid cation (**HCuby**<sup>+</sup>) from the self-consistent field in gas-phase calculations. From left to right: the highest occupied MO (HOMO), a corrin  $\pi$ -type orbital; the d<sub>x<sup>2</sup>-y<sup>2</sup></sub>-type Cu(II)-located singly occupied MO (SOMO); and the lowest unoccupied MO (LUMO), a corrin  $\pi$ -type orbital. Orbitals are seen from the upper side.

insights into the bonding interactions of a d<sup>9</sup>-Cu(II)-corrin were fully consistent with separately located calculated frontier molecular orbitals, either as  $\pi$ -type corrin ligand MOs or as the singly occupied  $d_{x^2-v^2}$ -type orbital on the Cu(II)-center (see Fig. 4 and ESI<sup>‡</sup> Fig. S13). We also tested computed models of cuprobyric acid (Cu(1)by) to shed light on the difficult<sup>32</sup> oneelectron reduction to a d<sup>10</sup>-Cu(I)-corrin (for details, see the ESI,‡ Fig. S14). The calculations suggest a large upper axial out of plane movement of the Cu(I)-ion, comparable to the position of the rather weakly bound Zn(II)-center in zincobyric acid (Znby).<sup>19</sup> Indeed, the iso-electronic nature of the closed shell d<sup>10</sup>-ions Cu(I) and Zn(II) suggested the likelihood of the complete removal of a Cu(1)-ion from reduced Cuby in a weakly acidic aqueous medium. In an exploratory experiment, Cuby was treated with Zn-powder in an aqueous NH<sub>4</sub>Cl solution, leading to the effective replacement of the Cu-center of Cuby by Zn(II), furnishing **Znby**,<sup>19</sup> and its tentatively (by mass- and UV/ Vis-spectroscopy) characterized dihydro-form H<sub>2</sub>-Znby, an unprecedented ring-reduced yellow corrinoid<sup>33,34</sup> (see ESI,‡ Scheme S1). We ascribe the observed formation of Znby from **Cuby** to a transient generation of an exchange-labile d<sup>10</sup>-Cu(I)center by the Zn-reduction, thus strategically circumventing Eschenmoser's postulate that a B-type transition metal could not be removed without destruction of the corrin-ligand.<sup>35</sup>

The replacement, by copper, of the biologically selected cobalt-center of a corrinoid B<sub>12</sub>-derivative<sup>1,36,37</sup> erases its fundamental organometallic redox-reactivity.7 The single unpaired electron of the paramagnetic Cuby does not contribute any (cobalt-mimetic) radical reactivity, but is 'buried' in a  $d_{x^2-y^2}$ orbital of its d<sup>9</sup> Cu(II)-center. Consistent with the EPR-spectral fingerprint of Cuby and its large <sup>14</sup>N-hfcs with the four inner corrin N-atoms, in particular, the unpaired spin is located in a  $d_{x^2-y^2}$  orbital of an effectively antibonding type with respect to the coordinating corrin N-atoms (Fig. 4). Compared to the d<sup>8</sup> Ni(II)-ion in Niby, the Cu(II)-N bonds in Cuby are, indeed, longer. Copper complexes of the superficially similar corroles represent a remarkably more complex situation:<sup>38,39</sup> there 'noninnocence' of the corrole ligand is caused by its extended  $\pi$ -system, assisting an intramolecular electron-shift and stabilizing the copper center in a higher oxidation state.<sup>40</sup>

The chelation of the fluorescent metal-free corrin **Hby**<sup>2,41</sup> by Cu(II)-ions in aqueous solution occurs cleanly at ambient temperature at pH 5. The Cu(II)-ions chelate **Hby** with a rate  $k^{\text{Cu(II)}} = 0.54 \pm 0.04 \text{ L} \text{ mol}^{-1} \text{ min}^{-1}$ , remarkably quicker by about  $2 \times 10^2$  times than the binding of the biologically crucial Co(II)-ions ( $k^{\text{Co(II)}}$  of about  $3 \times 10^{-3} \text{ L} \text{ mol}^{-1} \text{ min}^{-1}$ ), and five times faster than Zn(II)-ions ( $k^{\text{Zn(II)}} = 0.111 \pm 0.002 \text{ L} \text{ mol}^{-1} \text{ min}^{-1}$ , see the ESI‡). The chelation rates of these metal ions follow the trend established with Eschenmoser's model corrin<sup>35</sup> and with a water-soluble tetra-mesopyridyl-porphyrin.<sup>42</sup>

Obviously, the biological roles of  $\text{Co}^{7,8,43}$  and  $\text{Cu}^{44-47}$  do not match. However, the 4-coordinate  $\text{Cu}(\pi)$ -complexes of natural corrin ligands may serve as structural mimics of reduced  $B_{12}$ derivatives. In concert with the divergent reactivity profiles of copper- and cobalt-corrins, biologically interesting applications are likely. **Cuby** is structured similar to the corrin-core of enzyme-activated 4-coordinate Co( $\pi$ )-cobamides, first characterized in an ATP:Co( $\eta$ )-corrinoid adenosyltransferase that generates **AdoCbl** from 4-coordinate Co( $\pi$ )-Cbl.<sup>48</sup> With their largely inert 4coordinate d<sup>9</sup>- and d<sup>8</sup>-metal-centers, respectively, Cu( $\pi$ )- and Ni( $\pi$ )-corrins<sup>18</sup> may effectively mimic the structures of the highly activated 4-coordinate Co( $\pi$ )- and Co( $\eta$ )-corrins. Indeed, nibalamin (**Nibl**), the diamagnetic Ni( $\pi$ )-analogue of 'base-off' Co( $\pi$ )-Cbl, was shown to be an effective inhibitor of the corrinoid adenosyltransferase BtuR from *Brucella melitensis*.<sup>18</sup> The crystal structure of **Cuby** qualifies Cu( $\pi$ )-containing B<sub>12</sub>-derivatives, such as cupribalamin (**Cubl**), for similar inhibitory effects.

Transition metal analogues of vitamin B<sub>12</sub> and other cobalamins (Cbls), also classified as metbalamins (Metbls),<sup>49,50</sup> lack the precise cobalt-dependent reactivity of Cbls<sup>8,43</sup> and, when mimicking Cbl-structures, may represent genuine antivitamins  $B_{12}$ .<sup>50,51</sup> This is the case for rhodibalamins (Rhbls), the Rh(III)homologues of Cbls. Surprisingly, their Rh(m)-center has even been revealed to experience a slightly better fit to the corrin ligand than the naturally selected Co(III)-ions.<sup>13-15</sup> Whereas uptake and physiological activity of Metbls with stable 4coordinate corrin-bound metal centers are still unknown in humans and animals, microorganisms are typically more structure-promiscuous for B<sub>12</sub>-import, satisfying their supply with cobamides by *de novo* biosynthesis<sup>5</sup> or by partial assembly from salvaged natural corrinoids.52,53 As deduced for some Rhbls<sup>13,15</sup> and for Nibl,<sup>18</sup> transition metal-based structural mimics of B12-cofactors or of corrinoid B12-biosynthesis intermediates<sup>17</sup> may selectively inhibit bacterial growth. As mimics of enzyme-bound Cbl-structures in B12-dependent enzymes at intermediate stages of catalysis, Metbls may specifically act as very effective enzyme inhibitors. The Cu(II)analogues of natural B12-derivatives are, hence, EPR-active candidates for their applications as B12-antimetabolites for  $B_{12}$ -dependent microorganisms, an expansion of the toolbox of Cu-coordinating natural products<sup>47</sup> as antimicrobial agents.

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#### Conflicts of interest

There are no conflicts to declare.

#### Data availability

See the ESI.<sup>‡</sup> Crystallographic data for cupribyrate (Cuby) have been deposited at the Cambridge Crystallographic Data Center (CCDC) and are available under accession number CCDC-2402239.

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