

Title	Enhanced selectivity in molecular recognition under non-equilibrium condi-
	tions
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International Secondment	
PI	Prof. Jurriaan Huskens
Institute	University of Twente
Place, country	Enschede, Netherlands
# months (min.3)	=>3 months

## **Project description:**

Supramolecular chemistry has made enormous progress in the development of sensors, catalysis, and materials exploiting the thermodynamically controlled formation of noncovalent interactions between molecules. Yet, nature shows that operating under non-equilibrium conditions can lead to enhanced properties (e.g. selectivity in molecular recognition using kinetic proofreading) or is actually a prerequisite for certain processes (e.g. directional motion, pumping against a concentration gradient). Operating synthetic systems under non-equilibrium conditions is therefore expected to improve their functional properties [1].

The development of synthetic non-equilibrium systems requires the ability to design molecular systems capable of harnessing energy from a source to carry out work. Nature achieves this using chemical reaction cycles in which energy released from an exergonic chemical reaction is used to drive biochemical processes (Figure 1). Although many chemically fuelled synthetic reaction cycles that control transient responses, such as self-assembly, have been reported, the generally high complexity of the reported systems hampers a full understanding of how the available chemical energy is actually exploited by these systems [3]. This lack of understanding is a limiting factor in the design of chemically fuelled active matter.

In joined publications, the Prins- and Frezzato-groups have recently reported a minimalistic chemical reac-

tion network that produces a hydrazone using adenosine diphosphate (ADP) as a chemical fuel [4, 5]. The addition of ADP to a mixture of functionalized aldehyde and hydrazide results in the accelerated formation of a hydrazone product that turns out to be a catalyst for the hydrolysis of ADP into AMP and P<sub>i</sub> that is better than the reactants. In other words, ADP drives the formation of a catalysts for its own destruction. The minimalistic nature of this network, especially compared to natural equivalents, permitted a determination of all kinetic and thermodynamic parameters (i.e. rate



**Figure 1**. Schematic representation of the fuel-driven synthesis of a 'high-energy' molecular receptor.



and binding constants for all reactions and chemical equilibria occurring in the network). Kinetic models were built that provided an insight on how energy released from ADP hydrolysis was exploited and, importantly, provided insights in the design of future chemical reaction networks.

This project aims at exploiting the acquired knowledge for the design of new chemical reaction cycles in which turnover rate, precision and energy dissipation can be controlled. These systems will then be explored for their capacity to interact with analytes. The objective is to show that operating under non-equilibrium conditions enhances the recognition properties of a molecular receptor in terms of affinity and selectivity.

## Skills that will be acquired:

Organic chemistry: synthesis and characterization of organic molecules Supramolecular chemistry: determination of binding constants and rate constants Physical-organic chemistry: development of thermodynamic and kinetic models Physical chemistry: concepts of non-equilibrium chemistry

## International secondment:

The secondment will be carried out in the group of prof. Jurriaan Huskens (University of Twente, Netherlands) and will be dedicated to the determination of binding and rate constants using a variety of techniques (spectroscopies, ITC, ...).

## **References:**

1. Ragazzon, G.; Prins, L. J. Energy Consumption in Chemical Fuel-Driven Self-Assembly. *Nat. Nanotechnol.* **2018**, *13*, 882–889.

2. Das, K.; Gabrielli, L.; Prins, L. J. Chemically Fueled Self-Assembly in Biology and Chemistry. *Angew. Chem. Int. Ed.* **2021**, *60*, 20120-20143.

3. Marchetti, T.; Frezzato, D.; Gabrielli, L.; Prins, L.J. ATP Drives the Formation of a Catalytic Hydrazone through an Energy Ratchet Mechanism *Angew*. *Chem. Int. Ed.* **2023**, *62*, e202307530

4. Marchetti, T. (+); Roberts, B.M.W.(+); Frezzato, D.; Prins, L.J. A minimalistic synthetic metabolic cycle that consumes ADP, *Angew.Chem.Int.Ed.* **2024**, *63*. e202402965.