

## FIVE MOST IMPORTANT RESEARCH ARTICLES

Rulíšek, L.\*; Havlas, Z.: Theoretical Studies of Metal Ion Selectivity. 1. DFT Calculations of Interaction Energies of Amino Acid Side Chains with Selected Transition Metal Ions ( $\text{Co}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Hg}^{2+}$ ). *J. Am. Chem. Soc.* **2000**, *122*, 10428-10439. [**166 citations**/155 with all forms of self-citations excluded]

**Abstract:** The interaction energies of functional groups representing the side chains of amino acid residues with  $\text{Co}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Cd}^{2+}$ , and  $\text{Hg}^{2+}$  cations were computed with DFT/B3LYP method. Four coordination geometries, which are most frequently encountered in the metal-binding sites of metalloproteins and smaller-molecule crystal structures (octahedral, square planar, tetrahedral, and linear) were considered for each metal ion. The computational strategy consisted of several steps. First, the affinities of studied metal ions for  $(\text{H}_2\text{O})_n$  site, pre-organized in particular coordination geometry, have been evaluated. Second, the interaction energy of a single functional group with the transition metal ion of interest has been calculated, while the remaining coordination bonds were saturated with water molecules. Third, and finally, the effect of elongation of amino acid side chain has been calculated. Together, it gives an insight into the molecular structure of metal-binding sites of metalloproteins and provides an accurate quantification of the affinity and selectivity of amino acid side chains for the studied metal ions. These two quantities play a key role in the metal-binding properties of proteins and peptides. The important implications in an area of bioinorganic chemistry are discussed as well.

**Statement of Importance:** The first systematic computational investigation of the metal-ion selectivity in metalloproteins. Interactions of amino acid side chains with six divalent metal ions commonly encountered in the metal-binding sites were calculated at the DFT(B3LYP)/TZV level and the subtle differences in binding of studied ions described and analysed.

Srnc, M.; Chalupský, J.; Fojta, M.; Zendlová, L.; Havran, L.; Hocek, M.; Kývala, M.\*; Rulíšek, L.\*: Effect of Spin-Orbit Coupling on Reduction Potentials of Octahedral Ruthenium (II/III) and Osmium (II/III) Complexes. *J. Am. Chem. Soc.* **2008**, *130*, 10947-10954. [[44/33](#)]

**Abstract:** Reduction potentials of several  $\text{Ru}^{2+/3+}$  and  $\text{Os}^{2+/3+}$  octahedral complexes -  $[\text{M}(\text{H}_2\text{O})_6]^{2+/3+}$ ,  $[\text{MCl}_6]^{4-/3-}$ ,  $[\text{M}(\text{NH}_3)_6]^{2+/3+}$ ,  $[\text{M}(\text{en})_3]^{2+/3+}$ ,  $[\text{M}(\text{bipy})_3]^{2+/3+}$ , and  $[\text{M}(\text{CN})_6]^{4-/3-}$  - were calculated using the CASSCF/CASPT2/CASSI and MRCI methods including spin-orbit coupling (SOC) by means of first-order quasi-degenerate perturbation theory (QDPT). It was shown that the effect of SOC accounts for a systematic shift of approximately -70 mV in the reduction potentials of the studied ruthenium (II/III) complexes and an approximately -300 mV shift for the osmium(II/III) complexes. SOC splits the sixfold degenerate  $^2\text{T}_{2g}$  ground electronic state (in ideal octahedral symmetry) of the  $\text{M}^{3+}$  ions into the  $\text{E}_{(5/2)g}$  Kramers' doublet and  $\text{G}_{(3/2)g}$  quartet, which were calculated to split by  $1354\text{--}1573\text{ cm}^{-1}$  in the  $\text{Ru}^{3+}$  and by  $4155\text{--}5061\text{ cm}^{-1}$  in the  $\text{Os}^{3+}$  complexes. It was demonstrated that this splitting represents the main contribution to the stabilization of the  $\text{M}^{3+}$  ground state with respect to the closed shell  $^1\text{A}_{1g}$  ground state in  $\text{M}^{2+}$  systems. Moreover, it was shown that the accuracy of the calculated reduction potentials depends on the calculated solvation energies of both oxidized and reduced forms. For smaller ligands, it involves an explicit inclusion of the second solvation sphere into the calculations, whereas implicit solvation models yield results of sufficient accuracy for complexes with larger ligands. In such cases (e.g.,  $[\text{M}(\text{bipy})_3]^{2+/3+}$  and its derivatives), a very good agreement between the calculated (SOC-corrected) values of reduction potentials and the available experimental values was obtained. These results led us to the conclusion that, especially for  $\text{Os}^{2+/3+}$  complexes, an inclusion of SOC is necessary to avoid systematic errors of  $\sim 300\text{ mV}$  in the calculated reduction potentials.

**Statement of Importance:** Employing quasi-degenerate perturbation theory with the spin-orbit coupling, we have clearly demonstrated that the difference of  $\sim 300\text{ mV}$  in the redox potentials between the analogous complexes of  $\text{Ru}^{2+/3+}$  and  $\text{Os}^{2+/3+}$  can be understood in terms of the “in-state” spin-orbit coupling in the oxidized state of the complex that splits the formally degenerate  $^2\text{T}_{2g}$  ground electronic state into  $\text{E}_{(5/2)g}$  Kramers' doublet and  $\text{G}_{(3/2)g}$  quartet. This is a nice demonstration how the relativistic effects influence the observable properties of bioinorganic systems.

Gutten, O.; Rulíšek, L.\*: Predicting the Stability Constants of Metal-Ion Complexes from First Principles. *Inorg. Chem.* **2013**, 52, 10347-10355. [[42/38](#)]

**Abstract:** The most important experimental quantity describing the thermodynamics of metal ion binding with various (in)organic ligands, or biomolecules is the stability constant of the complex ( $\beta$ ). In principle, it can be calculated as the free energy change associated with the metal ion complexation, i.e. its uptake from the solution under standard conditions. Since this process is associated with interactions of charged species, large values of interaction and solvation energies are in general involved. Using the standard thermodynamic cycle (*in vacuo* complexation, and solvation/desolvation of the reference state and of the resulting complexes), one usually subtracts values of several hundreds of kcal.mol<sup>-1</sup> to obtain final results in the orders of units or tens kcal.mol<sup>-1</sup>. In this work, we use density functional theory (DFT) and Møller-Plesset second order perturbation theory (MP2) calculations together with the conductor-like screening model for realistic solvation (COSMO-RS method) to calculate the stability constants of selected complexes – [M(NH<sub>3</sub>)<sub>4</sub>]<sup>2+</sup>, [M(NH<sub>3</sub>)<sub>4</sub>(H<sub>2</sub>O)<sub>2</sub>]<sup>2+</sup>, [M(Imi)(H<sub>2</sub>O)<sub>5</sub>]<sup>2+</sup>, [M(H<sub>2</sub>O)<sub>3</sub>(His)]<sup>+</sup>, [M(H<sub>2</sub>O)<sub>4</sub>(Cys)], [M(H<sub>2</sub>O)<sub>3</sub>(Cys)], [M(CH<sub>3</sub>COO)(H<sub>2</sub>O)<sub>3</sub>]<sup>+</sup>, [M(CH<sub>3</sub>COO)(H<sub>2</sub>O)<sub>5</sub>]<sup>+</sup>, [M(SCH<sub>2</sub>COO)<sub>2</sub>]<sup>2-</sup> – with eight divalent metal ions (Mn<sup>2+</sup>, Fe<sup>2+</sup>, Co<sup>2+</sup>, Ni<sup>2+</sup>, Cu<sup>2+</sup>, Zn<sup>2+</sup>, Cd<sup>2+</sup>, and Hg<sup>2+</sup>). Using the currently available computational protocols we show that it is possible to achieve the *relative* accuracy of 2-4 kcal.mol<sup>-1</sup> (1-3 orders of magnitude in  $\beta$ ). However, since most of the computed values are affected by metal-dependent and ligand-dependent systematic shifts, the accuracy of the ‘absolute’ (uncorrected) values is generally lower. For metal-dependent systematic shifts we propose the specific values to be used for the given metal ion and the current protocol. At the same time, we argue that ligand-dependent shifts (which cannot be easily removed) do not influence the metal-ion selectivity of the particular site and therefore, it can be computed to within 2 kcal.mol<sup>-1</sup> average accuracy.

**Statement of Importance:** Employing state-of-the-art quantum chemical and solvation methods, we have shown that it is possible to predict relative binding constants to a very high accuracy. In principle, this may lead to a comprehensive list of “theoretical constants of stability” for any conceivable (bio)inorganic complex.

Straka, M.; Andris, E.; Vícha, J.; Růžička, A.; Roithová, J.\*; Rulíšek, L.\*: Spectroscopic and Computational Evidence of Intramolecular  $\text{Au}\cdots\text{H}^+-\text{N}$  Hydrogen Bonding. *Angew. Chem. Int. Ed.* **2019**, 58, 2011-2016. [[15/14](#)]

**Synopsis:** The phenomenon of hydrogen bonding to Au(I) ion and its effects on structure and dynamics of Au(I) molecules has been for decades a puzzle for experimentalists. Despite substantial evidence of short  $\text{Au}\cdots\text{H}-\text{X}$  contacts found in a number of X-ray structures of Au(I) compounds, the  $\text{Au(I)}\cdots\text{H}$  bonding had not been confirmed until now. In our work, we presented the first spectroscopic evidence for intramolecular  $\text{Au(I)}\cdots\text{H}^+-\text{N}$  hydrogen bonding, observed in a  $[\text{Cl-Au-L}]^+$  complex, where L is protonated N-heterocyclic carbene. The complex was prepared by in the gas phase and characterized by helium-tagging infrared photodissociation spectra (IRPD), which feature  $\text{H}^+-\text{N}$  vibrational mode derived bands evidencing clearly the intramolecular  $\text{Au(I)}\cdots\text{H}^+-\text{N}$  bonding. The quantum chemical calculations reproduced the experimental results and revealed intramolecular  $\text{Au}\cdots\text{H}^+-\text{N}$  bonding with a short  $r_{\text{Au}\cdots\text{H}}$  distance of 2.17 Å and interaction energy of *ca* -10 kcal.mol<sup>-1</sup>. Theoretical analysis of  $\text{Au}\cdots\text{H}^+-\text{N}$  interaction confirmed that the bond has moderate strength, of the order of hydrogen bonds, and originates in most part from dispersion forces and charge-transfer interactions between Au and  $\text{H}^+-\text{N}$ . Thus, our study not only solved a decades-old puzzle, but it also paves new ways in utilizing gold compounds in catalysis, material chemistry, and medicine.

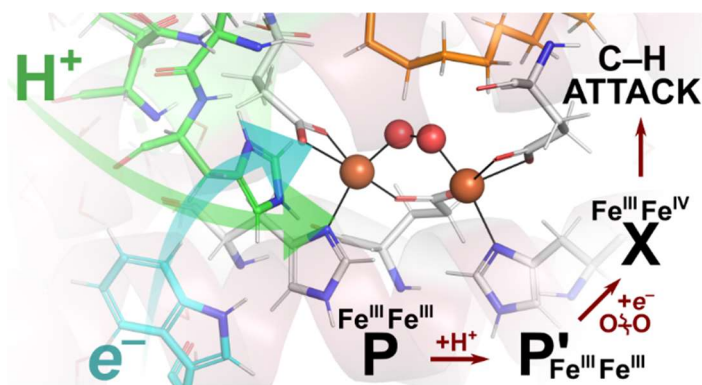
**Statement of Importance:** In two studies, published shoulder to shoulder, by our groups (Rulíšek&Straka, Růžička, and Roithová) and by our colleague Didier Bourissou (Univ. Toulouse, France), [1] an unambiguous experimental and theoretical proof of unprecedented  $\text{Au(I)}\cdots\text{H}^+-\text{N}$  bonding has been provided. Employing similar, yet complementary experimental and theoretical approaches (solvent vs. gas-phase, NMR/crystallography vs. IRPD spectroscopy), the two teams arrived to similar conclusions that defined a novel bonding in the Au(I) complexes, that can be clearly distinguished from the well-known agostic interactions in e.g. Au(III) complexes and Pt(II/IV) complexes. Both works were shortly afterwards highlighted by Hubert Schmidbaur, the most respected scientist in the area of aurophilic interactions. [2]

[1] Rigoulet, M. et al. *Proc. Natl. Acad. Sci.* **2019**, 116, 46-51.

[2] Schmidbaur, H. *Angew. Chem. Int. Ed.* **2019**, 58, 5806-580 .

Bím, D.; Chalupský, J.; Culka, M.; Solomon, E. I.; Rulíšek, L.\*; Srnec, M.\*: Proton-Electron Transfer to the Active Site Is Essential for the Reaction Mechanism of Soluble  $\Delta^9$ -Desaturase. *J. Am. Chem. Soc.* **2020**, *142*, 10412–10423. [2/2]

**Synopsis:** In a joint study with Martin Srnec (former Ph.D. student of Lubomír Rulíšek) which included contributions from colleagues at Stanford University led by Prof. Ed Solomon, we accomplished our (15-years') work on non-heme diiron  $\Delta^9$ -desaturase. The complete reaction cycle has been drafted and some of its parts confirmed experimentally (Figure 1). On the theoretical side, almost a whole arsenal of tools available in modern computational chemistry needed to be employed to explain why the enzyme carries out thermodynamically less favourable desaturation and not more favourable hydroxylation. A (promising) work is in progress to study the effects of the rationally designed mutations in  $\Delta^9$ -desaturase (based on the suggested reaction mechanism) to promote the hydroxylation.



**Figure 1:** Reaction mechanism of non-heme diiron  $\Delta^9$ -desaturase revealed by a combination of multiple theoretical and experimental approaches. **P** is the 1,2- $\mu$ -peroxo diferric intermediate characterized spectroscopically, **P'** is its protonated 1,2- $\mu$ -hydroperoxo cognate. After cleavage of the O=O bond, **X** carries out the H-atom abstraction which is the rate-determining step in the overall process.

**Statement of Importance:** Non-heme diiron enzymes represent one of the most intriguing systems in bioinorganic chemistry. They catalyse a broad spectrum of ‘difficult’ biochemical reactions, often with high specificity. This is mostly mediated by the presence of very reactive high-valent iron-oxo species which slightly contradicts the (desired) selectivity. We have shown the delicate balance between two reaction channels: desaturation (native) and hydroxylation (alternative and thermodynamically more favourable) and explained how the enzyme avoids the hydroxylation thermodynamic trap.

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