IL-26

Studying the unusual enzymes of phosphonate metabolism

Katharina Pallitsch, Kristof Braunsteiner, Tamara Dinhof, Thomas Kalina, Toda Stanković

Institute of Organic Chemistry,University of Vienna, 1090 Vienna.
e-mail: katharina.pallitsch@gmail.com

Phosphonates (Pns) and phosphinates are unique amongst all natural products, not only serving as a life limiting nutrient for microbes that live in phosphate depleted environments, but also as useful source of bioactive compounds.[1] Familiar examples of biogenic Pns and phosphinates include the cell membrane constituent 2-aminoethylphosphonic acid (**1**), the commercially used the antibiotic fosfomycin (**2**), or the herbicide phosphinothricin (**3**) (Fig. 1).

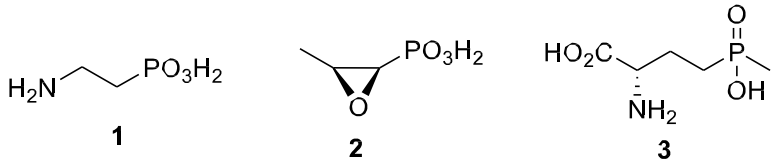

Figure 1. Examples of biogenic organophosphorus compounds of importance.

Pns were for a long time believed to be of low environmental importance due to the limited knowledge about their structures, occurrence, and pathways involved in their metabolism. This perspective has undergone a paradigm shift, largely driven by genomics, with the discovery that Pn biosynthesis and catabolism occurs widely in the microbial world. A survey in 2012 revealed the presence of Pn biosynthetic and catabolic genes in ~10% and 40%, respectively, of published microbial genomes.[2] Microbial Pn metabolism was proven to even influence the global P- and C-cycles: The degradation of methylphosphonic acid, the simplest Pn, was shown to lead to supersaturating levels of methane in ocean surface waters.[3] Despite their environmental and commercial importance, the enzymology encoded by Pn metabolic gene clusters still remains highly underexplored, and what has been characterized has often proven to be mechanistically unusual and unique. Synthetic probes of putative substrates and reaction intermediates are needed, alongside (isotopically labeled) substrate analogs and inhibitors to explore the involved metabolic pathways. Here we present a set (**4**-**7**) of examples of synthetic (enantiomerically pure) Pns that already became or will possibly become useful tools to investigate the unusual enzymology of Pn metabolism (Fig. 2).

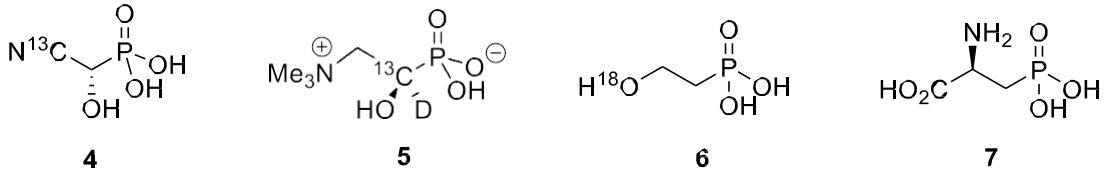

Figure 2. Examples of some target structures used to study Pn metabolism.

References

[1] G. P. Horsman, D. L. Zechel, *Chem. Rev.*, **2017**, *117*, 5704-5783.
[2] J. Villarreal, C. J. Quinn, *Front. Microbiol.*, **2012**, *3*, article 19.
[3] W. W. Metcalf, B. M. Griffin, R. M. Cicchillo, J. Gao, S. C. Janga, H. A.Cooke, B. T. Circello, B. S. Evans, W. Martens-Habbena, D. A. Stahl, *et al.*, *Science*, **2012**, *337*, 1104-1107.