Ahmad Bachir, 02/11/2022

From Selection to Instruction and Back: Competing Conformational Selection and Induced Fit Pathways in Abiotic Hosts

R. Z. Pavlović, R. F. Lalisse, A. L. Hansen, C. A. Waudby, Z. Lei, M. Güney, X. Wang, C. M. Hadad, J. D. Badjić, *Angewandte Chemie International Edition* **2021**, *60*, 19942–19948.

Who are the corresponding authors and what are their research areas?

Jovica D. Badjić is interested in designing host-guest systems and investigating their properties as guests usually experience different chemical environments and subsequently exhibit different reactivity, reacting inside the cavity and releasing the product. In his research, he is addressing three main problems related to the property aforementioned; How to efficiently encapsulate reactant and convert it to a useful product, how to easily functionalize the host, and lastly how to achieve this in a biological system (in an aqueous medium).

What is the main claim of the article?

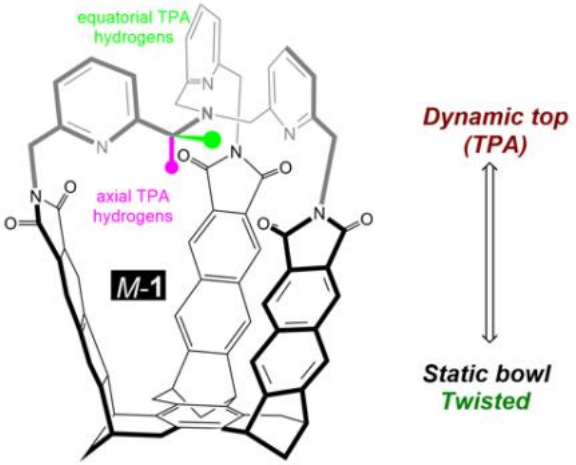

Figure 1. Host molecule of M-1 conformer.

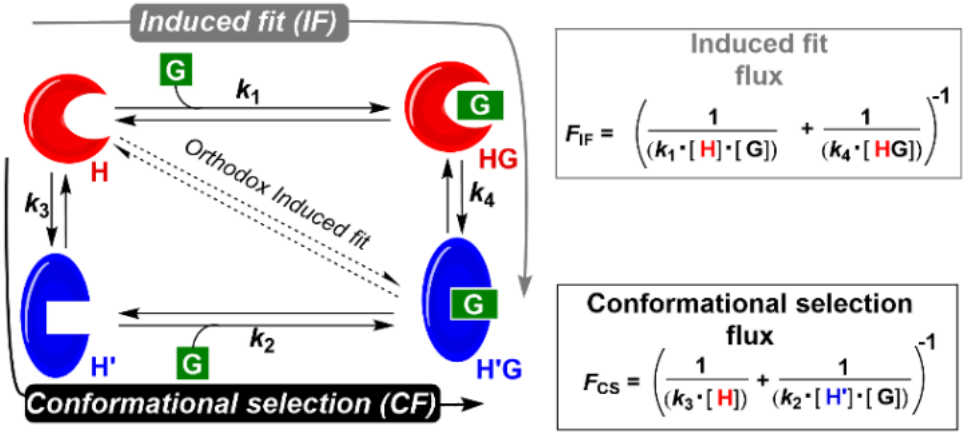

Figure 2. On the **left side**, a representative scheme of the host-guest system showing two different pathways (Conformational selection and induced fit). On the **right side**, the two equations represent the flux for both pathways as a function host-guest concentration.

Elucidating the mechanism of host-guest binding reveals two different pathways; Induced fit and conformational selection (figure 2) which are competing for all at the same time and that are not mutually exclusive. Moreover, they also showed how one pathway can dominate the other under specific conditions,

such an important feature cannot be determined by calculating the rate constant but by the flux of each pathway.

How is it demonstrated?

Using 2D EXSY proton and carbon NMR experiments, the group was able to monitor the association-dissociation of the host-guest chemical system, following specific proton H_A of two conformers (see figure 3) in both bound and unbound states, and they were able to deduce their rate constants. Having the necessary parameters and relying on the flux equation for each pathway, they succeeded to predict the mechanism and the stability of the system supported by theoretical study and which path at specific conditions is dominating the other (CS over IF or vice-versa).

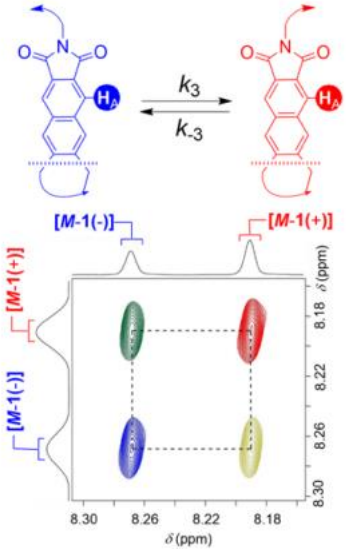

Figure 3: Example of 2D EXSY NMR experiment of the exchange between the M-1(-) and M-1(+) in the unbound state.

What are the typical experimental conditions?

By ^{1}H NMR, the host-guest system was studied at -95°C (suitable temperature to study by NMR) in NMR tube using CD_2Cl_2 as a solvent, and carbon tetrachloride or bromide was added for the titration experiment while the concentration of M_{-1} was 1-1.3 mM. The same temperature was used for the EXSY NMR experiment.

Which are the key related papers?

1) G. G. Hammes, Y.-C. Chang, T. G. Oas, Proc. *Natl. Acad. Sci. U. S. A.* **2009**, *106*, 13737.
2) Vauquelin, D. Maes, D. C. Swinney, *Trends Pharmacol. Sci*. **2020**, *41*, 923.

Additional comments, including additional elements of interest

The originality of this paper is quite impressive, where a solid understanding of both mechanisms is stated beside the fact that the authors and co-workers were able to give a deep explanation supported by great experimental evidence and other provided tools (fitting procedures+ theoretical study).