Capturing drug molecules in porous crystals

Studying pharmaceutical adsorption in cation-exchanged zeolites with density functional theory and machine learning interatomic potentials

***S. K. Mitro, M. Fischer**, Crystallography and Geomaterials Research, Faculty of Geosciences, University of Bremen*

In Short

- The adsorption of pharmaceuticals in cationic zeolites is important for potential applications in wastewater treatment and drug delivery.
- Density functional theory (DFT) calculations can provide atomic-level insights into the interactions between organic guests and zeolite hosts.
- DFT optimisations and DFT-based molecular dynamics simulations will be used to study the adsorption of the antibiotic sulfamethoxazole and the anti-leukemia drug 6-mercaptopurine in typical zeolite adsorbents, focusing on "multi-site" interactions and the co-adsorption of water.
- The adsorption of four environmentally relevant antibiotics in the novel extra-large pore zeolite ZMQ-1 will also be investigated.

Zeolites are crystalline porous materials whose structures are constituted by a framework of corner-sharing tetrahedra. Many natural and synthetic zeolites have an aluminosilicate framework, where silicon and aluminium atoms occupy the tetrahedrally coordinated positions. This results in a negative charge of the framework, and overall charge neutrality is achieved through the incorporation of positively charged species, such as metal cations, on extra-framework positions. These cations are usually exchangeable, and cation exchange has been established as a versatile strategy to tailor the properties of zeolites, for example, towards applications in catalysis or gas separation.[1] Other potential applications of zeolites that are not yet established on the large scale include the removal of emerging organic contaminants, such as pharmaceuticals and personal care products (PPCPs), from wastewater and the controlled release of pharmaceutically active species (drug delivery). Both of these potential usages involve the adsorption of larger organic molecules in the zeolite pores. Previous computational efforts in this area have primarily focused on highly siliceous, hydrophobic zeolites, which have an (almost) neutral framework and therefore contain no (or only few) extra-framework cations. The adsorption of PPCPs in such materials has been studied using both classical force field methods and dispersion-corrected density functional theory (DFT).[2,3]

As for other applications, cation exchange will change the affinity of a zeolite adsorbent to a given species, allowing to modify the adsorption behaviour in order to enhance selectivity towards a PPCP of interest (in wastewater treatment) or to modulate the drug release properties (in delivery applications). Exploiting this possibility in an efficient manner is, however, currently hampered by a lack of understanding of the interactions between cationic zeolites and adsorbed pharmaceuticals on an atomic level. In this project, electronic structure calculations in the framework of DFT will be used to enhance this understanding, which may ultimately contribute to the targeted development of optimised zeolite adsorbents.

The project is sub-divided in three parts. The first part will investigate the adsorption of sulfamethoxazole (SMX), an antibiotic that is of particular concern in an environmental context,[4] in zeolites having the faujasite (FAU) and mordenite (MOR) topologies. Both the type of metal cation and the total number of cations per zeolite cell (which is determined by the Si/Al ratio) will be varied among different zeolite models. Particular emphasis in the analysis will be placed on the role of "multi-site" interactions, visualised in Figure 1 for the example of 6-mercaptopurine. Moreover, DFT-based molecular dynamics (MD) simulations will be carried out to investigate the stability of the cation-SMX bonds at finite temperature and in the presence of water.

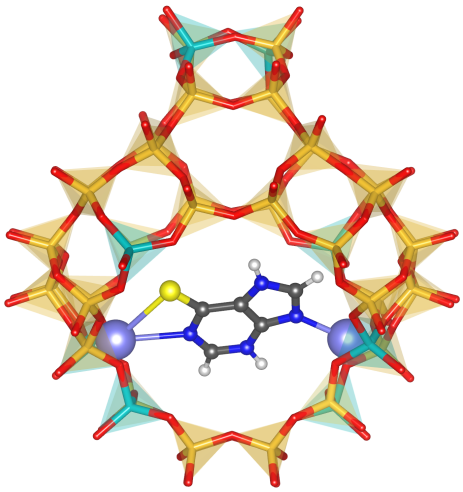

***Figure 1:** Adsorption complex showing multi-site interactions of MCTP in a pore of Ca-FAU.*

The second part of the project will investigate the adsorption of 6-mercaptopurine (MCTP), a drug that is used against leukemia. Zn-exchanged FAU-type zeolites have been proposed as promising adsorbents for the controlled delivery of MCTP in prior experimental work.[5] DFT calculations of MCTP@M-FAU complexes for different metal cations M (such as Na^+, Ca^{2+}, Zn^{2+}) have already provided evidence for multi-site interactions, *i.e.*, a simultaneous coordination of MCTP to more than one cation, as shown for the example of MCTP@Ca-FAU in Figure 1. Stabilising multi-site interactions vary rather markedly among different cation-exchanged FAU-type zeolites, depending on cation type and cation concentration. It can thus be expected that these two parameters will have a significant influence on the release behaviour, opening up possibilities to develop adsorbents with optimised properties for drug delivery. In order to obtain fundamental insights into the behaviour of drug-loaded zeolites under relevant conditions, MD simulations using machine learning interatomic potentials (MLIPs) will be run for different models of cationic FAU zeolites with adsorbed MCTP and co-adsorbed water. This method allows access to relatively long timescales (up to nanosecond range) at a relatively modest computational cost, at the same time having the potential to be considerably more accurate than empirical atomistic simulations with classical force fields. To ensure the suitability of the MLIPs to represent this complex system, the MLIP-MD simulations will be validated against short DFT-based MD simulations, which will cover on the order of 10 picoseconds.

In recent years, a number of highly siliceous zeolites with "extra-large" pores have been reported. A particularly intriguing example is ZMQ-1, which possesses oval pores outlined by assemblies of 28 tetrahedra (Figure 2).[6] Due to the size of these voids, it should be possible to adsorb large PPCP molecules that do not fit into the pores of conventional zeolites like FAU, as demonstrated in a recent molecular simulation study.[2] In the third part of the project, DFT calculations will be carried out to investigate the adsorption of four antibiotics of different size (ciprofloxacin, tetracycline, amoxicillin, clarithromycin) in the pores of cation-exchanged variants of ZMQ-1. All of these pharmaceuticals are of environmental concern, not least due to the possible development of antibiotic-resistant bacteria in wastewaters. Although the high synthesis cost of ZMQ-1 will likely preclude its application in PPCP removal in the near future, a detailed understanding of antibiotic adsorption based on DFT calculations may accelerate the development of novel zeolite adsorbents for environmental applications.

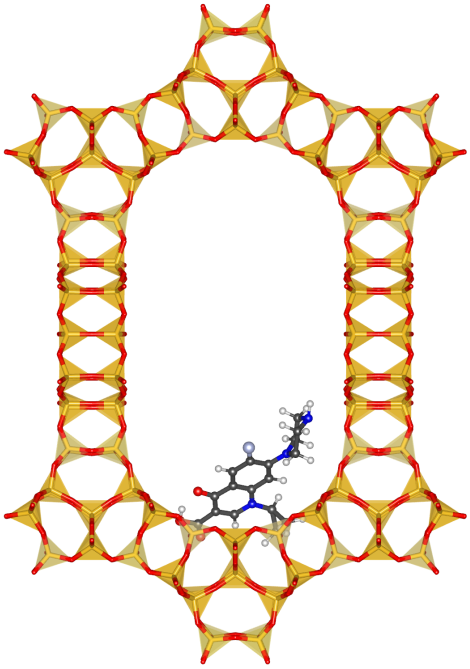

Figure 2: *Adsorption complex of ciprofloxacin in ZMQ-1. The shown configuration was generated in our previous molecular simulation study of all-silica ZMQ-1.[2]*

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More Information

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