Prediction of Solubility of Organometallic Compounds

Prediction of Solubility of Organometallic Compounds using Molecular Dynamics Simulations

***M. Sprick, G. Raabe**, Institute of Thermodynamics, TU Braunschweig, Germany*

In Short

- Molecular dynamics simulation of organometallic compounds with heterocyclic carbene ligands that are drug candidates for new anti-infectives
- Solubility study to determine octanol/water partition coefficient
- Improving GAFF/IPolQ-Mod force field by re-optimizing Lennard-Jones parameter

Organometallic compounds have extensively been used as pharmacological agents for many decades. Particularly successful are the platinum compounds widely used in chemotherapy. However, these compounds have serious disadvantages. They are ineffective against resistant tumors and cause severe side effects. Furthermore, the fight against multi-resistant strains of bacteria is an issue of global importance. In recent decades, the number of antibacterial agents discovered and brought to market has declined and failed to meet the new challenges. In both fields, the development of alternative classes of active pharmaceutical ingredients is therefore urgently needed. This work focuses on organometallic complexes with **heterocyclic carbene** (NHC) ligands as promising novel compounds containing silver and gold atoms. Since they are promising agents against tumors and multi-resistant strains, they are intensively investigates by our project partners [1] in the Lower Saxony doctoral program "Drug Discovery and Cheminformatics for New Anti-Infectives (iCA)".

Accurate prediction of the solubility and other thermophysical properties of these compounds is crucial for the rational drug development. The aim of this project is to improve the accuracy and predictive capabilities of molecular simulations by optimizing molecular models, targeting the octanol/water partition coefficient.

The **octanol/water partition coefficient** $log\ P_{O/W}$ describes the equilibrium concentration of the molecule in a binary octanol/water mixture. The partition coefficient is calculated from the **solvation free energy** ΔG_{Solv} in the water-rich and the octanol-rich phase. The information is also related to the biological activity. This properties are often used as measurement for the permeability, which is of particular interest in the research of new active substances. The octanol phase is often used as model for the lipid membrane of the cell, so that prediction of the diffusivity of the drug to the target can be derived.

Though, reliable molecular models and effective simulation algorithms are needed to predict these molecular properties. The molecular modelling of organometallic compounds is certainly particularly challenging due to their intrinsic properties. The aim of the project is the parametrization of force field models of these compounds. Therefore, the General Amber Force Field (GAFF) with partial charges obtained by modified implicitly polarized charges (IPolQ-Mod) and re-optimized Lennard-Jones parameter, that was already used in our group in preliminary work [2], will be further developed for these compounds in the proposed project.

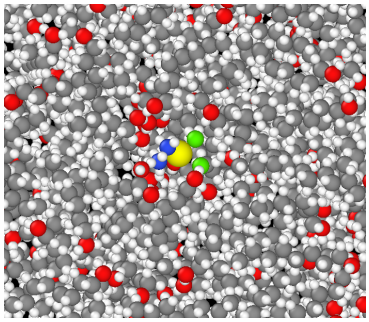

***Figure 1:** The model compound Cisplatin in octanol.*

In the solubility studies, the evaluation of the alchemical pathway is performed using the statistically optimized Multistate Bennet Acceptance Ratio (**MBAR**) method. Unlike classical evaluation methods, the MBAR method does not preserve hysteresis effects, so it is not directionally dependent. Though prior to the optimization of the molecular model, we will perform detailed studies on the most suitable softcore-core potential for ΔG_{solv} simulations for organometallic compounds. Additionally we will investigate the applicability of advanced sampling techniques, such as replica-exchange molecular dynamics, for efficient sampling in the octanol phase, which is known to form clusters in the liquid phase.

WWW

https://www.tu-braunschweig.de/pvz/projekte/drugdiscovery/projekte/news-detailansicht/project-ica-12-01-2022-molecular-properties-and-solubilities-of-organometallic-anti-infectiva

More Information

[1] M. Gil-Moles, I. Ott et al. *Chem. Eur. J.* **27**, 17928–17940 (2021). doi: 10.1002/chem.202103258

[2] A. Mecklenfeld, G. Raabe, *ADMET and DMPK* **8**(3), 274-296 (2020). doi:10.5599/admet.837

Funding

MWK no.21-78904-63-5/19

DFG Subject Area