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Biology and brimstone

Evolution has made intriguing choices in selecting the elemental components of living systems. Although metal ions are central to all of biochemistry, a group of elements clustered in the early part of the periodic table—carbon, nitrogen, oxygen and phosphorus—are highly represented in the molecules of life. Sometimes it is easy to overlook the biological importance of another essential element, sulfur, the fragrant neighbor of the elements that comprise most organic compounds. In fact, sulfur occurs in all the major classes of biomolecules, including proteins, sugars, nucleic acids, vitamin cofactors and metabolites, and is required by all living organisms. Although many sulfur-containing biomolecules have been known for decades, only now are researchers beginning to understand their complex biosynthetic origins and functional roles. These advances, some of which are highlighted in this issue of *Nature Chemical Biology*, are providing fascinating new insights into sulfur's role in biology.

The flexibility of sulfur-containing biomolecules follows from the versatile chemistry of this element. As members of the same periodic group, sulfur and oxygen share similarities in chemical reactivity. However, sulfur's position lower in the periodic table endows its compounds with distinct properties that are advantageous to biological systems. For example, thiols are superior nucleophiles compared with alcohols and also serve as versatile activating groups in thioester biochemistry. Disulfide bonds (RS-SR) are more stable than peroxide bonds (RO-OR), and biology has taken advantage of this stability by using disulfide bonds as structural features of proteins. Sulfur can adopt a wider variety of oxidation states than oxygen, for instance in the oxidation of cysteine to sulfenic (R-SOH), sulfinic ($R\text{-}SO_2H$) and sulfonic ($R\text{-}SO_3H$) acids. Sulfur is also less electronegative than oxygen, permitting it to more readily adopt a positive charge, which is used by a number of enzyme cofactors.

S-adenosylmethionine (SAM or AdoMet), which is formed by the reaction of methionine and ATP, is an important cofactor for numerous enzymes. SAM serves as the methyl donor for biological methylation, and this reaction proceeds readily based on the chemical reactivity of nucleophiles with its electrophilic sulfonium ion. In addition to being the cell's 'methyl iodide', SAM is associated with enzymes that catalyze a wide range of chemical reactions, including many radical reactions. These diverse transformations involving SAM are a consequence of the diverse reactions that can be supported at the cofactor's sulfur center, as highlighted in the biosynthesis of biotin.

Biotin is an essential enzyme cofactor that is involved in enzymes that catalyze carboxylation reactions. Despite widespread understanding of the important physiological roles of biotin, the final step in biotin synthesis is still not understood. This challenging reaction, which requires the insertion of sulfur between two unactivated carbons, is catalyzed by biotin synthase, an enzyme that contains two iron-sulfur [Fe-S] clusters and SAM. In biotin synthase, the chemical properties of sulfur, which feature in both SAM and the [Fe-S] clusters, are critical for promoting carbon-sulfur bond formation. The source of the sulfur for the reaction, and the mechanism of its insertion, are still unresolved and are actively debated. Proposed mechanisms for this reaction are discussed in a Commentary by Fontecave (p. 171) and a Review by Mueller (p. 185).

Cysteine desulfurases have increasingly been shown to have a key role in the generation of numerous sulfur-containing biomolecules. Cysteine desulfurases catalyze the generation of a cysteine persulfide (Cys-S-SH) by transferring a sulfur atom from a free cysteine to an active-site cysteine in the enzyme. The resulting persulfide can function in subsequent reactions as either an electrophile or a nucleophile to mobilize sulfur atoms into and out of biomolecules. The wide ranging utility of persulfides for sulfur trafficking is discussed in a Review by Mueller (p. 185). A News & Views article by Lauhon (p. 182) focuses on a recent study (*Mol. Cell* **21**, 97–108, 2006) that details an elaborate biosynthetic pathway, starting with a cysteine desulfurase, to generate the modified nucleoside, 2-thiouridine. Cysteine desulfurases are also involved in the generation of [Fe-S] clusters, but many aspects of the cluster biosynthesis are still completely unknown. The challenges in understanding this pathway are discussed in a Commentary by Fontecave (p. 171).

Given sulfur's diverse properties, opportunities abound to exploit the chemistry of sulfur for engineering biological systems. Recent examples include the development of a sulfotransferase system for generating new antibiotics (see Research Highlights on p. 184) and the modulation of cellular differentiation through the incorporation of thiols on the cell surface (*Nat. Chem. Biol.* **2**, 149–152, 2006). Thus far, chemical biology has focused on a limited set of chemical elements. However, the increased involvement of chemists, as explorers of the periodic table, offers great promise for uncovering the chemistry behind evolution's choices for essential elements. ■