

Tytuł projektu
Zastosowanie kompleksów metalonieorganicznych Ir(III) jako modeli do modulowania redokсового komorek.
Project title
Application of non-organometallic Ir(III) complexes as models for cellular redox modulation.
Dyscyplina /Area of science
Inorganic Chemistry
PROJECT DESCRIPTION
Project Outline Transition metal complexes can play an important role in the redox biology of cells as shown recently in a series of papers by Sadler and co-workers.¹⁻⁵ Organometallic complexes such as $[\text{Ir}^{\text{III}}(\text{Cp}^*)(\text{N}^{\wedge}\text{C})\text{py}]^+$ (Cp^* = pentamethylcyclopentadienyl, $\text{N}^{\wedge}\text{C}$ = N,C – donor chelating ligand, py = pyridine, can react with NADH as source for hydride (H^-) to form reactive oxygen species (ROS) such as hydroperoxide, $\text{O}_2 + \text{H}^- \rightarrow \text{HOO}^-$, that can cause oxidative stress.^{1,2} In these organometallic complexes, metal-carbon bonds labilize the metal center and induce a high reactivity for the interaction with NADH to control the redox balance and inflammation in living cells. Oxidative stress is an effective method to kill cancer cells, since an increase in the level of reactive oxygen species disturbs redox homeostasis inside cells and causes cell destruction. Project goals The goal of the proposal is to synthesize a series of non-organometallic polypyridyl Ir(III) complexes of the type $[\text{Ir}^{\text{III}}(\text{terpy})(\text{N}^{\wedge}\text{N})\text{Cl}]\text{Cl}_2$, where terpy = 2,2':6',2''-terpyridine and $\text{N}^{\wedge}\text{N}$ = 2,2'-bipyridine (bipy), ethylenediamine (en), N,N,N',N'-tetramethylethylenediamine (tmen), 2-(aminomethyl)pyridine (ampy) and 1,10-phenanthroline (phen), in order to enable a systematic tuning of the lability of the complexes through σ-donor, π-back bonding and steric effects of the spectator ligands. These complexes are expected to show a similar reactivity as the $[\text{Ir}^{\text{III}}(\text{Cp}^*)(\text{N}^{\wedge}\text{C})\text{py}]^+$ complexes referred to above, but with the advantage expected for non-organometallic complexes to be more bio-compatible than the organometallic complexes where hydrolysis in water can lead to destruction of the complexes. Following the successful synthesis of the complexes, a full characterization of their solid and liquid phase chemistry will be performed. Subsequently, the ability of these complexes to activate NADH as source of hydride and to form HOO^- as ROS will be tested, similar to the work performed on the organometallic complexes mentioned above. Significance of the proposal Our recent experience with the synthesis and characterization of a series of closely related non-organometallic polypyridyl Ru(II) complexes,^{6,7} demonstrated that these complexes can

catalyze hydride transfer reactions to reduce NAD^+ to NADH in the presence of formate, similar to that found for organometallic Ru(II) complexes by Sadler and co-workers. The application of non-organometallic complexes to play the same role as organometallic complexes could lead to a breakthrough in terms of their bio-compatibility.

Work plan

- Synthesis and characterization of complexes of the type $[\text{Ir}^{\text{III}}(\text{terpy})(\text{N}^{\wedge}\text{N})\text{Cl}]\text{Cl}_2$, where terpy = 2,2':6',2''-terpyridine and $\text{N}^{\wedge}\text{N}$ = 2,2'-bipyridine, ethylenediamine, N,N,N',N'-tetramethylethylenediamine, 2-(aminomethyl)pyridine) and 1,10-phenanthroline.
- Conversion of the chlorido complexes into the corresponding aqua complexes to test their reactivity towards NADH to release hydride that will react with dissolved oxygen to form ROS components.
- Execution of biological cell tests involving preparation of the cell culture, determination of cell viability, MTT assay and EC_{50} , determination of ROS content, and DNA binding.

References

1. Soldevilla-Barreda J. J., Romero-Canelón I., Habtemariam A., Sadler P. J., *Nature Commun.*, **2015**, 6, 6582.
2. Banerjee S., Soldevilla-Barreda J.J., Wolny J.A., Wootton C.A., Habtemariam A., Romero-Canelón I., Chen F., Clarkson G.J., Prokes I., Song L., O'Connor P.B., Schünemann V., Sadler P.J., *Chem. Sci.*, **2018**, 9, 3177.
3. Chen F., Soldevilla-Barreda J. J., Romero-Canelón I., Coverdale J. P. C., Song J.I., Clarkson G. J., Kasparkova J., Habtemariam A., Brabec V., Wolny J. A., Schünemann V., Sadler P. J., *Dalton. Trans.*, **2018**, 47, 7178.
4. Chen F., Romero-Canelón I., Soldevilla-Barreda J. J., Song J.I., Coverdale J. P. C., Clarkson G. J., Kasparkova J., Habtemariam A., Wills M., Brabec V., Sadler P. J., *Organometallics*, **2018**, 37, 1555.
5. Coverdale J.P.C., Romero-Canelón I., Sanchez-Cano C., Clarkson G.J., Habtemariam A., Wills M., Sadler P.J., *Nature Chem.*, **2018**, 10, 347–354.
6. Chrzanowska M., Katafias A., Impert O., Kozakiewicz A., Surdykowski A., Brzozowska P., Franke A., Zahl A., Puchta R., van Eldik R., *Dalton Trans.*, **2017**, 31, 12901.
7. Chrzanowska M., Katafias A., Kozakiewicz A., Puchta R., van Eldik R., *J. Coord. Chem.*, **2018**, 71, 1761.

Required initial knowledge and skills of the PhD candidate

- ➔ Basic understanding of transition metal coordination chemistry
- ➔ Basic understanding of reaction kinetics in solution
- ➔ Keen to learn new techniques and instrumentation
- ➔ Eager to work hard and contribute to the success of the project
- ➔ Keen to be part of a dynamic international research team

Zgłaszający projekt/ Author of the project	
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