

environment (13). However, the existence of a glymphatic system is much debated because of the lack of evidence for the ability of the ISF to transport solutes (14) and the evidence in favor of diffusion of small and large molecules without ISF flow (15). However, the brainwide pulsations in CBV that cause CSF inflow to brain ventricles every 20 s during SWS as shown by Fultz *et al.* suggest that CSF and ISF do mix during deep sleep and that SWS has important homeostatic functions (13).

The identified reversal of CSF flow during SWS by Fultz *et al.* facilitates the mixing of subarachnoid and ventricular fluids and may serve as a communication pathway between fluid compartments. The bidirectional CSF flow may also serve to keep the small apertures that link the ventricles and the subarachnoid space open to maintain free CSF flow from the choroid plexus to

“The [cerebrospinal fluid] oscillations in human sleep... may contribute to the disposal of waste products...”

the subarachnoid space. This will prevent accumulation of CSF and waste products within the brain and preserve low intracranial pressure, which is essential for brain survival. Disturbances of SWS commonly accompany aging, major depressive disorders, and dementia (2). It will be interesting to assess whether the CSF dynamics linked to SWS can be used as a biomarker for disease states and whether strategies that restore SWS can rescue brain function in neurodegeneration. ■

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MATERIALS SCIENCE

Order emerging from disorder

Entropy stabilization provides a new direction for developing functional materials

By Nita Dragoë and David Bérardan

Twenty-six metals are usually found in alloys. Combining five of those metals and varying the composition in 1% increments leads to 2,822,599,802,880 different possible compounds. For six metals, the number of possible combinations is 902,943,619,878,430. Not all of these combinations are stable, but adding more elements counterintuitively stabilizes simpler structures by increasing entropy, a measure of disorder. Creating new materials by using entropy as a driving force is an emerging topic in materials science. Initially, this concept was used to obtain high-entropy alloys (HEA), which typically consisted of five elements. These alloys exhibit intriguing structural properties (1, 2). Recently, the strategy of using the entropy of mixing to stabilize a new phase has been extended outside metallic alloys and into functional materials.

By analogy to HEAs, single-phase samples of entropy-stabilized functional materials (ESFMs) have been loosely named as high-entropy materials. More accurately, a new phase formed because of the configuration entropy should be called “entropy stabilized.” By contrast, multicomponent conventional solid solutions have a high entropy of configuration but are generally not entropy stabilized. The key distinction is the presence of a phase transition at a critical temperature for the entropic phase. Therefore, all reported entropy-stabilized materials are also high-entropy materials, but the opposite is not true.

Synthesizing ESFMs requires heating a multicomponent mixture at high temperature followed by quenching, when the system has a small positive enthalpy. The configuration entropy (S) is equal to $S = -R\sum x_i \ln(x_i)$, where x_i is the fraction of each component. Entropy is equal to $1.61R$ for five equimolar elements, neglecting other entropic contributions (such as vibrational or magnetic). Thus, at high temperature the entropy becomes the main component of the total Gibbs free energy $\Delta G = \Delta H - T\Delta S$. For example, a reaction temperature of

1000 K compensates for a 13.37 kJ/mol heat of formation. A high-entropy phase will be thermodynamically favored, and the elements will be distributed over the available crystallographic sites. The existence of disorder favors the formation of a new simple phase.

This entropy-stabilized high-temperature phase can be frozen at room temperature through quenching. It is important to note that the resulting materials are not simple “conventional” solid solutions but metastable, entropy-stabilized solid solutions, with properties that are difficult to predict. As such, not only are these new materials, they represent a new paradigm in the design of functional materials, having a stability driven by the entropy of configuration.

One of the first entropy-stabilized oxides, (Mg,Co,Ni,Cu,Zn)O, was reported in 2015 (3). Heating the mixture of five oxides above 1150 K and quenching resulted in material with a simple rock salt structure (see the figure). This structure was not expected because some of the binary oxides do not crystallize in the rock salt structure and do not form a solid solution. The material is metastable because it will separate into several constituents when heated below 1150 K, but the structure is preserved at 300 K. In other words, (Mg,Co,Ni,Cu,Zn)O is kinetically stable at room temperature.

The formation of this type of new material is governed by entropy, which forces the cations to occupy randomly cationic sites. All five cations of (Mg,Co,Ni,Cu,Zn)O occupy similar octahedral sites at high temperature. This allows placement of cations in uncommon configurations or geometries that may result in new and unexpected properties.

Other ESFM structures have been claimed since 2015 with different classes of oxides, including perovskites (4), fluorite (5), spinels (6), as well as carbides (7), silicides (8), and borides (9). Some of these compounds still need to be tested in order to verify whether they are complex solid solutions or entropy-stabilized compounds.

Although cations have been used for entropic stabilization up to now, we have no reason to rule out anionic stabilization, and we can imagine this leading to increased structural complexity. Moreover, several cationic sites can be present. The perovskite

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(ABO_3) structure, for example, presents three different possible entropy-stabilized structures with a distribution of cations on the crystallographic A site, on the B site, or on both sites.

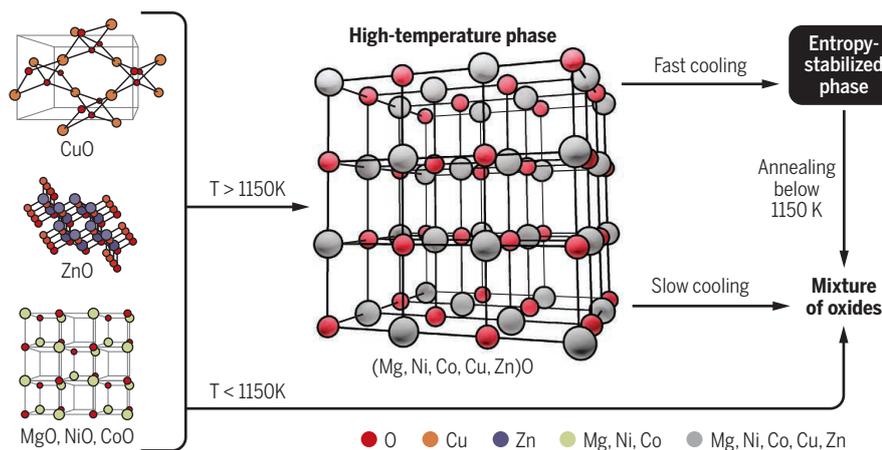
Although more materials are being added to the list of ESFMs, their properties have just begun to be investigated. The huge complexity of the systems and the dominant role of the entropy in their stabilization make the properties unpredictable. For example, doping (Mg,Co,Ni,Cu,Zn)O with alkali ions resulted in compounds with a colossal dielectric constant ($I0$) and superionic conductivity ($I1$). As a consequence, the system may be important for energy storage applications ($I2$). In general, doping allows fine-tuning of the composition and increases the already huge compositional space.

not limited to 3d electron-based systems because 4d and 5d transition-metal oxides also provide distinct properties owing to the interplay between electron correlation and spin-orbit coupling. Applying entropy-stabilization to more-complex oxides could give rise to intriguing physical properties, including thermoelectric materials, thermal barrier coatings, catalysis, or multifunctional properties.

Until now, such disordered systems have been almost completely overlooked in the search for new materials properties in solid-state physics. We believe that entropy-stabilized materials can provide a new impetus for the exploration of exotic properties and functions. However, one important challenge is deciding which of the staggering number of compounds to focus on. ■

Entropy-stabilized oxides

Oxides with different crystal structures may not easily combine together. Increasing the disorder, otherwise known as entropy, by increasing the number of elements can stabilize simple crystal structures at high temperatures. Keeping these materials stable at lower temperatures requires fast cooling.



The random cationic distribution of ESFMs suggests the potential for glass-like physical properties. For example, low electrical mobility, glass-like thermal transport, diamagnetism, or paramagnetism may stem from the disorder. (Mg,Co,Ni,Cu,Zn)O has a very low thermal conductivity ($I3$) and is electrically insulating ($I0$). However, this compound has peculiar magnetic properties, such as giant enhancement of exchange coupling in heterostructures ($I4$) and long-range magnetic order ($I5$). The long-range magnetic order is surprising in a chemically disordered system. The type of neighboring magnetic ion can change the magnitude or even the sign of the interaction. As a result, magnetic interactions might vary throughout the crystal structure. These types of systems are promising for studying the emergence of exotic magnetism. The electronic properties are

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ENZYMOLGY

The immune system mimics a pathogen

A host metabolite binds a bacterial enzyme and traps its B₁₂ cofactor in an inactive state

By Amie K. Boal

Microbes evolve diverse chemical strategies to survive in restrictive environments. *Mycobacterium tuberculosis* (*Mtb*) infection is a notable example of microbial persistence in a harsh milieu. *Mtb* causes tuberculosis (TB), a disease that kills more than 1.3 million people annually (I). On page 589 of this issue (2), Ruetz *et al.* describe how the immune system fights back against *Mtb* by stealing a page from the bacterial chemical warfare playbook.

When attacked by macrophages—immune cells that kill bacteria by engulfing them in an acidic intracellular compartment—*Mtb* undergoes metabolic changes that allow it to subsist in severely nutrient-limited conditions (3). The creative strategies that *Mtb* uses to hide in this persistent state are still being discovered. For example, recent analysis of lipid profiles in patient-derived *Mtb* strains revealed that the pathogen coats itself with a lipid- and nucleotide-derived antacid molecule (4), which serves as chemical body armor for the macrophage-entrenched bacterium.

Mtb-infected immune cells respond by diverting a common aerobic metabolite, *cis*-aconitate, to large-scale production of the host immunomodulator itaconate (5). Although the antibacterial properties of itaconate have been known for more than 30 years, the recent discovery that it accumulates to millimolar concentrations in activated macrophages sparked renewed interest in its molecular mechanism. Itaconate can be appended to the key metabolic cofactor coenzyme A (CoA) to yield itaconyl-CoA (I-CoA). Itaconate and I-CoA resemble intermediates in bacterial pathways for lipid

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