ers, through an imide moiety to cereblon (CRBN), the substrate receptor of an E3 ubiquitin ligase complex. CRBN-binding, imide-containing drugs cause ubiquitination and degradation of a set of "neosubstrate" proteins, including the transcription factors Ikaros (IKZF1) and Aiolos (IKZF3), which underlies the activity of lenalidomide and related immunomodulatory drugs (IMiDs) against multiple B cell–derived cancers (*9*). PROTACs that target BTK are "specific" in that they add only BTK to CRBN's set of neosubstrates, which remain targeted but can vary: NRX-0492 and NX-2127 catalyze the degradation of IKZF1 and IKZF3, but another BTK degrader, NX-5948 (currently being tested in NCT05131022), does not (*11*). Therefore, it is uncertain how much of NX-2127's activity is due to degradation of BTK, versus other CRBN neosubstrates, especially because the combination may be synergistic (*12*).

Whether as a kinase or scaffold, functional BTK protein is needed in B cell cancers and therefore degraders are likely to be effective, even after BTKi resistance develops. The study of Montoya *et al.* predicts a promising clinical future for degraders, and further development of PROTACs is ongoing, such as for increased specificity of neosubstrates (*13*). However, many questions remain about BTK degraders. Will they be best used after BTKi resistance develops, or should they be used first, especially given that CRBN-modulating degraders have other desirable targets for treating B cell cancers? It is unknown whether resistance to CRBN-modulating BTK degraders will emerge, as for IMiDs in myeloma treatment (*14*), such as through mutations in BTK at the PROTAC binding site or in PLC-γ2. Will BTK degraders replace BTKis and/or IMiDs in targeted combinations that are showing promise in clinical trials (*15*)? Patients and oncologists look forward to the answers. ■

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ACKNOWLEDGMENTS

J.R.W. has advised or received clinical research support from Abbvie, ADC Therapeutics, AstraZeneca, Bristol-Myers Squibb, Genentech, GenMab, Kite, Janssen, Kymera, Merck, Morphosys/Incyte, Novartis, Regeneron, and SeaGen.

10.1126/science.adn4945

MATERIALS SCIENCE

Plastics that lose their temper on demand

Multiple properties can be programmed into a single dynamic material by using heat

By **Haley P. McAllister** *and* **Julia A. Kalow**

As humans continue to explore harsher and less predictable settings, tools designed for specific use cases are not sufficient. Furthermore, survey vessels for oceanography and spacecraft for planetary exploration have limited space and thus must prioritize equipment on the basis of adaptability and versatility. The tools developed for sea and space exploration are deliberately unspecialized (*1*). A truly utilitarian invention warrants a single material that can be fashioned with many different properties. In a resource-scarce environment, it must also be reusable. Imagine an astronaut performing wheel repair on a rover by converting a single material into a wrench, adhesive, and a patch. On page 545 of this issue, Boynton *et al.* (*2*) report a class of polymeric materials with reversible, temperature-programmable mechanical properties that could be envisioned in such a scenario.

Using temperature to determine the mechanical properties of materials is not a new phenomenon. Thousands of years ago, through trial and error, blacksmiths developed tempering processes involving heating and rapid cooling to tune the properties of steel, including hardness, strength, and ductility (*3*). As a result, steel can be used for diverse applications, from knives to springs to structural beams. Compared with steel, plastics are lightweight and can be processed at lower temperatures, making them ideal for supporting the exploration of resource-scarce environments. Processes such as chemical cross-linking can transform thermoplastic polymers (those that can be readily melted and recast) into tough, elastic polymer networks. Traditional cross-linking, however, is based on irreversible bond formation, and plastic "tempering" requires reversible changes in structure.

In covalent adaptable networks, reversible covalent bonds allow the network of constituent polymer chains to rearrange. This ability underlies materials that are dynamic and responsive to stimuli (*4*). Many types of reversible covalent chemical reactions are used in adaptable networks, including disulfide exchange, transesterification, and Diels–Alder cycloaddition. The thermodynamics of the reversible cross-link determine the topology, and thus the mechanical properties, of the network. Boynton *et al.* used a dynamic cross-link based on the reversible addition of thiols to benzalcyanoacetates, known as a Michael addition (*5*). This reaction does not require a catalyst and is activated by mild heating. Like most dissociative reactions, the equilibrium constant for carbon-sulfur bond formation is sensitive to temperature, with higher temperatures favoring the dissociated state and lower temperatures favoring the bound state. The bound state is further favored by electron-withdrawing groups on the acceptor molecule. Therefore, when a donor molecule that bears multiple thiol groups (a multi-arm thiol) is combined with linkers bearing benzalcyanoacetate acceptors, the resulting network is tightly cross-linked at room temperature—that is, a stiff thermoset. When heated, the material softens and becomes extensible before completely disassembling into monomers at around 140°C.

Qualitatively, such behavior is typical of a covalent adaptable network and is not suitable for "tempered" multi-use plastics because distinct mechanical properties are only achieved at specific temperatures. Under service conditions, the stiff thermoset is reformed. The key advance that allows Boynton *et al.* to lock in the desired properties achieved at elevated temperatures is dynamic reaction–induced phase separation (*6*), which is proposed to kinetically freeze the network topology formed at a higher temperature. Thus, materials may be tempered at temperatures between their glass transition temperature (T_g; the temperature at which an amorphous glassy polymer material becomes rubbery) and the upper transition temperature at which disassembly occurs (T_{UT}). To lower the T_g and thereby widen the tempering window, Boynton *et al.* used a mixture of tetra- and bifunctional thiols. For a single formula-

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tion, the material was held at temperatures between 60° and 120°C for 24 hours before being cooled on a metal block. Depending on tempering temperature, the resulting material ranged from a hard, brittle thermoset similar to polypropylene, to a tough thermoplastic with stiffness comparable with that of high-density polyethylene, to a soft, extensible polymer that can be used as an adhesive (see the figure). Overall, for a single material, a greater than 10-fold change in Young's modulus (a measure of stiffness) and 20-fold change in strain at break were achieved through tempering.

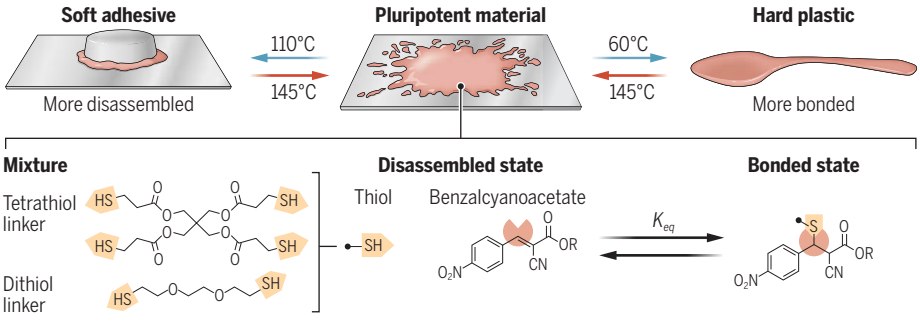
The mechanism for temperature-induced changes in mechanical properties proposed by Boynton *et al.* is supported through simultaneous Raman spectroscopy and mechanical measurements, which showed that as the material softens at higher temperatures, the fraction of bound cross-links decreases. Furthermore, these changes are fully reversible, so a single sample may be interconverted repeatedly between different states. Notably, the properties associated with each state were maintained for at least a month at room temperature but may be entirely "reset" by heating above the critical temperature, 140°C. Although many of the experiments were performed in a low-humidity, oxygen-free environment, these materials were also shown to be compatible with ambient atmosphere and did not form detectable amounts of disulfide.

To achieve the remarkable strength and toughness of hierarchically assembled biological materials (such as tendons or bone), researchers have created multimaterial structures through patterned cross-linking (*7*) or crystallization (*8*). Although patterning is often achieved with the application of light, heat may also be applied with spatial control. Historically, bladesmiths used differential tempering to create swords with tough spines and sharp edges. Boynton *et al.* patterned their material by subjecting stiff polymer network films, tempered at lower temperatures, to heated conductive surfaces. The resulting selectively softened region of the material underwent preferential deformation or failure. The material also exhibited shape memory behavior, allowing simple actuation, such as picking up and lifting a heated object.

The material developed by Boynton *et al.* is described as "pluripotent," analogous to a stem cell, which can differentiate into different cell types. Although researchers have sought to achieve reversible changes in material properties, the study of Boynton *et al.* demonstrates the value of arresting a material's properties in distinct states. A better understanding of the mechanism by which properties are "locked in" could further extend the lifetime of differentiated states under harsher conditions. The findings establish a new design goal for the materials science field and will inspire the development of other pluripotent polymers with an even wider range of useful properties accessed from a single material. ■

Pluripotent plastics

A pluripotent plastic material can be heated to temperatures between 60° and 120°C to achieve distinct properties, which are maintained upon cooling. The ratio of bonded to disassembled linkers is determined by the equilibrium constant of a reversible reaction, which is sensitive to temperature. Above 140°C, the bonds are completely disassembled, making the material circular in addition to versatile.



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ACKNOWLEDGMENTS

H.P.M. and J.A.K. receive support from the National Science Foundation under award CHE-1847948.

10.1126/science.adn3980

PHYSIOLOGY

Arterial pulses link heart-brain oscillations

A central baroreceptor monitors arterial pressure to modulate brain activity

By **Owen P. Hamill**

In 1942, the electrophysiologist E. D. Adrian published recordings from the hedgehog olfactory bulb (OB) indicating three basic classes of electrical oscillation: a respiration-nasal-airflow–related oscillation (RRO), a sensory-odor–induced oscillation, and an oscillation considered intrinsic to the local neural network (*1*). These oscillations are important because by moving the neuronal resting membrane potential toward and away from the spike threshold, they can synchronize spike activity in local and remote neural networks. All three classes of oscillation are dependent on synaptic transmission; have been recorded in other brain regions, most notably in the human cerebral cortex and hippocampus; and are considered fundamental to how the brain normally processes information (*2*). On page 494 of this issue, Jammal Salameh *et al.* (*3*) report a fourth class of oscillation—a heartbeat-related oscillation (HRO) evoked by arterial pressure pulsations and transduced by central baroreceptors.

Jammal Salameh *et al.* focused on understanding the mechanism underlying a prominent local field potential (LFP) oscillation of ~4 Hz recorded in the rat OB mitral cell (MC) layer. LFPs are electrical signals generated in the local extracellular space surrounding cells and include the combined activity of excitatory and inhibitory synapses as well as any spike activity. As with the studies of Adrian, the large rodent OB provided a highly accessible region of the brain for recording. But, in the case of the study of Jammal Salameh *et al.*, the nature of the nose-brain preparation (NBP) rat model (*4*) meant that respiratory- and sensory-evoked mechanisms could be excluded because of the lack of lungs, nasal airflow, and ascending respiratory pathways. Also, the absence of the heart

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