Supramolecular chemistry

Nanoscale scythe cuts molecular tethers

Iwona Nierengarten

Nanoscale systems that release small molecules have potential therapeutic and industrial uses, but can result in low numbers of molecules reaching their target. A release system triggered by mechanical force offers a fresh approach. **See p.320**

There are many potential applications for nanometre-scale systems that release molecules on demand — for example, to deliver biologically active compounds to a specific compartment of the human body, or to dispense catalysts for use in an industrial process. These often involve release mechanisms that are triggered by irradiation with light[1] or by changes in physical parameters, such as pH (ref. 2) or temperature[3]. In the past few years, mechanical forces have emerged as an alternative trigger for releasing small molecules. On page 320, Chen *et al.*[4] report a molecular device that successively releases cargo molecules when compressive forces or ultrasound are applied.

The use of mechanical forces for molecular release requires systems that actively discharge their cargo only in the presence of an external mechanical stimulus. For this purpose, Chen and colleagues constructed a system based on a rotaxane[5] (Fig. 1) — a structure composed of a ring threaded onto a long axle. For the ring, the authors chose a rigid pentagon-shaped molecule called pillar[5]arene (ref. 6) and the axle was a long molecular chain. Because the two components of the rotaxane were not connected by a chemical bond, the ring could move freely along the axle, with a large stopper at the axle's end preventing the ring from becoming unthreaded.

Controlling such nanometre-scale motions is challenging. To make the ring move along the axle in a chosen direction using mechanical forces, Chen *et al.* attached one long polymer chain to the end of the axle and another to the ring. The authors also equipped the axle with several connecting points to which cargo molecules can be securely tethered, allowing their safe transport with the rotaxane. When mechanical energy — from ultrasound, for example — is absorbed by the system, the resulting forces cause the long polymer chains to extend, pulling the ring along the axle.

But that's not all. When the ring reaches the first cargo molecule on the axle, the mechanical forces break the tether, releasing the cargo. The ring then continues on its way until it reaches the second cargo unit, at which point the release process begins again. The authors demonstrated that the ring subunit is essential for the release process, and that molecules can be liberated only when the ring comes into contact with the cargo molecule with sufficient force to cleave it from the axle. No traces of free cargo could be detected in a model system that lacked the ring component. This shows that uncontrolled liberation of the transported molecules is fully prevented.

Chen and colleagues' cargo-release system can be thought of as a molecular machine. When it is subjected to mechanical forces, the induced monodirectional motion of the ring along the axle provides sufficient energy to sequentially unhook the cargo molecules. The process continues as long as the mechanical forces are maintained, until all the molecules are liberated from the rotaxane platform.

The authors observed that cargo release could be promoted not just in solution, but also through compression of a solid sample of the rotaxane, and with greater efficiency than was seen in previously reported mechanically activated systems[7]. Moreover, each rotaxane system could release up to five cargo molecules; for comparison, previously reported force-activated molecular devices generally released only one. These results pave the way for more-complex systems with hundreds of such multi-cargo systems incorporated into 3D networks, each with long, flexible polymer chains attached to the rotaxanes. This would enable the simultaneous release of cargo from multiple rotaxanes when subjected to mechanical forces, greatly multiplying the number of molecules that are liberated at once.

Chen *et al.* also demonstrated that their rotaxane system can release different cargoes, including organocatalysts — small organic molecules used to speed up specific chemical reactions[8] — and the widely used chemotherapy drug doxorubicin. The latter finding suggests that such molecular machines have potential for mechanical-force-triggered drug deliveries.

It should be noted that the preparation of rotaxane systems bearing several cargo molecules remains difficult. Future work will therefore be essential to simplify their synthesis, and to make them affordable and readily

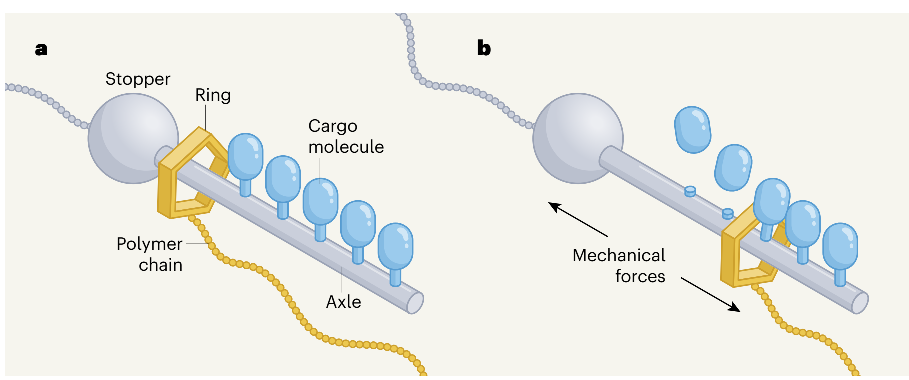

Figure 1 | Mechanically controlled release of molecules. **a**, Chen *et al.*[4] report a nanometre-scale device consisting of a ring threaded onto a rigid axle. The ring and axle each have a long polymer chain attached, and up to five cargo molecules can be tethered to the axle. The cargo molecules and a stopper prevent unthreading of the ring from the axle. **b**, When mechanical forces applied to the system pull on the polymer chains, the ring slides in one direction along the axle and successively breaks the tethers that restrain the molecules. Such a system could potentially be used for drug delivery in the body, or in industrial processes that require the transport and controlled release of catalysts.

available for practical purposes — especially for biomedical applications. Nevertheless, Chen and colleagues' findings represent a key step in the design of efficient molecular machines that can be activated by external mechanical forces. Their results will undoubtedly inspire research towards the design of more-universal mechanosensitive systems that allow controlled release of an even greater diversity of cargo molecules.

Iwona Nierengarten is in the Laboratory of the Chemistry of Molecular Materials, University of Strasbourg, and at CNRS (LIMA UMR 7042), European School of Chemistry, Polymers and Materials, 67087 Strasbourg Cedex 2, France.
e-mail: iosinska@unistra.fr

1. Liu, J., Kang, W. & Wang, W. *Photochem. Photobiol.* **98**, 288–302 (2022).
2. Liu, J. *et al. Biotechnol. Adv.* **32**, 693–710 (2014).
3. Karimi, M. *et al. ACS Appl. Mater. Interfaces* **8**, 21107–21133 (2016).
4. Chen, L., Nixon, R. & De Bo, G. *Nature* **628**, 320–325 (2024).
5. Bruns, C. J. & Stoddart, J. F. in *The Nature of the Mechanical Bond: From Molecules to Machines* Ch. 1 (Wiley, 2016).
6. Ogoshi, T., Kanai, S., Fujinami, S., Yamagishi, T. & Nakamoto, Y. *J. Am. Chem. Soc.* **130**, 5022–5023 (2008).
7. Versaw, B. A., Zeng, T., Hu, X. & Robb, M. J. *J. Am. Chem. Soc.* **143**, 21461–21473 (2021).
8. Naidu, V. R., Ni, S. & Franzén, J. *ChemCatChem* **7**, 1896–1905 (2015).

The author declares no competing interests.

Conservation biology

Climate change predicted to exacerbate bee declines

Nicole E. Miller-Struttmann

What effects will climate change have on insect communities? Analyses of data collected over decades robustly document consequences specific to bee populations, and this evidence might aid future conservation efforts. **See p.337 & p.342**

Although most modern cases of extinction are attributed to habitat loss, invasive species and over-exploitation[1], climate change is rapidly becoming a prominent threat. Research suggests that climate extremes are contributing to declines in bees, butterflies, flies and moths[2] and increasing their extinction risk. However, those results have mainly been correlational rather than providing direct causal evidence, making assessments of conservation status based on them tenuous. Two papers now make key strides in filling that knowledge gap. On page 342, Kazenel *et al.*[3] provide evidence of the direct physiological effects of extreme climate conditions on the long-term population stability of bees, and on page 337, Ghisbain *et al.*[4] predict striking declines in bumblebees, including in many species currently listed in the 'least concern' category of threatened species in the influential listings by the International Union for Conservation of Nature (IUCN).

Documenting species declines in response to changes that occur over decades, such as climate change, requires long-term data sets that are exceedingly rare. The species for which we have those kinds of data tend to be large and charismatic. For the insect world, bumblebees fill that role (Fig. 1a). In response to increasing temperatures, bumblebees have shown contractions in their dispersal ranges, population declines and local extinctions[5–7]. Those declines have been linked to a lack of physiological tolerance of high temperatures as demonstrated through experiments[8] and because of the observed historical climate limits for these species[5]. Together, those studies provide strong support for the role of temperature in driving bumblebee declines.

However, most bee species are ecologically and evolutionarily different from bumblebees. Bees are generally small and solitary, whereas bumblebees are relatively large and social. As such, solitary bees might respond differently to climate change, particularly if their physiological tolerances are more constrained than are those of bumblebees. Kazenel and colleagues address this issue using a 16-year study of 339 bee species, many of which are solitary, in drylands in the southwestern United States. The authors used a robust combination of data for natural variation in climate, and experimental evidence to predict which species would be negatively affected by climate change. They project that of the 243 species that they found were sensitive to drought, 46% will experience population declines with continuing climate change (Fig. 1b).

Previous research in this area has focused mainly on temperature limits that would prevent bee survival[5,9–11] but this metric, although important, does not reflect all the physiological effects of climate change, such as those driven by drought. The species predicted by Kazenel *et al.* to persist despite climate change are tolerant not only of heat but also of dry conditions (desiccation). The authors experimentally determined thermal and desiccation tolerances for a subset of 12 bee species and found that those species that are best able to handle both were more resilient to previous climate change. The 12 species represent 3.5% of those studied by the authors, but they are spread across the evolutionary tree of life (taxonomically diverse) and represent five of the seven bee families found globally.

Although projecting future declines is a crucial step in identifying species' extinction risks, responding with meaningful conservation actions remains challenging. Many governmental protections rely on descriptors of conservation status, such as those established by the IUCN. Such metrics are based on documented population declines. However, as climate change escalates, species that were historically stable might rapidly become threatened, making current conservation-status assignments misleading. Indeed, Ghisbain *et al.* demonstrate that reliance on past declines is insufficient for predicting future effects of climate change on European bumblebees. Using a compilation of historical and contemporary data sets collected between 1901 and 1970, and 2000 and 2014, the authors report (Fig. 1a) that changes in climate, land use and human population size have made parts of Europe less suitable for many bumblebee species. On average, decreases in habitat suitability were relatively low (4.5%), however, local suitability declined by up to 33%. Moreover, those declines are projected to continue or intensify for up to 76% of species.

Similar patterns have been demonstrated previously[5], however, Ghisbain and colleagues go one step further by assessing whether species' current conservation status can predict future habitat suitability (Fig. 1c). Unfortunately, it can't. An estimated 32–76% of species that are currently considered of least concern by the IUCN are predicted to lose at least 30% of their suitable habitat by 2080, a level of decline that would move them to threatened status. Notably, these patterns are consistent regardless of the approach (niche model or climate scenario parameters) used to estimate habitat suitability.

Important unknown factors still hinder our ability to predict species distributions. Foremost among them is dispersal. Current climate 'safe sites' (refugia) for bumblebees, such as regions in eastern Scandinavia, remain intact under several climate scenarios (Fig. 1a), but whether bumblebees can migrate to them remains unclear. Bumblebees occasionally