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Austrian Science Fund Project P-33059: Transition Metal-Analogues of Natural Cobalt-Corrins – Chemistry of Metal-Corrins, Antivitamins B_{12} and other B_{12}-Mimics

The B_{12}-cofactors are metabolic players essential in all three kingdoms of life, including humans and animals, giving them the role of the most broadly relevant organometallic biological catalysts. They were subjects of recent discoveries concerning B_{12}-biosynthesis, B_{12}-uptake and metabolism in humans and bacteria, and the biological uses of B_{12}-cofactors in enzymes and in metabolic regulation.

Vitamin B_{12}, an indispensable nutrient for humans, is the only complex natural product dependent upon cobalt. We are intrigued by the specific role and its interaction of this transition metal with the complex corrin macrocycle, a unique chemical structure only found in the B_{12}-cofactors. The present project is founded on our recently gained access to metal-free B_{12}-derivatives for the rational syntheses of analogues of the B_{12}-cofactors with other transition metals but cobalt, a 'holy grail' in the B_{12}-field. Such B_{12}-analogues may represent metabolically inert structural B_{12}-mimics including exceptional 'antivitamins B_{12}'. These latter are expected to effectively cause B_{12}-deficiency in B_{12}-dependent organisms, generating crucial insights into the metabolic activity of the B_{12}-cofactors.

In this contribution to the B_{12}-field the novel transition metal analogues of the B_{12}-cofactors are synthesized, selected on the basis of their hypothetical structural properties and chemical reactivity. We develop a rational and direct, chemical biological synthesis approach to transition metal analogues of the natural cobalt-corrins, applying preparative methods hardly explored in the B_{12}-area. We will study the chemistry of non-cobalt transition metal-ions, when bound to the unique natural corrin ligand. This work will provide first insights into the coordination chemistry of such metal-ions bound by natural corrins, and open up new means for studying the molecular basis of the biological roles of B_{12}-cofactors. Modern spectroscopic, crystallographic and electro-chemical methods will be used for the characterization of the new B_{12}-analogues and of their biomimetic molecular features.

From the further planned collaborative biochemical, biological and bio-structural studies, new insights into the bio-macromolecular interactions of B_{12}-cofactors, into hypothetical modes of action of B_{12}-dependent enzymatic transformations and into the molecular mechanisms of B_{12}-dependent gene regulation are expected, using our metal analogues.

The proposed studies of 'metal mimics' of the fascinating organometallic B_{12}-cofactors, their structures and reactivity will help the researchers involved to gain experimental expertise and training at the state-of-the-art level in an exciting exploration of new horizons in chemistry and chemical biology, embedded in a collaborative, interdisciplinary research environment.