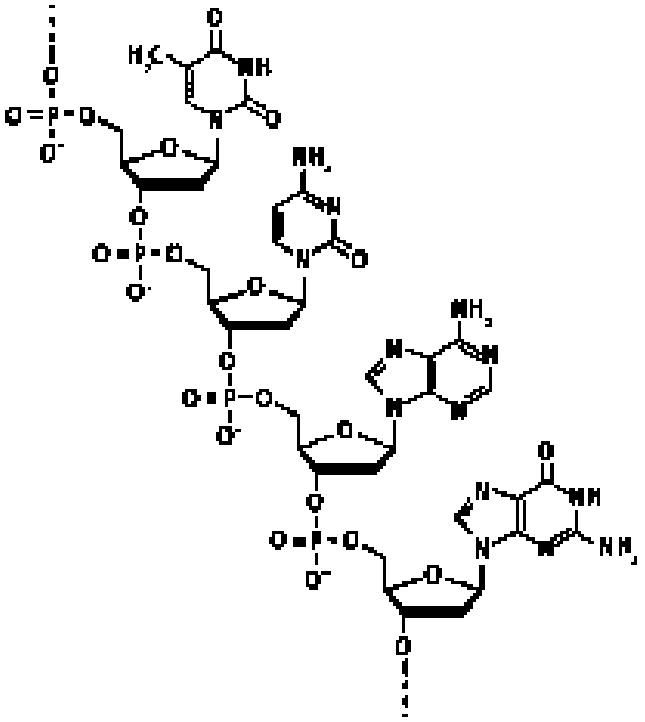
IOCN 2020

2nd International Online-Conference on Nanomaterials

15–30 NOVEMBER 2020 | ONLINE

nanomaterials

MDPI



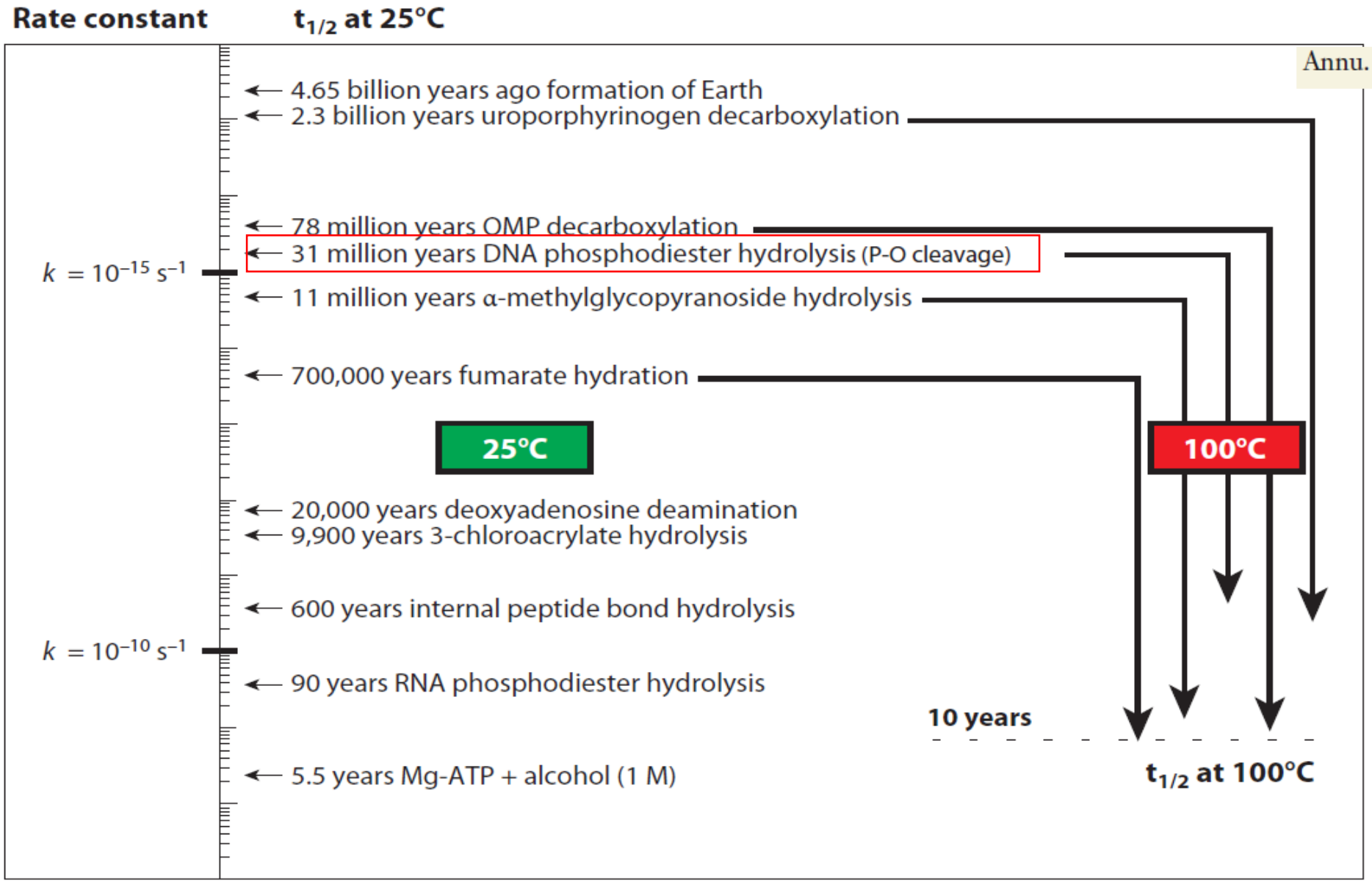
Phosphate Diesters and DNA Cleavage by Gold Nanozymes

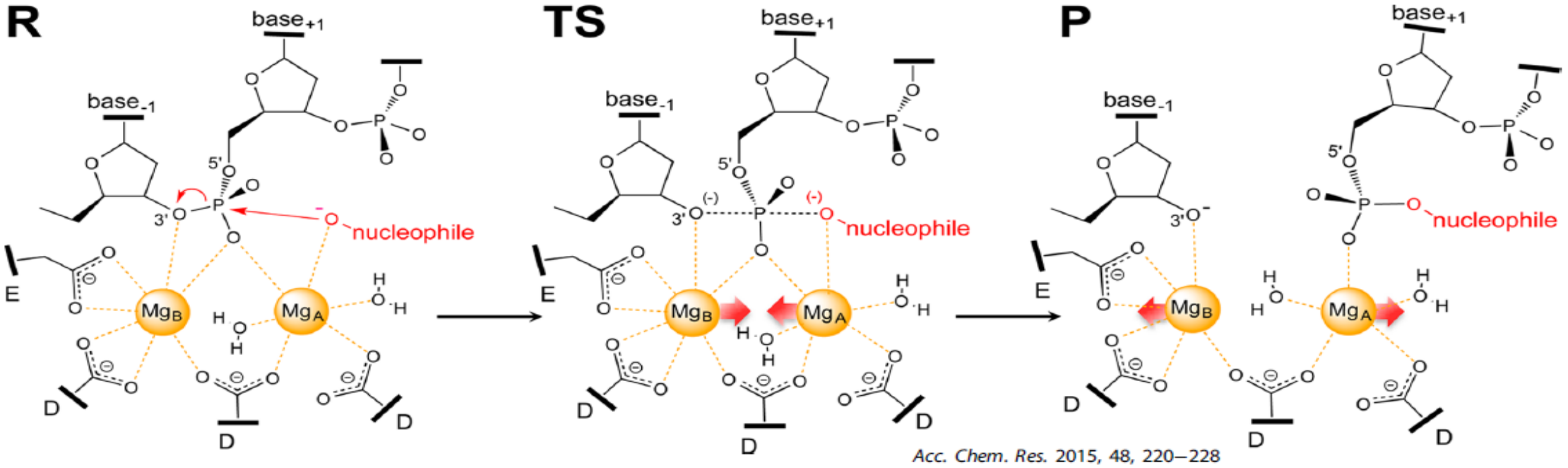
Paolo Scrimin, Joanna Czescik

University of Padova, Italy

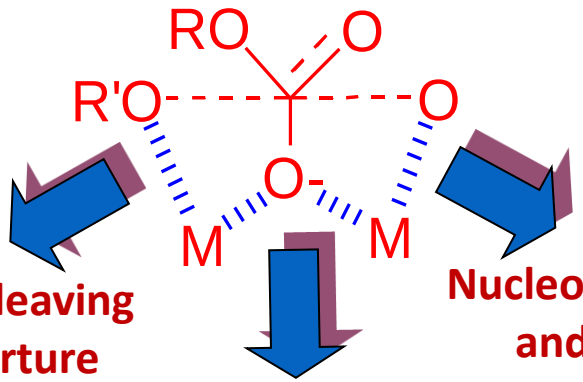
Department of Chemical Sciences

The P-O bond of phosphate diesters hydrolyzes very slowly!





Acc. Chem. Res. 2015, 48, 220−228



Assistance in leaving group departure

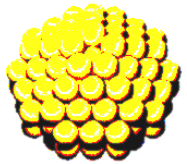
Nucleophile delivery and activation

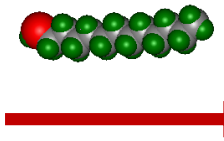
Lewis acid catalysis

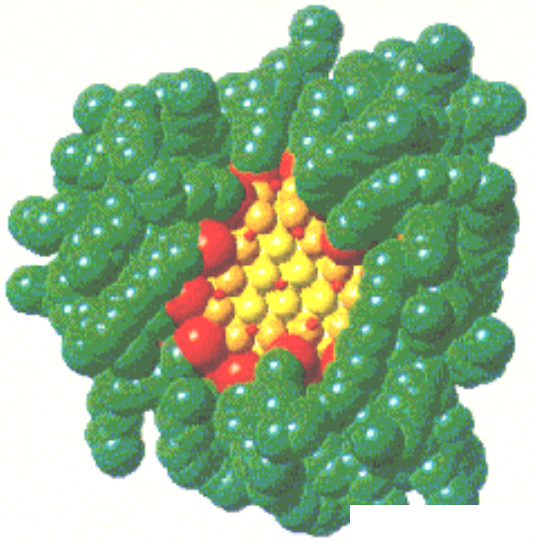
Overall ca. 10^{16}-fold rate acceleration possible

Phosphate cleavage constitutes an excellent testing ground for a synthetic catalyst

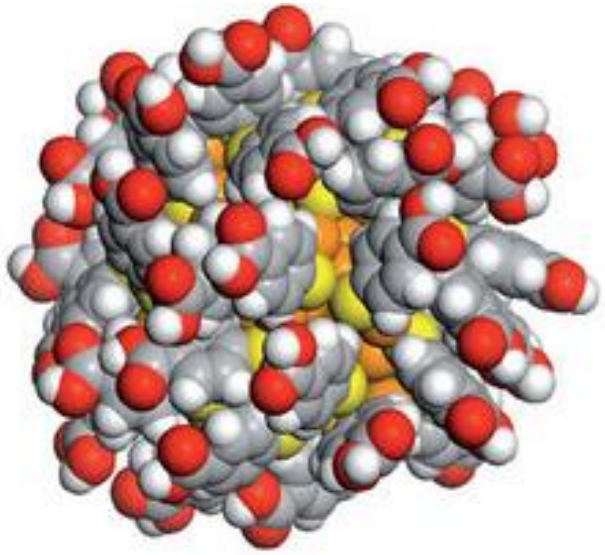
Our approach: create a catalytic site on the monolayer passivating a gold nanoparticle

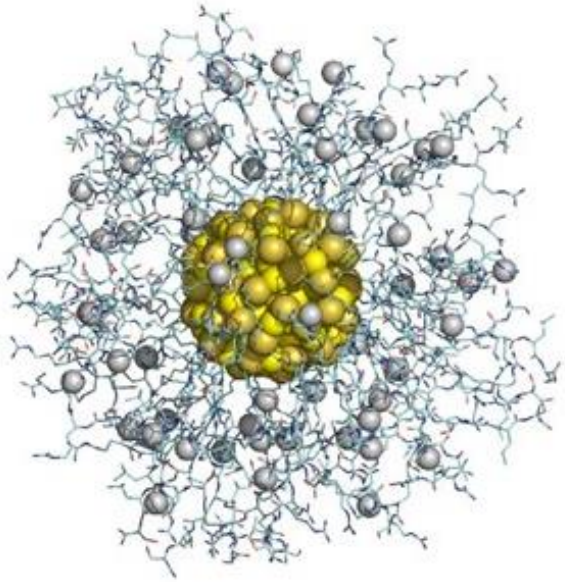




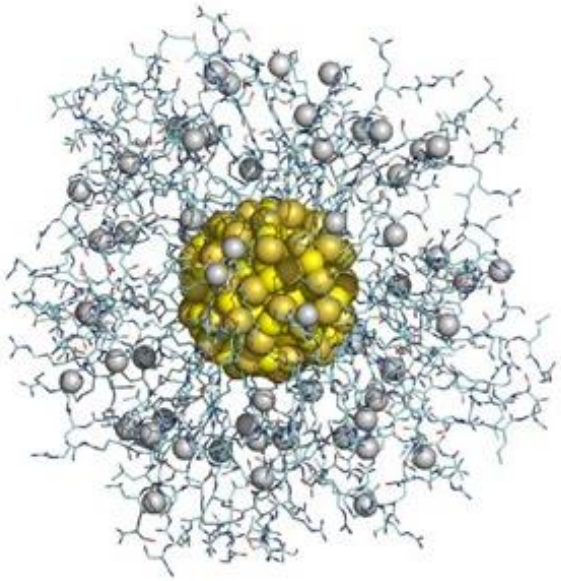


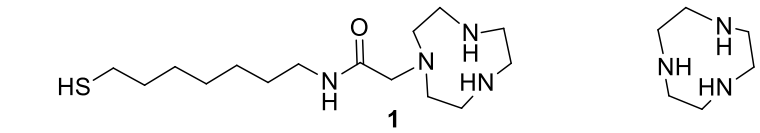
- Spontaneous self assembly of thiolated molecules on the surface of the gold cluster;
- design limited to the constituent thiolated ligands

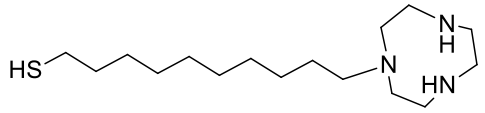


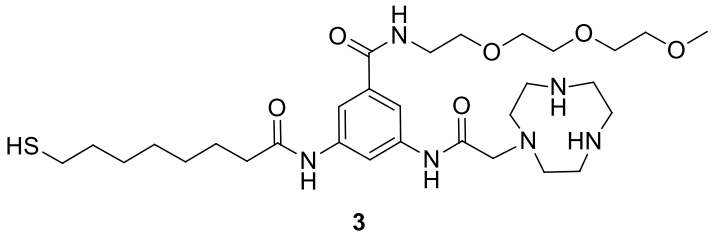


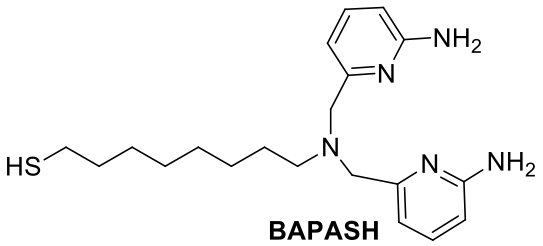
In the enzyme catalytic site the metal ions are surrounded by ancillary cationic groups that provide assistance in the transformation

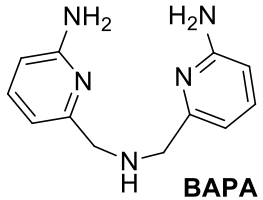


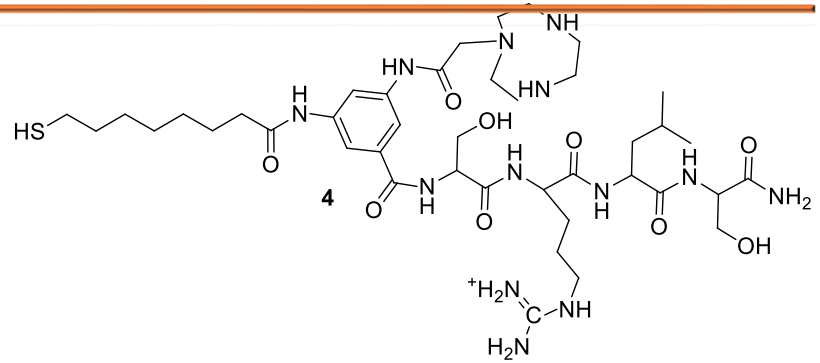


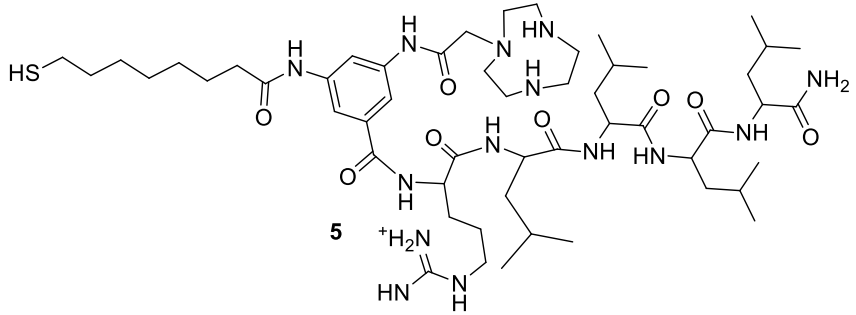


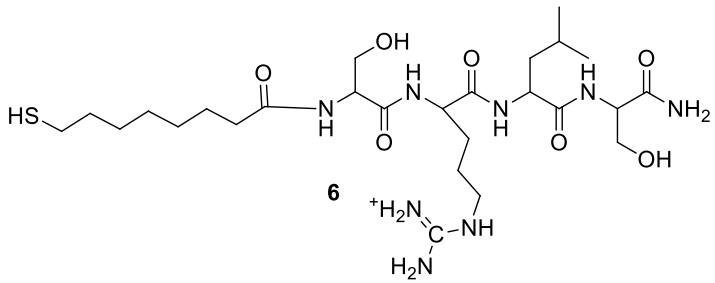








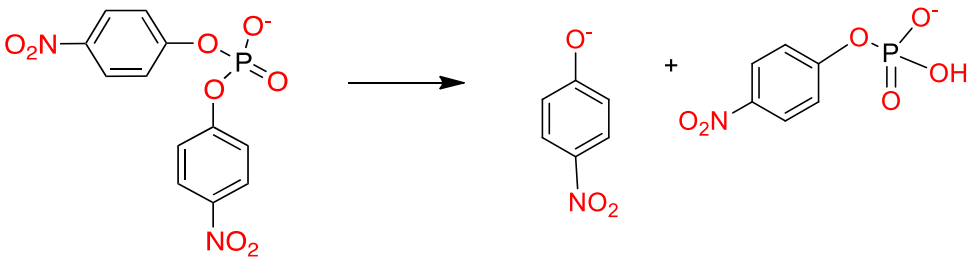




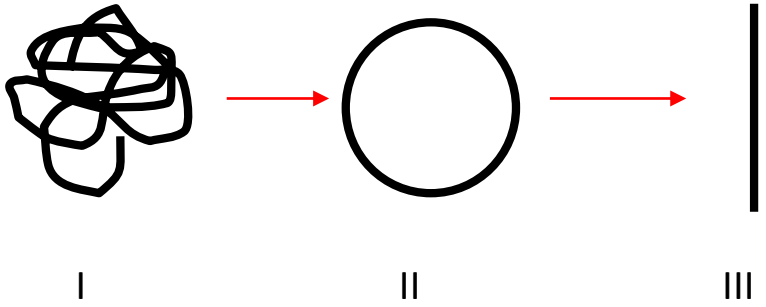
J. Am. Chem. Soc. **2008**, *130*, 15744-15745

Previous work on HPNP cleavage*:* **Czescik** *Molecules*, **2019**, *24*, 2814

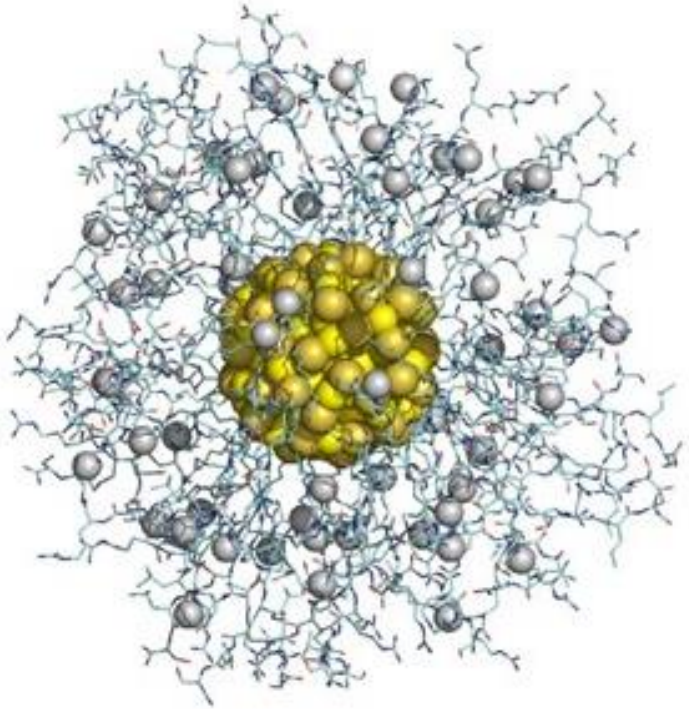
Our substrates



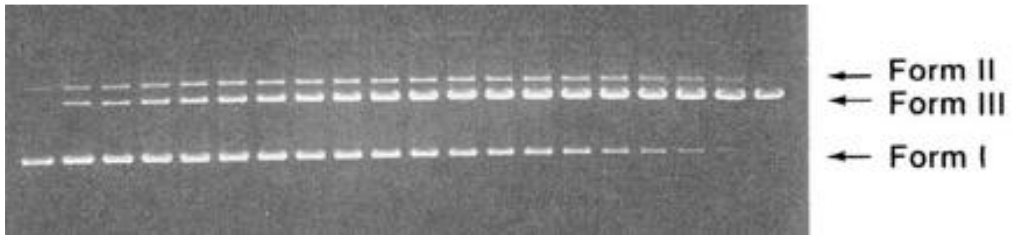
Model substrate: BNP



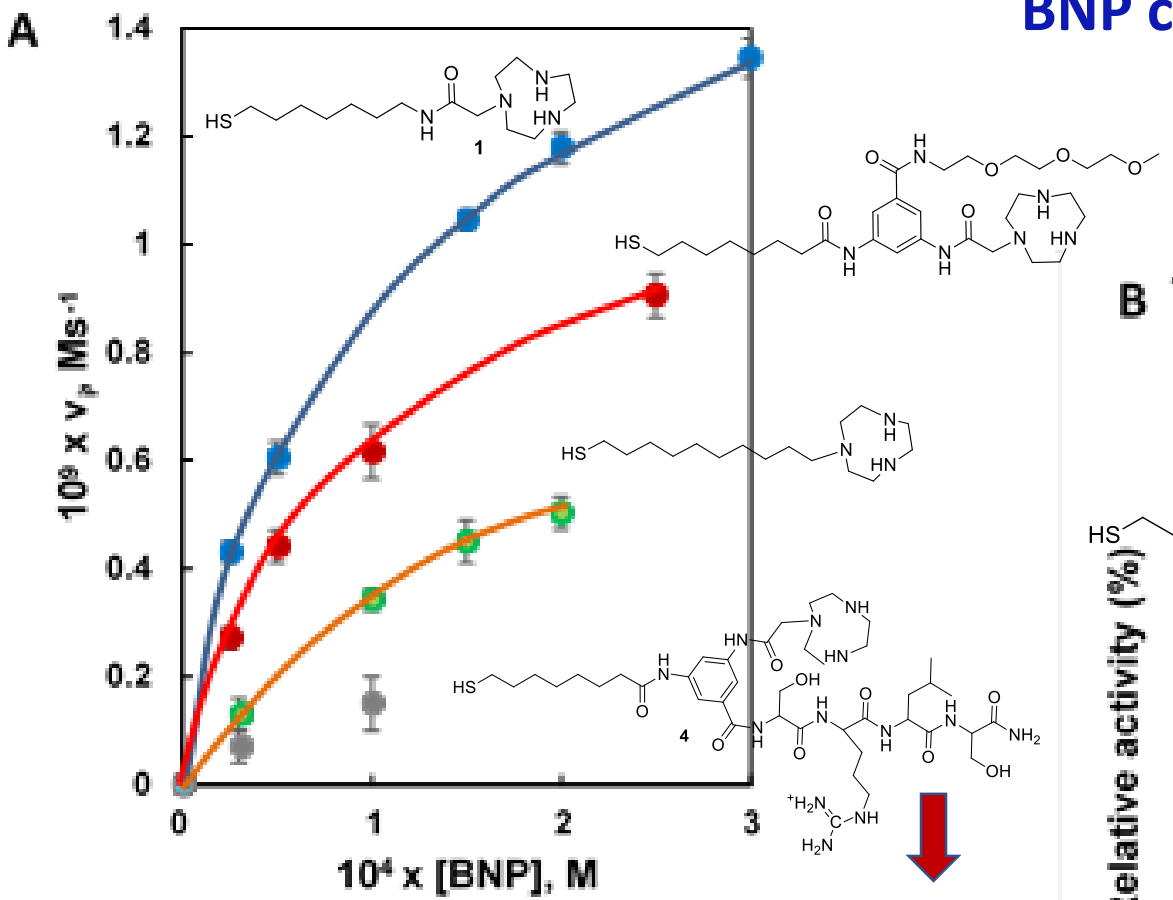
pBR322 Plasmid DNA



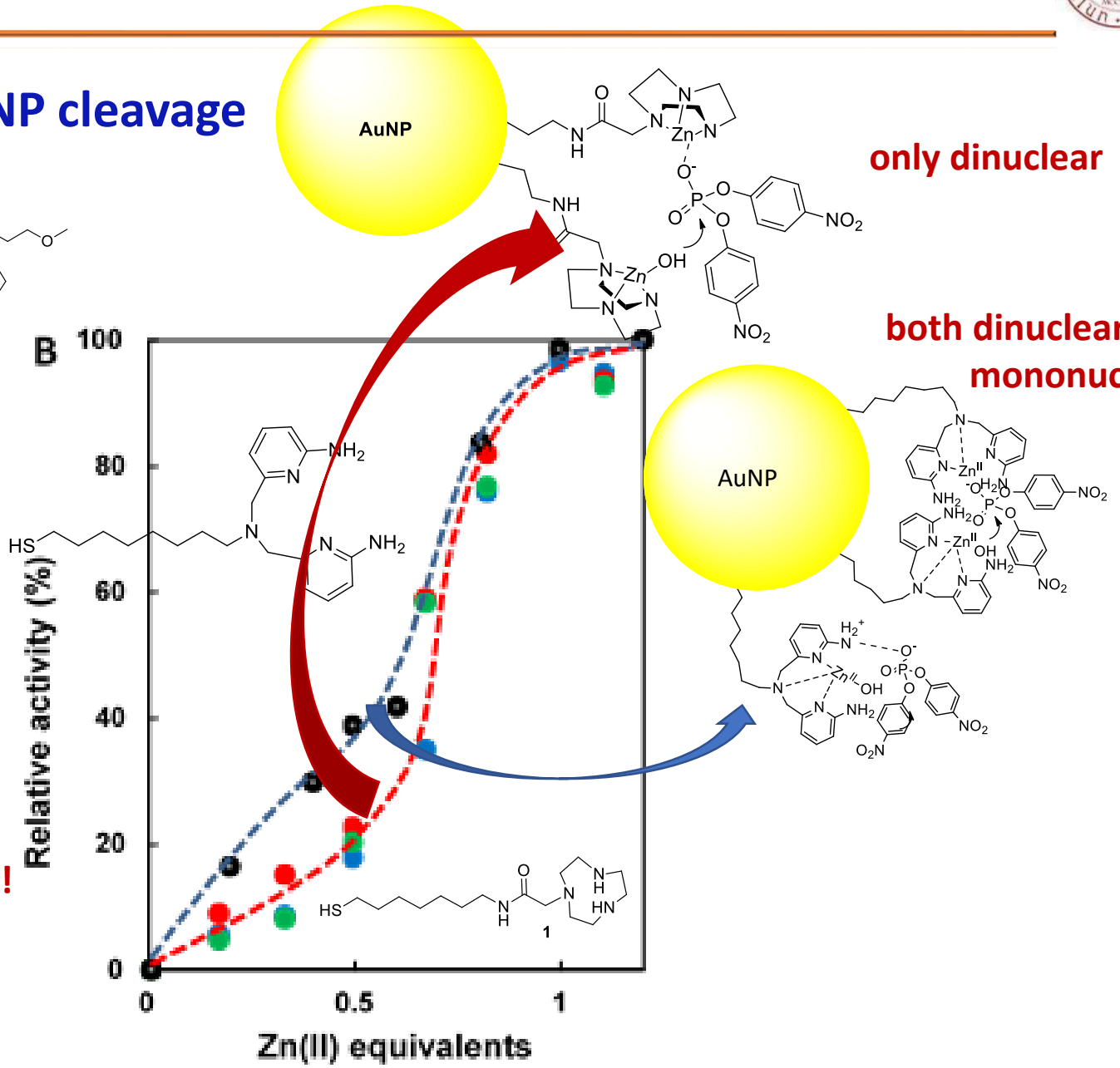
Molecular dynamic simulation of AuNP4-Zn(II)



BNP cleavage



Poorly active: mononuclear!

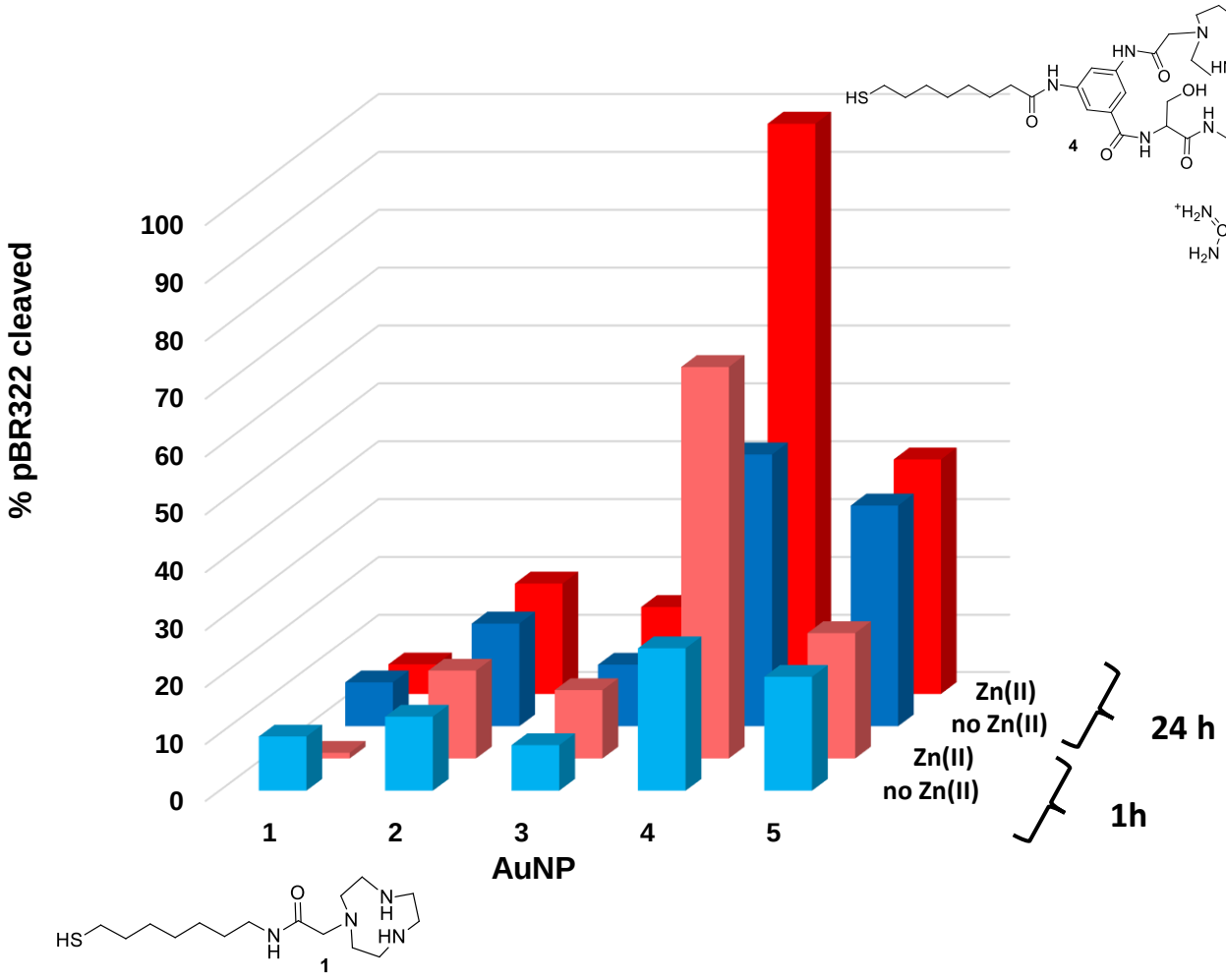


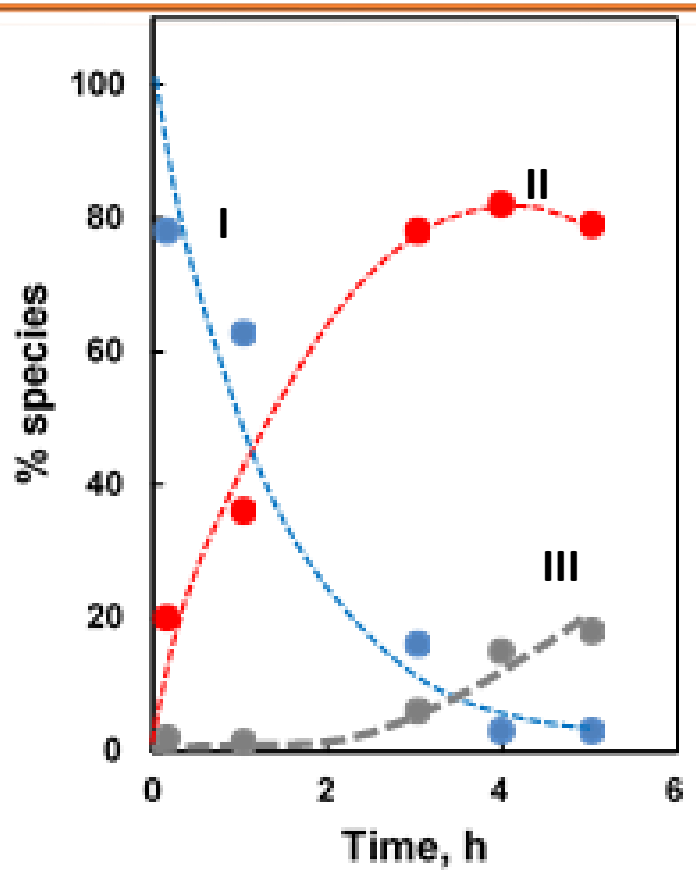
only dinuclear

both dinuclear and mononuclear

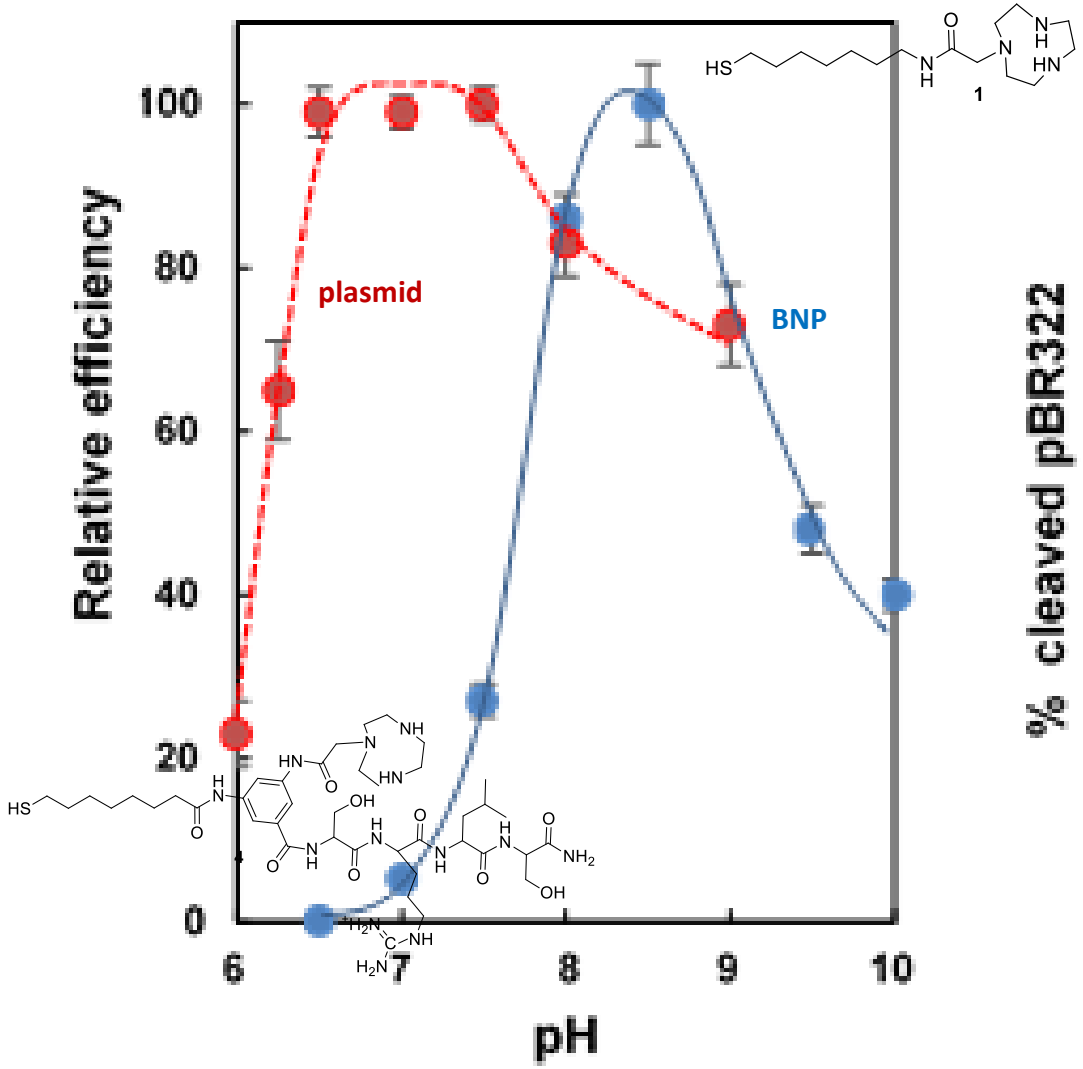
Joanna Czescik, PhD thesis, submitted

When we turn to pBR322 plasmid DNA the picture is totally reversed

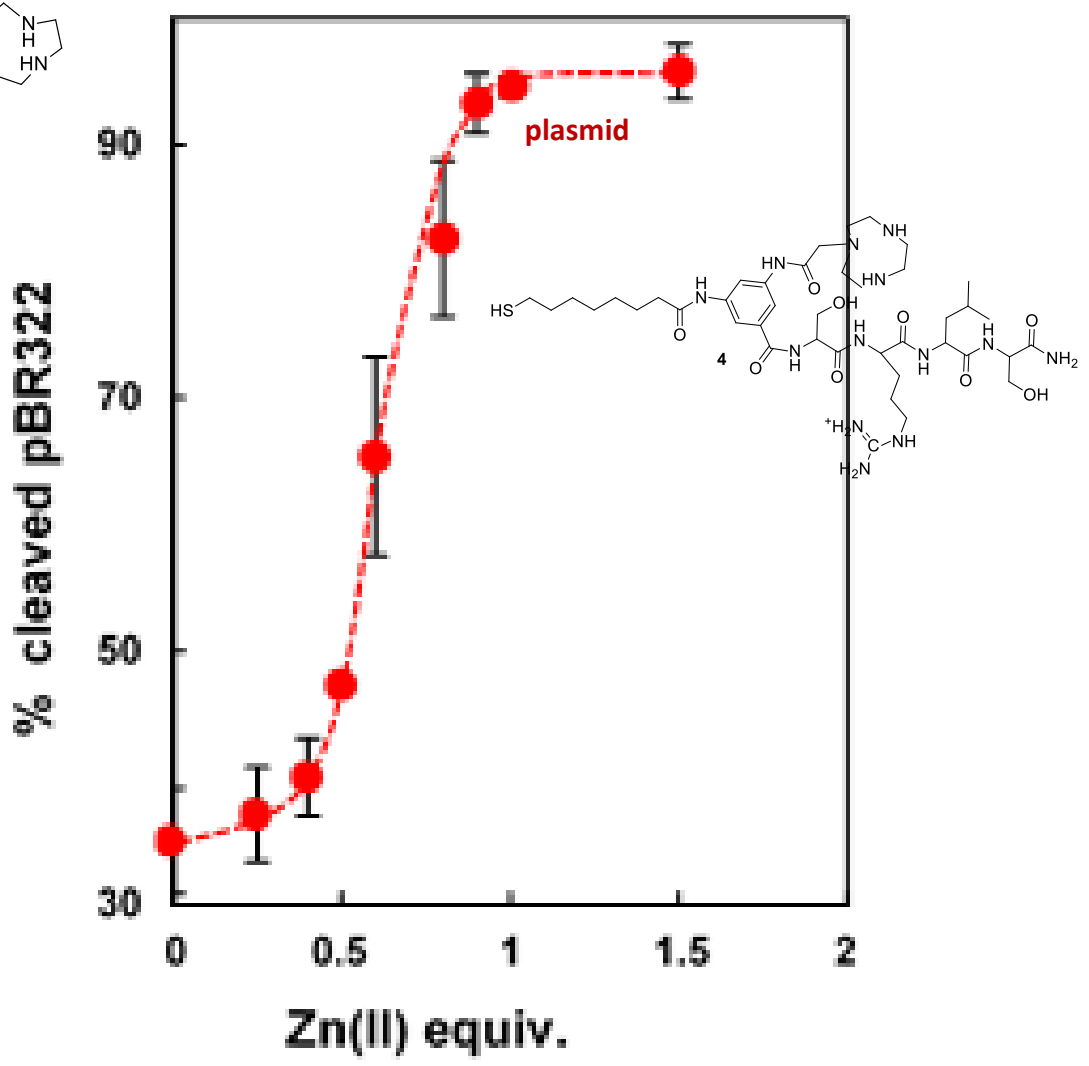


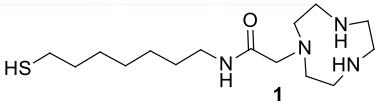


The pH-dependence profile reveals a striking difference between DNA and the model phosphate diester



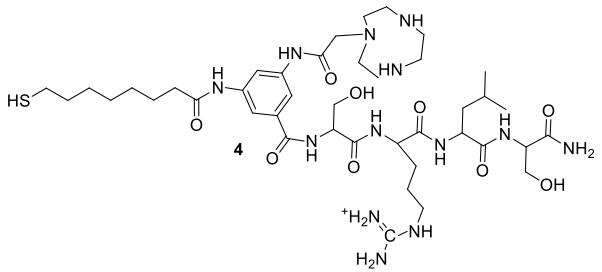
The best catalyst for DNA cleavage is mononuclear. Yet, the titration with Zn(II) still gives a sigmoidal profile

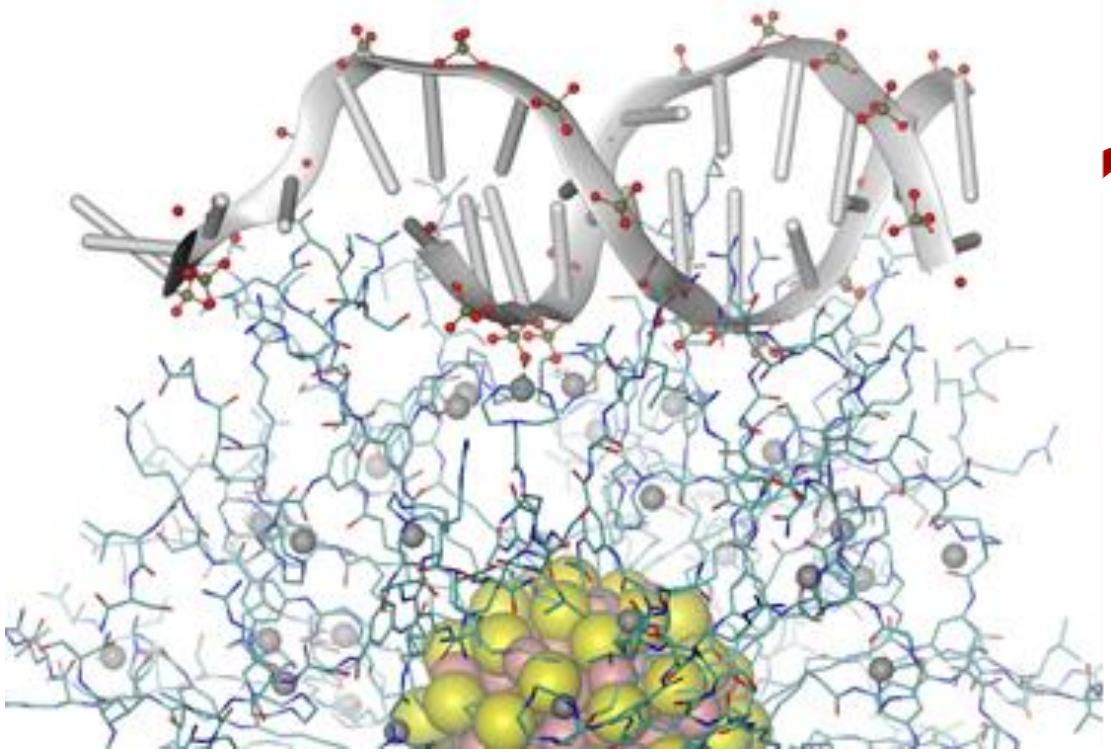


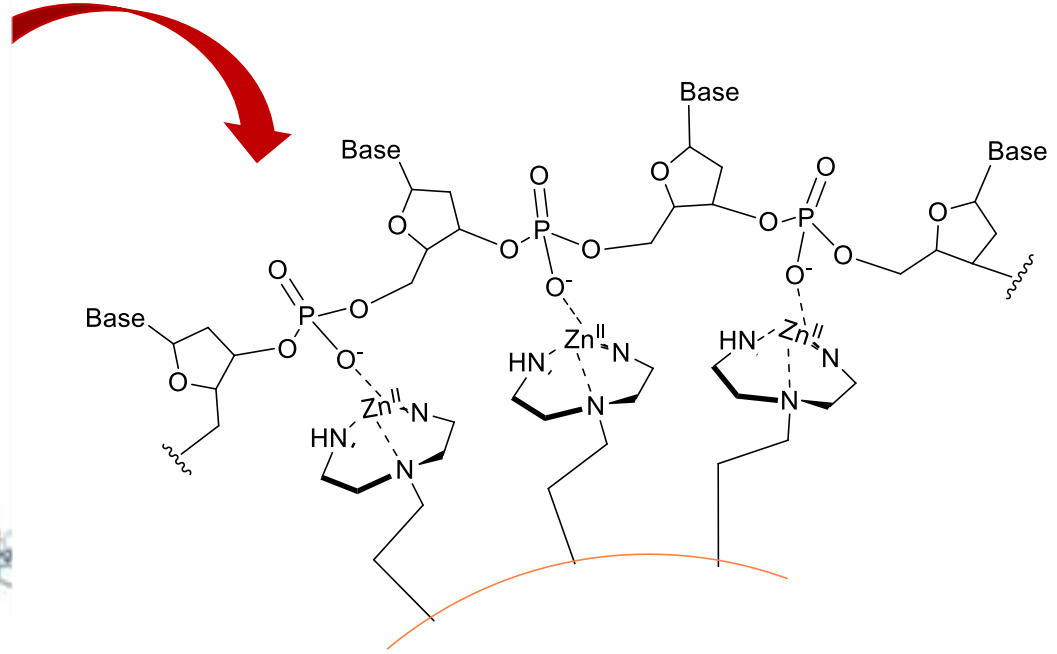


The AuNP-DNA is very strong because both are polyvalent species. Each phosphate binds a Zn(II): they cannot cooperate!

Only the system operating as a mononuclear catalyst can be active with DNA. Since TACN is not active as a mononuclear catalysts it requires flanking groups for catalysis!

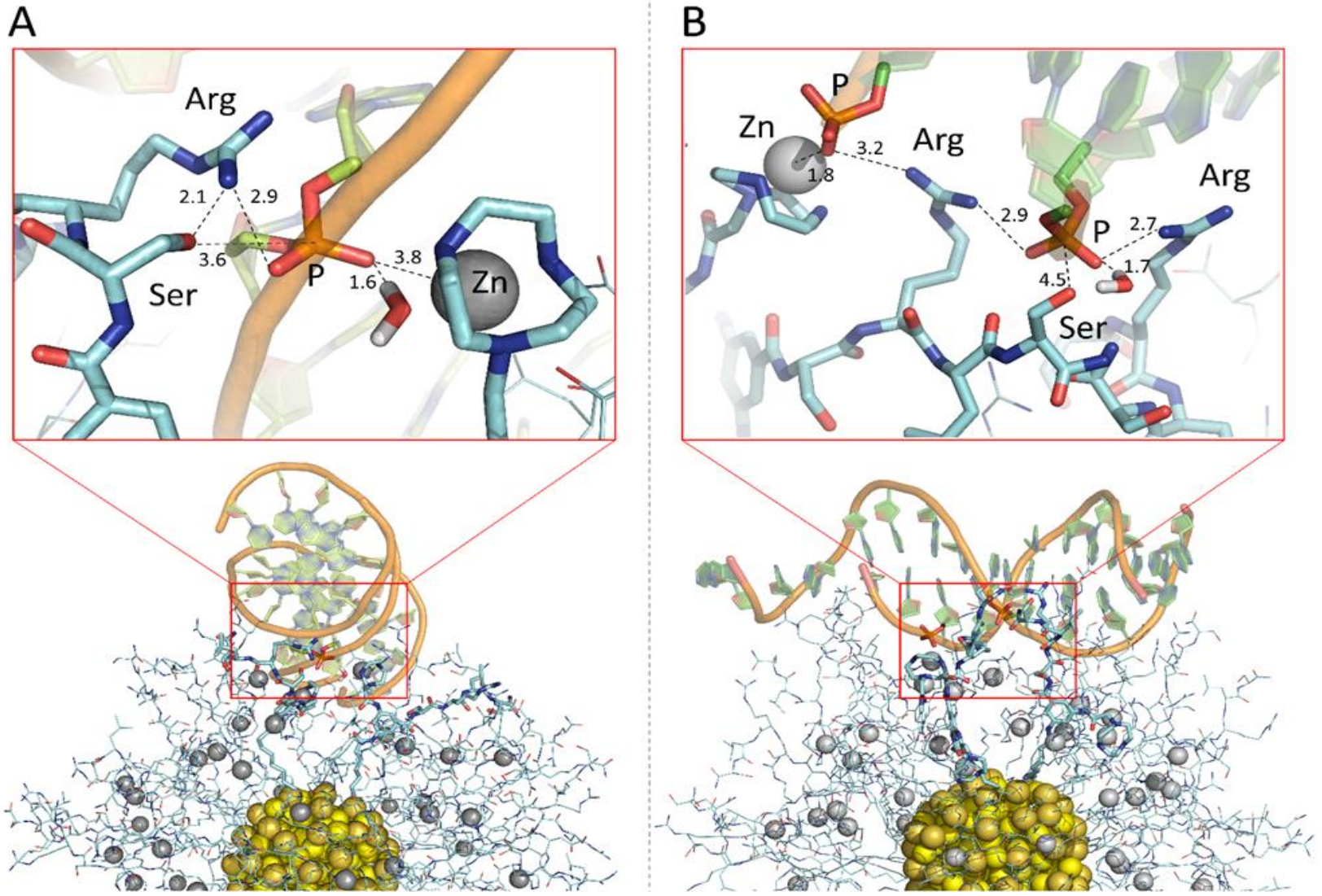




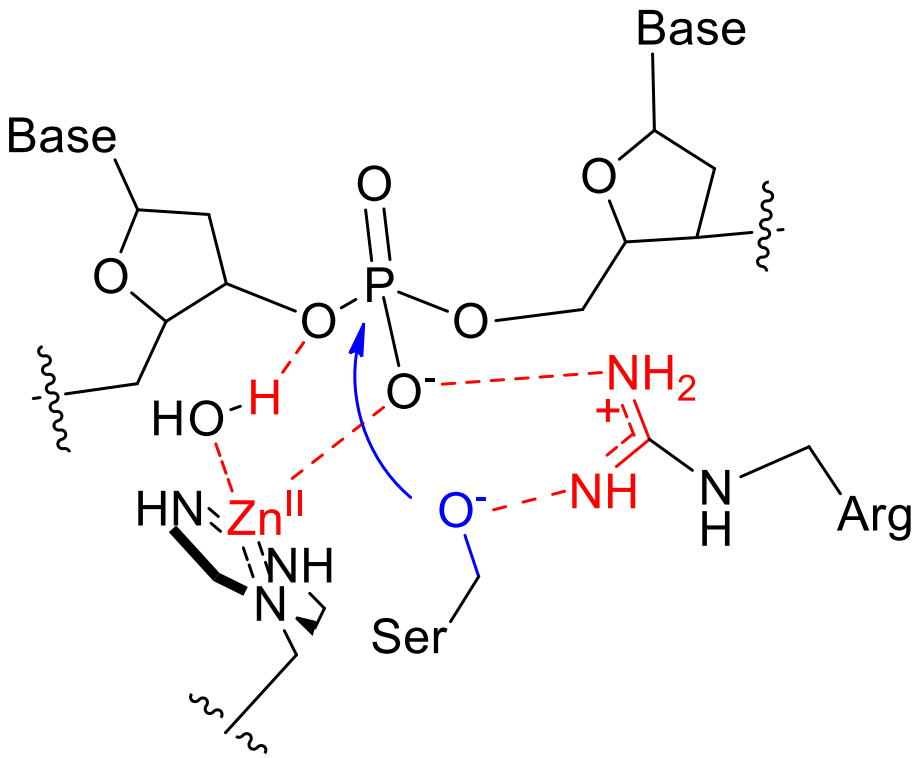


Pre-catalytic binding complexes formed between AuNP4 and dsDNA during the MD simulations

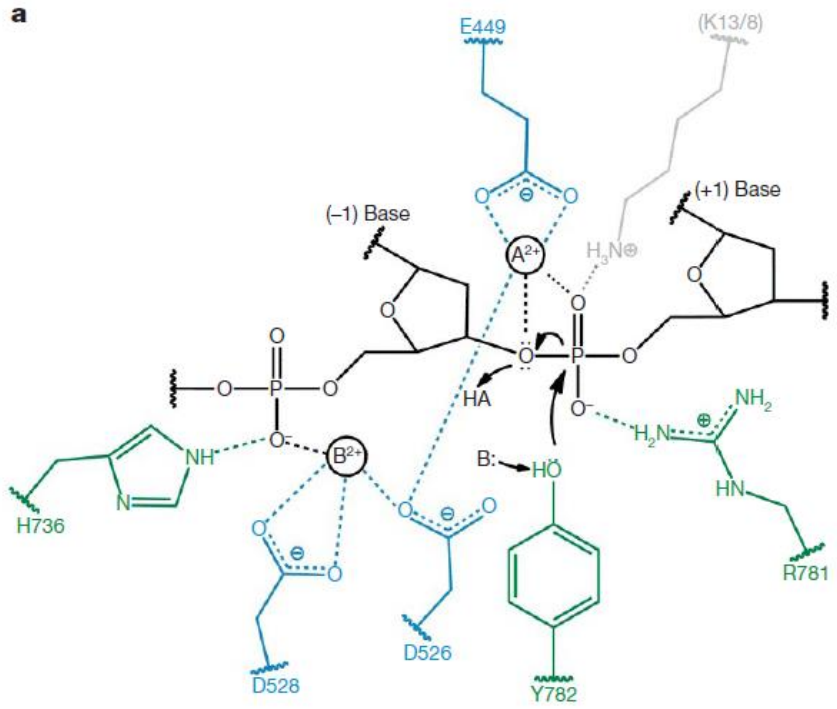
This complex is the most frequently formed pre-catalytic site (~17 % of the simulations time). In this complex, one phosphate group is coordinated on top of the Zn(II) ion, electrostatically stabilized by the arginine, with the nucleophilic serine properly oriented in order to perform nucleophilic



In this Complex (~11.7 % of the simulations time), the Zn(II) ion anchors one phosphate of the substrate, while one serine is properly oriented for nucleophilic attack at the proximal phosphate, which is chelated by two arginine residues



This mechanism is strikingly similar to that proposed for DNA cleavage by type II and IA topoisomerases where only one of the two metal ions present in the catalytic site is directly involved in substrate transformation.



The most plausible mechanism calls for the involvement of a single TACN-Zn(II) complex, a guanidinium from Arg and an alcohol from Ser

Schmidt, B., Burgin, A., Deweese, J., Osheroff, N., Berger, J. (2010). **A novel and unified two-metal mechanism for DNA cleavage by type II and IA topoisomerases.** Nature 465(7298), 641-4.