

## Most Significant Research Contributions, Leigh Group (www.catenane.net)

### Summary

The Leigh group are one of the pioneers of molecular nanotechnology and nanotopology. Over the last quarter-century they have developed fundamental methods to control molecular-level dynamics and entanglement. They have introduced numerous new and influential concepts for the synthesis of interlocked molecular architectures (such as benzylic amide catenanes, rotaxanes and molecular shuttles [1995-2006] and catalytic ‘active template’ synthesis [2006]), pioneered the control of molecular-level motion using ratchet mechanisms [2003], synthesized many of the most complex molecular knots and links to date, and initiated the fields of small-molecule robotics [2016] and 2D molecular weaving [2020].

The introduction of Brownian ratchet mechanisms into synthetic molecules in the early 2000s is regarded as one of the most significant developments in the control of molecular-level dynamics to date [‘...perhaps the most important result so far accruing from the synthesis of molecular machines is the insight provided into the fundamental mechanisms by which molecular motors function’, R. D. Astumian, *Chem. Sci.* **2017**, 8, 840]. Seminal contributions from the Leigh group in this regard include the first molecular Brownian ratchets [2003 & 2004], the first molecular energy ratchet [2003], the first molecular information ratchet [2007], and the first linear molecular motor (a non-adiabatic molecular incarnation of the Maxwell Demon thought experiment [2007]). The group have developed increasingly complex molecular machines, including examples that synthesize peptides in a programable sequence reminiscent of the ribosome [2013] (recently extended to continuous-carbon-backbone polymers [2020]). They developed the first synthetic molecules that ‘walk’ along tracks [2010], the first autonomous chemically-fueled molecular motors [2016], motors driven by pulses of chemical fuel [2017], small-molecule robotics [2016] and a programable ‘molecular assembler’ [2017] described in an accompanying N&Vs article as ‘*Science fiction becomes fact*’.

Over the last decade the Leigh group have advanced mechanically interlocked molecular architectures beyond simple catenanes and rotaxanes to increasingly complex knots and links. They have used molecular knots to induce both chiral [2016] and allosteric [2017] catalysis, studied the effects of entanglement across length scales [2018], synthesized the most complex knots and links to date [2012-2020], extrapolated these concepts to the two-dimensional weaving of polymer chains [2020], and forged a burgeoning new field of ‘molecular nanotopology’.

### 1. Catenanes, rotaxanes and hydrogen bonded molecular shuttles

In 1995 the Leigh group reported the serendipitous discovery of benzylic amide catenanes, assembled in one step from commercially available reagents [*Angew. Chem. Int. Ed.* **34**, 1209 (1995)]. Carrying out a similar process under thermodynamic control (organic ‘magic’ rings—the first ring-opening-ring-closing olefin metathesis reaction) gave virtually quantitative yields [*J. Am. Chem. Soc.* **121**, 1599 (1999)]. Structural and mechanistic studies enabled related rotaxanes to be designed [*J. Am. Chem. Soc.* **118**, 10662 (1996)]. Divergent hydrogen bonding sites occur in adjacent amino acid residues in peptide chains, leading to the synthesis of the first peptide rotaxanes [*Angew. Chem. Int. Ed.* **36**, 728 (1997)] and shuttles [*J. Am. Chem. Soc.* **119**, 11092 (1997)].

Over the next decade (1997-2007) the group introduced numerous novel and influential methods for controlling component dynamics in catenanes and rotaxanes and developed an array of stimuli to induce movement in molecular

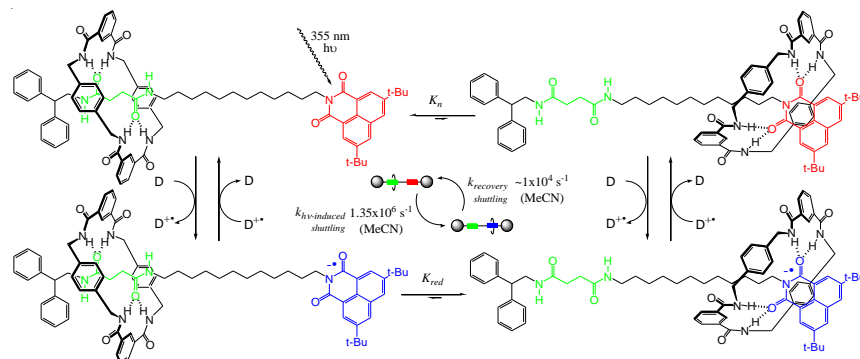
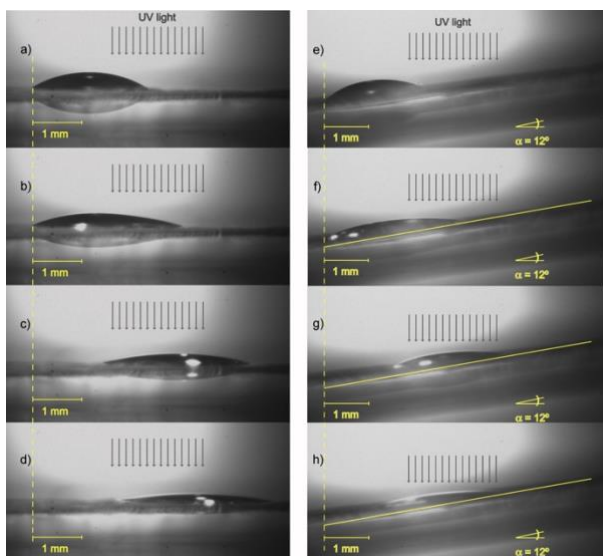


Fig. 1. Light-fueled molecular shuttle (2001).

shuttles, including polarity changes [*J. Am. Chem. Soc.* **119**, 11092 (1997)], light [*Science* **291**, 2124 (2001). Fig. 1; *J. Am. Chem. Soc.* **123**, 11327 (2001); *Angew. Chem. Int. Ed.* **42**, 2296 (2003); *Science* **328**, 1255 (2010)], anion binding [*Angew. Chem. Int. Ed.* **43**, 1222 (2004); *Angew. Chem. Int. Ed.* **47**, 8036 (2008)], electrochemistry [*J. Am. Chem. Soc.* **125**, 8644 (2003); *J. Am. Chem. Soc.* **130**, 2593 (2008)], entropy-driven changes [*Angew. Chem. Int. Ed.* **42**, 5886 (2003)], reversible covalent chemistry [*Chem. Commun.* 2262 (2004)], competitive binding [*Angew. Chem. Int. Ed.* **45**, 77 (2006)] and allosteric binding [*Angew. Chem. Int. Ed.* **45**, 1385 (2006)].

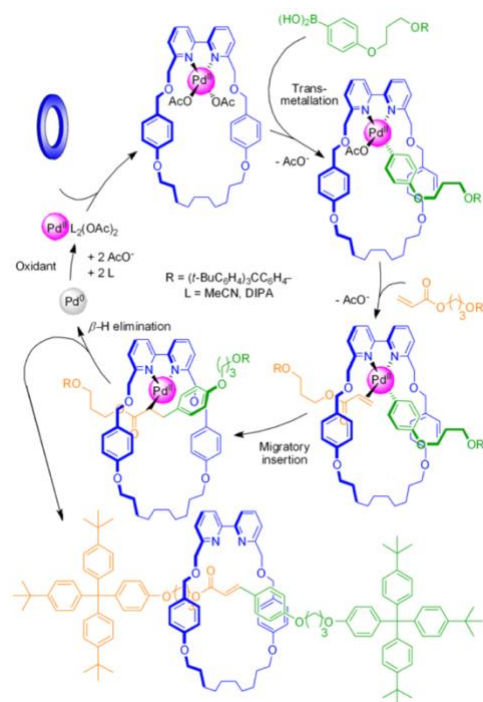


**Fig. 2.** Macroscopic transport by artificial molecular machines (2005).

These brought about property changes in some of the earliest functional molecular machines, including: photoswitches for fluorescence [*J. Am. Chem. Soc.* **126**, 12210 (2004)] and chirality [*J. Am. Chem. Soc.* **125**, 13360 (2003)], dissipative catalysis [*Angew. Chem. Int. Ed.* **58**, 9876 (2019)] and early examples that operated in polymer films [*Angew. Chem. Int. Ed.* **44**, 3062 (2005)], on surfaces [*Science* **299**, 531 (2003)], with mechanisms and dynamics characterized at the single-molecule level [*Nat. Nanotech.* **6**, 553 (2011)]. A landmark demonstration was the use of the light-switchable response of a monolayer of fluorinated hydrogen bonded shuttles to change the contact angle of liquid droplets [*Nat. Mater.* **4**, 704 (2005), Fig. 2]. The effect proved sufficiently powerful to transport droplets across a surface, the first example of macroscopic transport by synthetic molecular machines.

Other significant assembly and recognition motifs introduced by the group included the strongest contiguous triple [*J. Am. Chem. Soc.* **129**, 476 (2007); *J. Am. Chem. Soc.* **131**, 14116 (2009)] and quadruple [*Nat. Chem.* **3**, 244 (2011)] hydrogen bonded complexes measured to date.

Classical template syntheses involve stoichiometric quantities of an otherwise passive template. For mechanically interlocked molecules the recognition motifs often 'live on' in the final molecule. In 2006 the Leigh group introduced the conceptually new 'active template' approach [*J. Am. Chem. Soc.* **128**, 2186 (2006), Fig. 3; *Chem. Soc. Rev.* **38**, 1530 (2009)] in which a metal ion plays a dual role, acting as both a template for entwining the precursors and catalyzing covalent capture of the threaded reactants. It proceeds under kinetic control, generally requires only a catalytic quantity of the template, and is traceless. The active template strategy has been successfully applied to numerous metal-catalyzed reactions (CuAAC 'click' reaction [*J. Am. Chem. Soc.* **128**, 2186 (2006); *J. Am. Chem. Soc.* **129**, 11950 (2007)], Glaser and Ullmann couplings [*Angew. Chem. Int. Ed.* **46**, 5709 (2007); *Angew. Chem. Int. Ed.* **47**, 4392 (2008)], oxidative Heck [*J. Am. Chem. Soc.* **129**, 12092 (2007)], Pd-catalyzed Michael addition [*Angew. Chem. Int. Ed.* **47**, 3381 (2008)], Ni- and Cu-catalysed coupling reactions and cycloadditions [*J. Am. Chem. Soc.* **132**, 315 (2010); *J. Am. Chem. Soc.* **132**, 5309 (2010); *J. Am. Chem. Soc.* **132**, 6243 (2010)], Goldberg reaction [*J. Am. Chem. Soc.* **137**, 7656 (2015)] and adopted by many groups around the world [see Goldup, S. M. et al, *The active template approach to interlocked*



**Fig. 3.** Active template synthesis (2006).

molecules, *Nat. Rev. Chem.* **61** (2017)]. Recently, the Leigh group extended the active template concept to metal-free systems [*J. Am. Chem. Soc.* **139**, 8455 (2017); *J. Am. Chem. Soc.* **140**, 6049 (2018)].

## 2. Brownian ratchets: controlling molecular-level dynamics

Engineering approaches to control dynamics in the macroscopic world naturally focus on Newtonian mechanics (momentum, inertia etc), but these are not useful design concepts for the nanoscale where statistical mechanisms dominate. The idea of using random thermal fluctuations to drive directed motion has its origins in the visionary works of von Smoluchowski [*Phys. Z.* **13**, 1069 (1912)] and Feynman [*The Feynman Lectures on Physics* (1963)], but breakthrough papers from Astumian (theory) and the Leigh group (experiment) in the late 1990s and early 2000s, respectively, explained how these concepts apply to, and can be used in the design of, molecular motors and other out-of-equilibrium chemical systems.

Astumian described theoretical energy and information Brownian ratchets in 1998 [*Eur. Polym. J.* **27**, 474 (1998)]; the Leigh group showed how these physical principles could be applied to the design of synthetic molecular systems in landmark papers in 2003 and 2004 [*Nature* **424**, 174 (2003), Fig. 4; *Science* **306**, 1532 (2004)]. In particular, Leigh's team recognized that mechanically restricted molecular components (e.g. the rings in catenanes or rotaxanes) could be considered as Brownian particles on a potential energy surface (the track) and their dynamics thus controlled by incorporating Brownian ratchet mechanisms into synthetic molecular designs: "The way in which the principles of an energy ratchet can be applied to a catenane architecture is not to consider the whole structure as a molecular machine, but rather to view one macrocycle as a motor that transports a substrate—the other ring—directionally around itself" and demonstrating for the first time that "Mechanisms formulated from non-equilibrium statistical mechanics can be successfully used to design synthetic molecular motors" [*Science* **306**, 1532 (2004)].

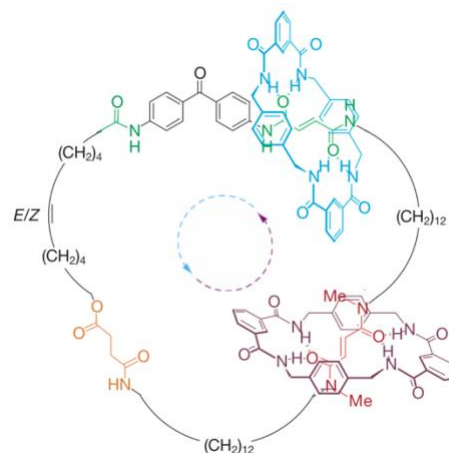


Fig. 4. Brownian ratchet molecular motors (2003).

This realization marked a conceptual breakthrough that enabled the design and synthesis of genuine chemical engines, modules that power molecular motors and other complex machines such as pumps. The Leigh group's contributions include the first molecular energy ratchets [*Nature* **424**, 174 (2003); *Science* **306**, 1532 (2004)], the first molecular information ratchets [*Nature* **445**, 523 (2007)], the first linear molecular motors [*J. Am. Chem. Soc.* **128**, 4058 (2006)], and the first autonomous chemically-driven molecular motors [*Nature* **534**, 235 (2016)].

In addition to ratchets and motors, the Leigh group have produced a number of other major advances in this field. Their examples of complex synthetic molecular machinery that operate through the integrated interaction of multiple functional component parts include synthetic molecules that 'walk' along tracks

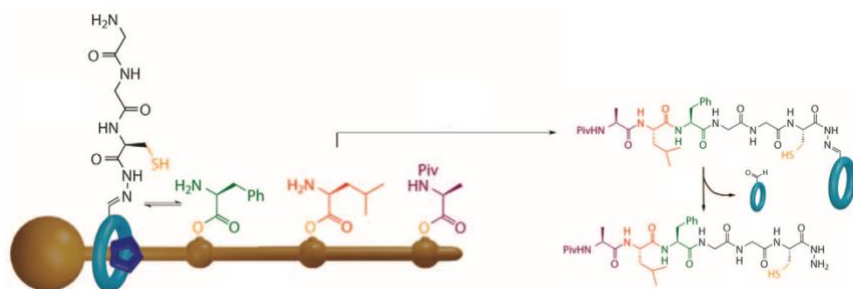


Fig. 5. Molecular peptide synthesizer (2013).

along tracks [*Nat. Chem.* **2**, 96 (2010); *Angew. Chem. Int. Ed.* **50**, 285 (2011) & *Angew. Chem. Int. Ed.* **51**, 5480 (2012)], programmable small-molecule robotics [*Nat. Chem.* **8**, 138 (2016) & *Nature* **549**, 374 (2017), Fig. 6], and ribosome-like molecular synthesizers [*Science* **339**, 189 (2013), Fig. 5; *Nat. Nanotech.* **13**, 381 (2018) & *Chem* **6**, 2964 (2020)].

The introduction of ratchets and other complex mechanisms into synthetic molecular systems has transformed the understanding and design of molecular machinery—biological, chemical and physical—from the simple concepts of the 1990s to the sophisticated designs of mechanisms that underpin out-of-equilibrium research in the molecular sciences today.

### 3. Molecular Nanotopology

The physical significance of topological complexity (knots and links) is apparent in areas as diverse as colloids, liquid crystals, optical beams, soap films, super fluids and the origins of the early universe. In molecular terms knots are found in DNA and proteins, and form spontaneously in any polymer of sufficient length and flexibility. Over the last decade the Leigh group have led advances in the field of ‘molecular nanotopology’ (the topological counterpart to ‘molecular nanotechnology’; see Stoddart, J. F. *Dawning of the age of molecular nanotopology*. *Nano Lett.* **20**, 5597 (2020)). The Leigh group have developed both general and specific methods for the synthesis of increasingly complex molecular knots and links, and demonstrated unique characteristics and effects that topology can impart. In 2012 the Leigh group reported the first higher order knot (five crossings) using a circular helicate strategy to generate the necessary number of crossings and the correct connectivity [*Nat. Chem.* **4**, 15 (2012), Fig. 7]. Circular double and triple helicates have subsequently been used to make 3- [*J. Am. Chem. Soc.* **136**, 13142 (2014); *J. Am. Chem. Soc.* **140**, 4982

Science fiction becomes fact: a machine that assembles molecules  
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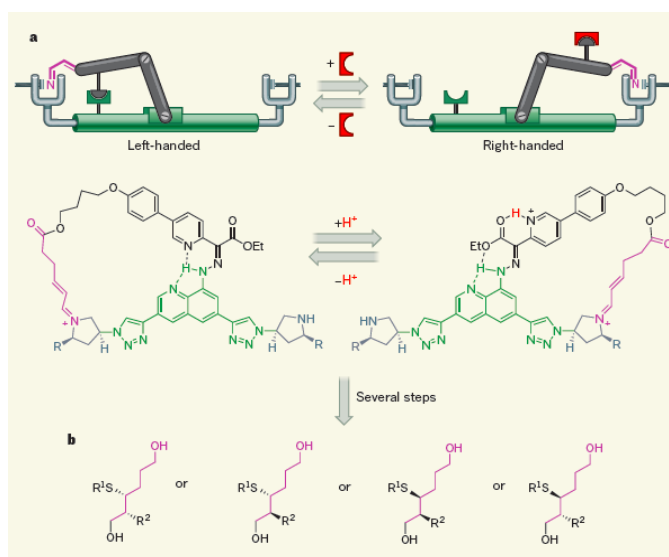


Fig. 6. Molecular robotics (2017).

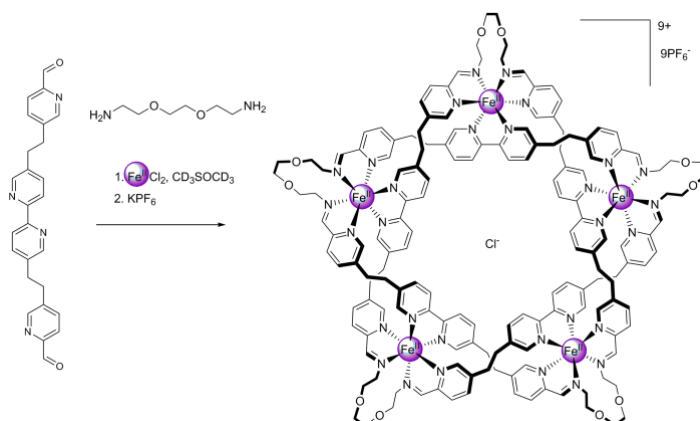


Fig. 7. Molecular pentafoil knot (2012).

(2018)], 5- [*Science* **352**, 1555 (2016)], 8- [*Science* **355**, 159 (2017), Fig. 8] and 9- [*Nat. Chem.* **10**, 1083 (2018)] crossing knots, and links with up to 9 crossings, sometimes with intrinsic writhe [*Angew. Chem. Int. Ed.* **57**, 13833 (2018)], including a Star of David [2]catenane, a triply-interlocked link [*Nat. Chem.* **6**, 978 (2014)].

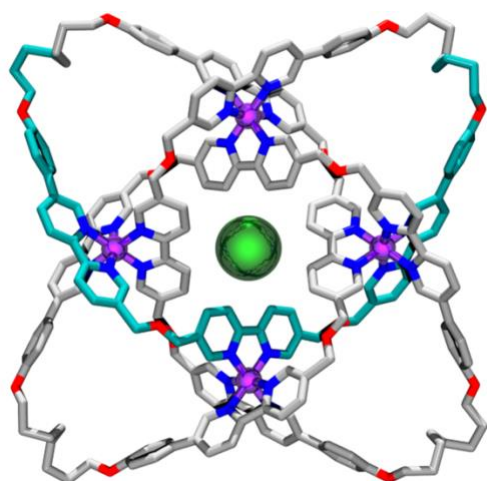


Fig. 8. Triple-braided molecular  $8_{19}$  knot (2017).

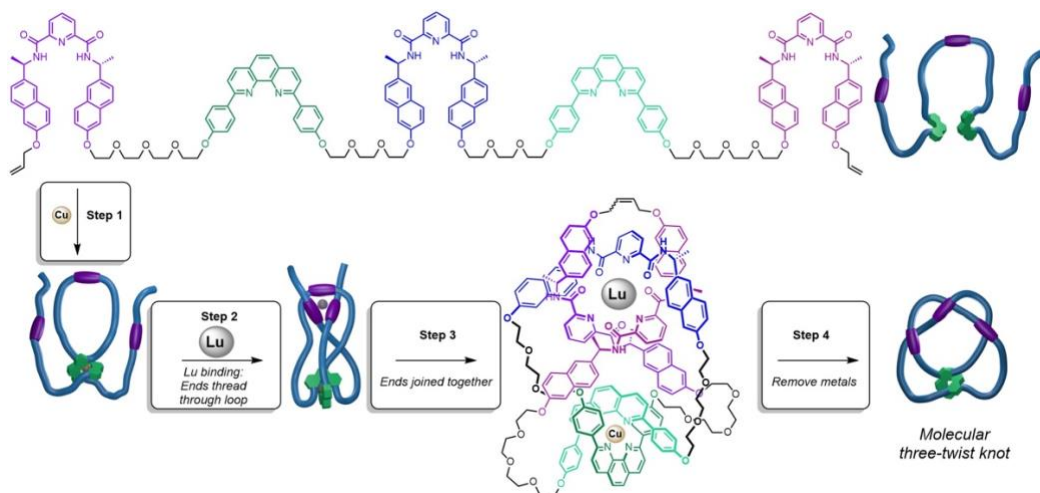


Fig. 9. Knot synthesis by folding and entangling a molecular strand with metal ion ‘chaperones’ [2020].

Biology uses chaperones to direct the folding of peptide chains into precise 3D protein structures. The Leigh group have introduced a similar concept for folding and entangling single synthetic molecular strands into different knots by interspersing different metal ion binding sites along the thread [Nature 584, 562 (2020), Fig. 9]. The resulting strand can be programmed to fold into different knot topologies according to the sequence of different metal ions it is exposed to.

In 1992, less than a decade after the first template synthesis of a catenane, Daryle H. Busch (the ‘Father’ of template synthesis) suggested that “*The ultimate aspiration of chemists working on interlocked structures might be to weave molecules as if they were macroscopic threads*” [D. H. Busch. *Structural definition of chemical templates and the prediction of new and unusual materials*. J. Inclusion Phenom. Mol. Recognit. Chem. 12, 389 (1992)].

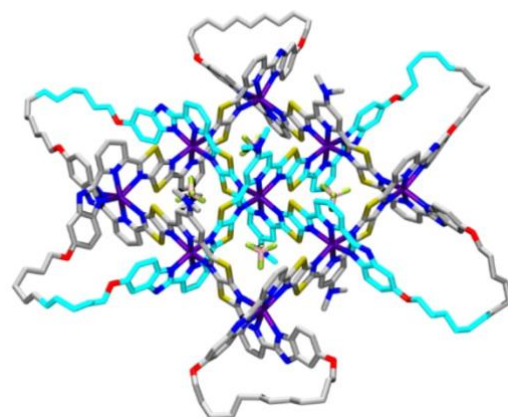


Fig. 10. Molecular endless (7<sub>4</sub>) knot (2020).

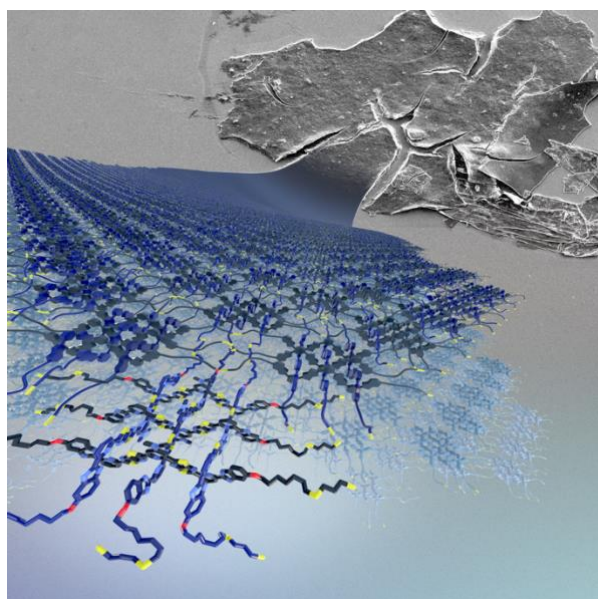


Fig. 11. Layered 2D-molecularly-woven fabric (2020).

In 2020 the Leigh group reported the first weaving of ligands to form an interwoven 3x3 grid. This was used to synthesize both a molecular endless (7<sub>4</sub>) knot [Nat. Chem. 13, 117-122 (2021), Fig. 10] and to weave polymer chains in two-dimensions [Nature 588, 429 (2020), Fig. 11]. The layered two-dimensional molecularly woven material has long-range order, is twice as stiff as the constituent linear polymer, and delaminates and tears along well-defined lines in the manner of a macroscopic textile. When incorporated into a polymer-supported membrane it acts as a net, slowing the passage of large ions while letting smaller ions through.

The ability to weave molecular chains in two-dimensions—forming molecularly woven fabrics—brings Busch’s ‘ultimate aspiration’ for interlocked structures within reach. In doing so it opens up new possibilities and research directions at the intersection of three major fields: polymer science, two-dimensional materials, and molecular nanotopology.