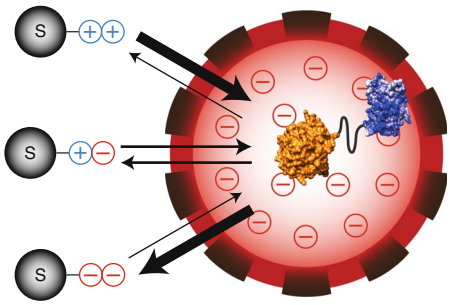
CATALYST ENCAPSULATION

An artificial proteasome

J. Am. Chem. Soc. **140**, 860–863 (2018)



Credit: American Chemical Society

Life on Earth employs compartmentalization to organize and regulate biological processes. These natural compartmentalization systems can be optimized for application in drug delivery, bioimaging and catalysis. Previously, a team led by Donald Hilvert at ETH Zürich engineered a capsid system — originally used by viruses to enclose their genetic material — to have a negatively supercharged interior.

Now, the team has used this system to encapsulate a protease from the tobacco etch virus that cleaves its substrates within a defined amino acid recognition sequence. The authors demonstrate that this proteolytic nanoreactor promotes uptake and hydrolysis of positively charged peptides and proteins while excluding negatively charged competitors based on electrostatic interactions. Thus, substrate specificities can be easily tuned by changing the substrate's net charge via suitable amino acid tags. Impressively, following this approach, the system facilitated a several hundred-fold inversion of the inherent substrate specificity of the protease.

Although the substrate sorting mechanism is different from its natural counterpart, the engineered capsid system can be considered as an artificial, simple version of the proteasome. In living cells, the proteasome degrades unneeded or damaged proteins that are tagged with ubiquitin. Genetic engineering allows, in principle, the design of capsids with alternative, desired substrate sorting and selection mechanisms. The proteolytic nanoreactor in this work forms spontaneously under a wide range of conditions, enabling applications in vitro and in vivo. Thus, it can be employed to modulate natural metabolisms or as an organelle in artificial biological systems. In general, the presented strategy has the potential to improve diverse chemical reactions by controlling substrate specificity, increasing catalyst stability and preventing unwanted reactions.

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Published online: 7 February 2018
https://doi.org/10.1038/s41929-018-0035-3