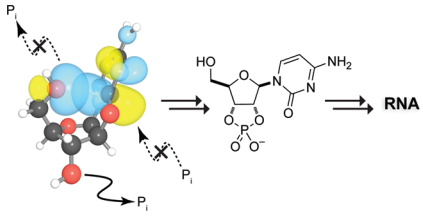
In this ISSUE

A Remarkable Stereoelectronic Effect

While the origin of life remains a mystery, the origin of the regioselectivity of a reaction that could have occurred in prebiotic conditions and would have yielded an RNA building block is no longer quite so mysterious. The reaction is the phosphorylation of an anhydroarabinonucleoside, which activates the compound and potentially enables the generation of ribonucleotide polymers capable of self-replication, storage of genetic information, and catalytic activity. Steric hindrance dictates that the phosphorylation would occur on the primary alcohol of the anhydroarabinonucleoside rather than its secondary alcohol (a reaction that would not yield an activated ribonucleotide). Yet, the opposite is true. Now, Choudhary *et al.* (DOI: 10.1021/cb100093g) uncover why the primary alcohol is less reactive than its secondary counterpart.

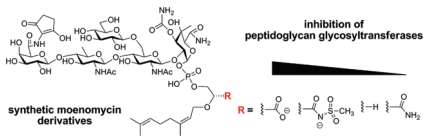
Examination of the crystal structure of the anhydronucleoside, along with quantum mechanical calculations, offered an explanation for the unexpected regioselectivity. Specifically, the primary alcohol is positioned such that its electron density is delocalized over a specific carbon–nitrogen double bond, which decreases its intrinsic nucleophilicity. This remarkable stereoelectronic effect may have set the stage just right for the creation of life as we know it.



The Function of a Phosphoglycerate

The increasing emergence of bacteria that have outsmarted the drugs targeted against them has fueled efforts for the discovery of both new bacterial drug targets and novel drug candidates. Moenomycin A is a promising new antibiotic, as it has a unique structure and is the only known natural product inhibitor of peptidoglycan glyocyltransferases, which are important enzymes in the biosynthesis of the bacterial cell wall. Recent elucidation of the crystal structures of four peptidoglycan glycosyltransferases in complex with moenomycins have offered much insight into the structural basis of inhibition. However, differences in the binding of the phosphoglycerate moiety within the moenomycin structure prompted Fuse *et al.* (DOI: 10.1021/cb100048q) to design six novel moenomycin analogues to help decipher the role of the phosphoglycerate in moenomycin function.

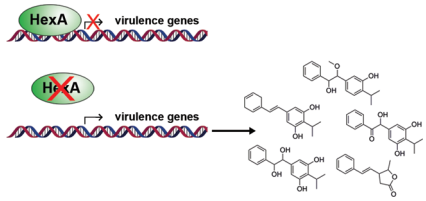
The moenomycin analogues were analyzed for their enzymatic and antibacterial activity, and the involvement of the phosphoglycerate was assessed using X-ray crystallography and molecular modeling. The details of the interaction revealed through these studies may facilitate the creation of moenomycin analogues with improved physicochemical properties, potentially leading to the much needed clinical use of a promising new class of antibiotics.



Maximizing Metabolites

Secondary metabolites are rich sources of structurally diverse, biologically active compounds, many of which are valuable biological probes or have intriguing therapeutic potential. However, there is a large disconnect between the number of known bacterial secondary metabolites and the number of biosynthetic genes within bacterial genomes capable of producing such compounds. In an effort to bridge this gap, Kontnik *et al.* (DOI: 10.1021/cb100117k) explore the downstream regulation of metabolite production in *Photorhabdus luminescens*, a Gamma proteobacteria whose secondary metabolite production is a vital component of its symbiotic relationship with nematodes and insect larvae.

Metabolomic profiling of a strain *P. luminescens* in which the gene for the transcriptional regulator HexA had been knocked-out showed a dramatic increase in concentration of numerous metabolites, including various stilbene derivatives. This approach sheds light onto the regulatory control of secondary metabolite generation and points to a promising strategy for novel small molecule discovery.



Published online July 16, 2010 • 10.1021/cb100184t