COMPUTER-AIDED STUDY OF THE DNA-BASED ARTIFICIAL METALLOENZYMES, AIMING AT ELUCIDATING STRUCTURE-FUNCTION RELATIONSHIPS IN DNA-BASED ASYMMETRIC CATALYSIS

E. Pantatosaki[1,*], J. Guo[2], D. Wang[2,3], H. Kuang[2], Tsapatsis, M.[2,3,4], Kokkoli, E.[2,3], G. K. Papadopoulos[1,5,*]

[1] School of Chemical Engineering, National Technical University of Athens, 157 80 Athens, Greece
[2] Institute for NanoBiotechnology, Johns Hopkins University, Baltimore MD, USA
[3] Depart. of Chemical and Biomolecular Engineering, Johns Hopkins University, Baltimore MD, USA
[4] Applied Physics Laboratory, Johns Hopkins University, Laurel MD, USA
[5] Inst. for Medical Engineering and Sci., Massachusetts Instit. of Technology, Cambridge MA, USA
* evpanta@chemeng.ntua.gr
* gkpap@chemeng.ntua.gr

ABSTRACT

We present a just-published work [1] on modeling DNA-based artificial metalloenzymes (DNA-ArMs) aiming at elucidating structure-funtion relationships in DNA-based asymmetric catalysis. DNA-ArMs combine the chiral environment of the DNA scaffolds and the catalytic activity of transition metals and have demonstrated high enantioselectivity for a wide range of reactions (e.g. Diels-Alder, Friedel-Crafts alkylation, Michael addition). However, despite progress in correlating the catalytic performance of DNA-ArMs with their DNA sequence, pinpointing which of the many possible chiral microenvironments created by the interaction between the DNA and the bound metal, or metal complex, is responsible for enantioselective catalysis remains elusive. Molecular dynamics (MD) simulations of DNA-ArMs, consisting of a Cu(II) complex with 4,4'-dimethyl-2,2'-bipyridine (dmbipy-Cu) bound to short double-stranded DNA (dsDNA) molecules, revealed that the dmbipy-Cu is groove-bound to the DNA, and different DNA sequences induce dissimilar sequence-dependent binding patterns for the dmbipy-Cu. The dissimilar binding patterns identified by MD simulations conducted at the National Technical University of Athens provide a possible microscopic mechanism for the highy enantioselective catalytic activity observed for the specific DNA-ArMs in experiments conducted at the Johns Hopkins University. Our results demonstrate that a DNA-ArM based on dmbipy-Cu and a short dsDNA comprising only two contiguous central G•C pairs (G for guanine and C for cytosine) were sufficient to create a chiral environment for the catalysis of a highly enantioselective Diels-Alder reaction in water.

KEYWORDS: DNA asymmetric catalysis, Stereoselectivity, Computer simulation, Nucleic acid structure

REFERENCES

[1] Guo, J., Wang, D., Pantatosaki, E., Kuang, H., Papadopoulos, G. K., Tsapatsis, M., Kokkoli, E. A Localized Enantioselective Catalytic Site on Short DNA Sequences and their Amphiphiles. *J. Am. Chem. Soc. Au*: DOI: 10.1021/jacsau.1c00513