Perhaps hormone–hormone receptor pairs evolved from acylated lactones (or hydrophobic amino acids or peptides) and their target transcriptional regulators. Such origins are attractive because acylated lactones, owing to their hydrophobicity, can diffuse into a cell without a specialized transmembrane receptor, as well as diffuse out without a specialized secretion apparatus (*19*). Similarly, hydrophobic amino acids and peptides are transported by permeases with a rather low degree of specificity. *Rhizobium* nodulating a leguminous plant plays on an autoinducer-related theme in which flavonoids from the plant enter and control NodD transcriptional activators in the bacterium (*20*). NodD defines another family of activator proteins structurally unrelated to LuxR. Nevertheless, the number and variety of LuxR-like proteins are already large, as is the number of lactones with which they interact (*21*). Each element in a quorum-sensing system has the freedom to evolve greater complexity or specificity without compromising the overall system function, provided that it retains a capacity to interact effectively with its partners.

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Molybdenum Bolsters the Bioinorganic Brigade

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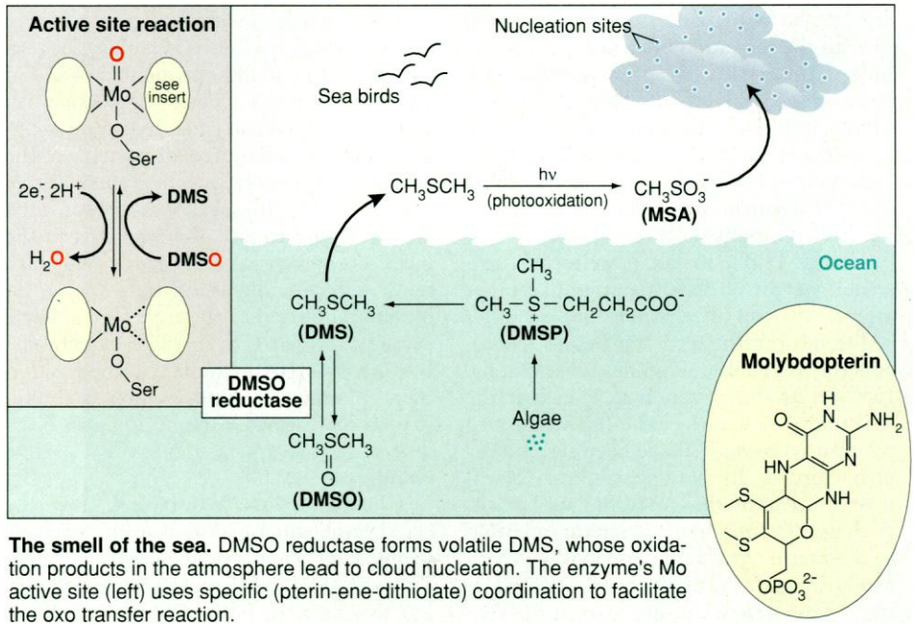
Plants, animals, and microorganisms need molybdenum (Mo) (*1*). Among the elements in the second transition row of the periodic table, only Mo has known biological functions, which involve more than 30 distinct enzymes (*1–3*). Although rare on Earth, Mo is abundant and soluble (as molybdate) in natural waters, exceeding in concentration such essential trace elements as manganese, iron, cobalt, copper, and zinc (*4*). This availability and a remarkable chemical versatility make Mo a crucial component of catalysts for both industrial (*2*) and enzymatic systems (*1–3*). In this issue, Schindelin *et al.* (*5*) report the crystal structure of the simplest known Mo enzyme, the dimethyl sulfoxide (DMSO) reductase (*6*) of *Rhodobacter spheroides*, which catalyzes the conversion of DMSO to dimethyl sulfide. The structure of this environmentally important enzyme should help elucidate how the tandem pair of protein and cofactor interacts to effect catalysis.

The Mo enzymes fall into two broad classes (*1–3*). Nitrogenase, responsible for biological nitrogen fixation, contains the special multimetal cluster called the iron-molybdenum cofactor and is the sole member of one class. The other class, embodying all other Mo enzymes, uses variants of the Mo cofactor (Moco), which contains a mononuclear Mo site. All Mo cofactors share a common nonprotein organic component, called molybdopterin, that acts as a ligand to Mo and was first shown to be a pterin with an ene-dithiolate (dithiolene) side chain (see figure) in the pioneering work of Rajagopalan and coworkers (*7*). Molybdopterin is also the ligand for tungsten (W) in enzymes from thermophilic microorganisms, which use tungsten, apparently in place of Mo (*8*). The full cofactor unit, metal plus specialized ligand, is designated Moco (or the tungsten cofactor).

DMSO reductase is one of several Moco enzymes—including sulfite oxidase, tetrathionate reductase, and polysulfide reductase—that are important in the sulfur cycle (*1–3*). Other Mo enzymes, such as nitrogenase, nitrate reductase, and a variety of heterocyclic *N*-oxidases, are critical for the global nitrogen cycle, highlighting the environmental and agronomic importance of Mo. The mammalian Mo enzymes xanthine oxidase (implicated in reperfusion injury and selectively inhibited in the treatment of gout), sulfite oxidase (necessary for sulfite detoxification and whose absence leads to



The smell of the sea. DMSO reductase forms volatile DMS, whose oxidation products in the atmosphere lead to cloud nucleation. The enzyme's Mo active site (left) uses specific (pterin-ene-dithiolate) coordination to facilitate the oxo transfer reaction.

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retardation and death), and retinal (aldehyde) oxidase (involved in development) are biomedically important. The ubiquitous Mo-containing enzymes are clearly crucial to the mainstream metabolism of many organisms (*1–3*).

DMSO is a molecule well known to chemists and pharmacologists (*9*). It has reputed therapeutic effects when rubbed on the skin and a legendary ability as a polar solvent that allows it to carry with it into cells any compound that it dissolves. Less well appreciated is that DMSO is a common component of the natural, especially the marine, environment (*10*).

DMSO is produced by the oxidation of dimethyl sulfide (DMS) formed by the hydrolysis of dimethyl sulfoniopropionate (DMSP) (used by algae for osmotic balance, methylation, and S metabolism) (see figure). The enzyme DMSO reductase, found in many bacteria and fungi, converts the water-soluble DMSO to the insoluble and quite volatile DMS, the predominant volatile compound of sulfur in the oceans (*10*). Some bacteria use this reaction to oxidize organic substrates, with DMSO substituting for oxygen as the terminal electron acceptor. The production of DMS consequently depends on the presence of organic matter in the marine environment, and DMS is therefore easily detectable where organic productivity is high (*10*). Thus, coastal regions and other productive areas of the sea have the characteristic smell of DMS. (The distinctive smell of "salt" air may arise more from DMS than from salt.) The volatile DMS serves as a beacon to certain birds who apparently recognize it as an indicator of productivity in the ocean below (*11*). Moreover, the atmospheric DMS, upon oxidation, eventually forms methylsufonate (MSA) or other oxidized acidic forms, which serve as nucleation sites for the formation of clouds (see figure). Indeed, it has been suggested that the sulfur cycle, involving DMS and DMSO, serves as a biological feedback system to modulate the temperature of Earth by controlling cloud formation and hence the albedo of the planet (*12, 13*). There is some experimental support for this hypothesis (*14*).

The DMSO reductase protein has a molecular weight of 85,000 and, unlike other known Mo and W enzymes, has no other additional prosthetic group besides Moco, which considerably simplifies spectroscopic (*15*) and kinetic (*16*) analysis. Moreover, the structure is now one of the few where two relevant redox states have been structurally characterized. In both states, the Mo is bound to two pterin-ene-dithiolate ligands. Both ligands contain the pyran ring addition to the pterin core, found previously in both Mo (*17*) and W (*18*) aldehyde oxidoreductases. The presence of one oxo in the oxidized form and no oxo ligands in the reduced form (see figure) is consistent with the simple oxo transfer formulation (*19*) of the substrate conversion step of this enzyme

$$Mo^{IV} + DMSO \rightarrow Mo^{VI} = O + DMS$$

The reaction is, however, unusual insofar as most oxo transfer reactions on Mo centers (*2, 3, 19*) involve the conversion of a dioxo $[Mo^{VI}O^{2+}]$ to a monooxo site $[Mo^{IV}O^{2+}]$. Here the conversion is of a monooxo to a nonoxo site. The dithiolene ligation and the protein milieu must impart special characteristics to the Mo site that facilitate this particular change in coordination. Most unusually, the dithiolene ligands coordinate unsymmetrically to the Mo—a situation not known in the structural chemistry of simple Mo complexes. The unprecedented looseness of the binding to Mo of one of the dithiolene ligands implicates this ligand in the catalytic process in ways that are not yet fully appreciated. Perhaps one dithiolene, the strongly bound ligand, is required to activate the Mo site for oxo transfer, as in the xanthine oxidase family (*2, 3*). The other, more loosely bound, ligand may then be involved in electron or proton transfer, in effect mimicking the action of an additional prosthetic group, which this protein lacks.

The structural results on DMSO reductase delineate a now clearly recognizable subclass of the Moco enzymes, which includes trimethylamine *N*-oxide reductase, nitrate reductases, and formate dehydrogenase. In contrast to the enzymes that resemble xanthine oxidase, which have one pterin dithiolene ligand (*17*), the enzymes in the DMSO reductase subclass have two pterin dithiolene ligands per Mo, like the W enzyme aldehyde oxidoreductase (*18*). Unlike the W enzymes, they have, in addition, a coordinated protein ligand. Sequence homology suggests that the serine found coordinated to Mo in DMSO reductase is replaced by a cysteine in nitrate reductase and trimethylamine *N*-oxide reductase, and by a selenocysteine in the formate dehydrogenase from *Escherichia coli*. The enzymes in this subclass probably use the protein ligand to tune the reactivity of the metal site, much in the way that hemoproteins use the extra ligand trans to the O_2 binding site to adjust the reactivity of heme toward dioxygen. (For example, cytochrome P-450 has a cysteine thiolate in the position trans to where O_2 binds, which facilitates oxygen activation; in hemoglobin, a histidine in this position facilitates the reversible binding of O_2.)

Clearly, Mo and W in biology use a specific ligand, which nature seems to have assembled to elicit the required reactivity. Thus, the Mo and W cofactor systems join the pantheon of bioinorganic active sites (*20*) alongside B_{12}, heme, iron-sulfur centers, and others as examples of coordination compounds that nature has recruited to supplement the catalytic abilities of proteins. The scope of the redox and molecular activation capabilities thus acquired significantly enhances the range of enzymic catalysis. The variation seen in Moco, as illustrated by the structure of DMSO reductase, shows that a given cofactor unit can be intricately manipulated by its host protein to perform the varied chemistry required by drastically different enzyme systems. Chemists have a long way to go to comprehend the subtleties and acquire that sort of power in their synthetic (ergo biomimetic) arsenals.

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