MECHANISTIC INSIGHT INTO POLYFUNCTIONAL COOPERATIVE CATALYSIS FROM COMPUTATION

Patrick M. Becker, Johannes Kästner

Institut für Theoretische Chemie, Universität Stuttgart, Germany

The origin of life is one of the most, if not the most, intriguing question for mankind. Closely related to this is the fascination for molecular transformations of enlivened nature. Tailor-made for their specific tasks, enzymes enable highly selective chemical reactions under mild conditions. Thereby multiple functionalities of the system must work hand in hand. Polyfunctional cooperative catalysis tries to translate this concept from nature to artificial systems. Just like enzymes, those catalysts consist of several different functional groups interacting in a cooperative manner.

Following Neese's modified version of Charles Coulson's famous statement "give us insight *and* numbers" [1], we use DFT computations to gain a detailed picture of the modus operandi of two structurally similar catalysts: Both catalysts use a cooperation of a Lewis acidic Cu(II) center, an external or internal Brønsted base and an azolium moiety as a hydrogen bond donor in the periphery. Careful comparison of computational results with experimental findings provides a detailed picture of how the catalysts work [2,3].

In concrete terms, our DFT studies highlight the role of the acetate anion/ acetic acid couple in case of the first catalyst: The acetate anion acts as Brønsted base for deprotonation of the 1,3-dicarbonyl pronucleophiles, while the corresponding acetic acid activates the maleimides through a hydrogen bond in the subsequent 1,4-addition. Additionally, the catalyst's hydrogen bond donor ensures, that the acetate anion/ acetic acid doesn't dissociate from the system. At the same time, it also activates the maleimides or stabilizes the nucleophile; showcasing the high cooperativity [2].

In case of the second catalyst, the nucleophile generation from the C(4)-substituted pyrazolone pronucleophile results in an intramolecular hydrogen bonding within the catalyst to create a structurally well-defined chiral cage as binding pocket. This arrangement is found to be crucial for high stereocontrol in the subsequent 1,4-addition to the nitroolefin electrophile. In contrast to other literature know catalysts the nitroolefin is activated by a single hydrogen bond to the azolium moiety within the described binding pocket. Control experiments suggest that this activation is, like expected, considerably more efficient the stronger the hydrogen bond donor capability of the used azolium moiety. In combination with the enzyme-inspired arrangement of the catalyst, this underlines the highly cooperative modus operandi once more [3].

———

[1] F. Neese, M. Atanasov, G. Bistoni, D. Maganas, S. Ye, *J. Am. Chem. Soc.* **2019**, *141*, 2814–2824.

[2] A. C. Hans, P. M. Becker, J. Haußmann, S. Suhr, D. M. Wanner, V. Lederer, F. Willig, W. Frey, B. Sarkar, J. Kästner, R. Peters, *Angew. Chem. Int. Ed.* **2023**, *62*, e202217519; *Angew. Chem.* **2023**, *135*, e202217519.

[3] D. M. Wanner, P. M. Becker, S. Suhr, N. Wannenmacher, S. Ziegler, J. Herrmann, F. Willig, J. Gabler, K. Jangid, J. Schmid, A. C. Hans, W. Frey, B. Sarkar, J. Kästner, R. Peters, *submitted for publication.*