doi:10.2533/chimia.2024.443 Chimia 78 (2024) 443–444

Swiss Science Concentrates

A CHIMIA Column

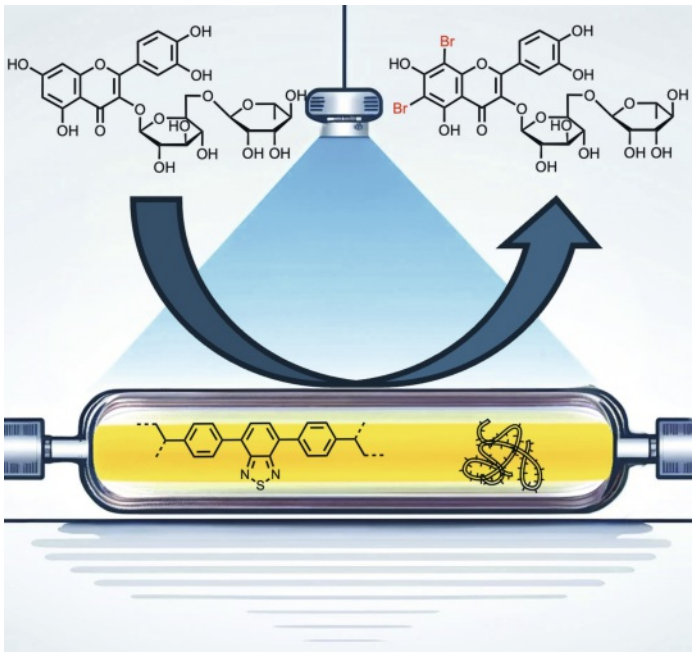
Short Abstracts of Interesting Recent Publications of Swiss Origin

Engineering a Dual-Functionalized PolyHIPE Resin for Photobiocatalytic Flow Chemistry

Emmanouil Broumidis and Francesca Paradisi*
Angew. Chem. Int. Ed. **2024**, e202401912, https://doi.org/10.1002/ange.202401912
University of Bern

The utilization of a dual resin system for photobiocatalysis, integrating both a photocatalyst and an immobilized enzyme, presents several challenges such as effective immobilization, maintaining the activity of both the photocatalyst and enzyme, and ensuring adequate light penetration. However, the benefits including streamlined processes, reusability, simplified product separation, and potential scalability outweigh these challenges, making dual resin systems highly promising for efficient and sustainable photobiocatalytic applications. In this study, photosensitizer-containing porous emulsion-templated polymer was employed as a functional support to covalently anchor a chloroperoxidase from *Curvularia inaequalis* (CiVCPO). It was demonstrated that the material enables the bromination of four aromatic substrates, marking the first example of continuous flow biotransformation using a photobiocatalytic resin.

***Authors' comments*:**
"This work was a very successful example of what we can achieve when two different sets of skills are blended together, Manos brought us photoactive materials and we stuck an enzyme on it!"



A Billion Years of Evolution Manifest in Nanosecond Protein Dynamics

Philipp J. Heckmeier*, Jeannette Ruf, Charlotte Rochereau, and Peter Hamm
Proc. Nat. Acad. Sci. USA (PNAS) **2024**, *121* (10) e2318743121, https://doi.org/10.1073/pnas.2318743121
University of Zurich

Proteins exist as dynamic ensembles, undergoing constant rearrangements, folding, and unfolding processes. Understanding this dynamic in nature is crucial for comprehending protein function. However, the impact of evolution on these ultrafast processes within proteins remains largely unexplored. Using time-resolved infrared spectroscopy, we resolved the nanosecond dynamics of a protein family with a conserved role in cellular survival spanning nearly a billion years. Our analysis unveiled a cascade of rearrangements within all examined family members, uncovering processes virtually unchanged over hundreds of millions of years. Through the introduction of species-specific kinetic footprints, our study facilitates the comparative analysis of species based on their ultrafast protein dynamics. In doing so, our approach complements traditional methods in molecular paleontology, bridging the gap between the shortest time scales in living matter (10^{-9} s) and the largest (10^{16} s).

***Authors' comments*:**
"Here we observe the effect of a billion years on processes that take place in a billionth of a second. Unimaginably many generations of living beings must have passed on the same information over and over again, so that protein space has been conserved in an unchanging form. Over a billion years."

Prepared by Cesare Berton, Patrick A. Cieslik, Fan Liu, Stanislav Prytuliak, Simon Klinger, Jonas Genz, Eda Nisli, Ben Boback, Perle Hermant and Jason P. Holland*
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Structural Changes in the Carbon Sphere of a Dirhodium Complex Induced by Redox or Deprotonation Reactions

Clara Schweinzer[a], Peter Coburger[b], and Hansjörg Grützmacher[a,c]
Adv. Sci. **2024**, 2400072, https://doi.org/10.1002/advs.202400072
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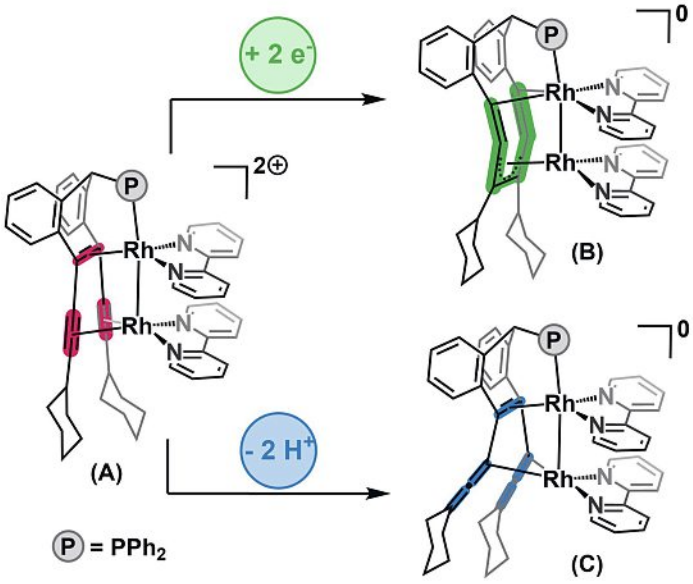
Structural rearrangement reactions can sometimes take place within the ligands of homogeneous transition metal complexes. The bimetallic $Rh^{I}Rh^{I}$ complex (A) presented in this study falls into that category. The carbon rich binding pockets within the ligand respond to redox and deprotonation reactions. Diverse C–C bond rearrangements within the carbon framework are observed: ring expansion (C_7 to C_{11}) upon two electron reduction (B) (no structural change takes place after a one electron reduction) and alkyne to allene isomerisation upon removal of propargylic C-H protons (C). These findings shed light on electronic structure alterations induced by metal centers in a carbon-rich milieu, with potential implications for metal particles on carbon support materials exposed to hydrogen, electrons, or protons.

***Authors' comments*:**
"The most striking observation was the cleavage of the C=C bond within our well-studied 'trop' molecule. We also found the presence of both rhodium atoms as well as the bipyridine ligands to be necessary to form stable rearrangement products."



In vivo Activation of FAP-cleavable Small Molecule-drug Conjugates for the Targeted Delivery of Camptothecins and Tubulin Poisons to the Tumor Microenvironment

Matilde Bocci*, Aureliano Zana, Lucrezia Principi, Laura Lucaroni, Luca Prati, Ettore Gilardoni, Dario Neri, Samuele Cazzamalli*, and Andrea Galbiati*
J. Controlled Release **2024**, *367*, 779, https://doi.org/10.1016/j.jconrel.2024.02.014
Philochem AG

Small molecule-drug conjugates (SMDCs) are a new tool for targeted cancer therapy that can be used as an alternative to Antibody-drug conjugates (ADCs). In this article, the authors report new SMDCs containing the OncoFAP binding motif to target the Fibroblast Activation Protein (FAP), a stromal tumour-associated antigen overexpressed in a wide variety of solid tumours. Linkers and payloads of three conventional ADCs were adapted to the small molecule targeting vector. A next generation of SMDCs was designed containing linkers that can be cleaved directly by the target's intrinsic proteolytic activity. The therapeutic efficacy of all new SMDCs was benchmarked using a murine cancer model by monitoring tumour growth. Constructs using the FAP-cleavable linker system showed the highest therapeutic effect, demonstrating the synergic effects of co-optimizing targeting vectors and cleavable linkers in SMDCs. For the most effective construct Phase I clinical trials are currently being initiated to bring the drug from the bench to the patient.

***Authors' comments*:**
"In this work, we highlighted the impact of linkers and cytotoxic payloads on the activity of SMDCs targeting FAP. The conjugates with MMAE and Exatecan proved effective in preclinical models, paving the way to the Phase I Clinical Trial."