Chem

CellPress

Preview

Knots by design: Turning a polymer entanglement into a topological synthon

Patrick S. Doyle[1,*]
[1]Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA, USA
*Correspondence: pdoyle@mit.edu
https://doi.org/10.1016/j.chempr.2026.103214

Knots form spontaneously in long polymers, yet their *de novo* synthesis with precise control over topology, backbone, and dispersity has remained elusive. In *Nature Chemistry*, Du et al. introduce a metal-templated knot as a versatile topological synthon that generates trefoil knots with controlled molecular weights and defined chemistries. Chemically matched sets of topoisomers enable systematic study of topology-property relationships.

Every sufficiently long, flexible strand— a fishing line, a human hair, a DNA molecule, or a chain in a polymer melt—will eventually knot itself. This is not bad luck but statistical mechanics: the probability that a chain is knotted approaches unity exponentially as its length increases.[1] When the ends of the chain are joined, the knot becomes topologically permanent and a mathematical nomenclature has been developed to classify and tabulate them.[2] Knots are therefore woven into the physics of essentially every macromolecule, where they modulate chirality, size, diffusion, rheology, and mechanical strength. Polymer knots have long fascinated physicists and chemists, but preparing macromolecules with a prescribed knot type, controlled chain length, narrow dispersity, and tunable chemical composition remains a formidable synthetic challenge.

DNA provided one of the earliest experimentally tractable polymers for generating and quantifying knots. In classical ring-closure experiments, linear DNA bearing complementary single-stranded ends were allowed to equilibrate before its ends associated to form a ring.[3] A DNA molecule that happened to be self-entangled at the moment of closure became knotted, with trefoils dominating the resulting distribution. This approach enabled quantitative studies of knotting probability and DNA excluded volume, but the topology of any individual product was determined statistically rather than prescribed. External electric fields subsequently provided a way to generate knots in single linear DNA molecules without ring closure, and single-molecule experiments have shown that knots are dynamic entities that can diffuse, convect, and jam on a polymer backbone.[4] These experiments made it possible to generate and manipulate polymer knots; however, the knot types remained stochastic, and chemistry of the polymer was fixed to DNA.

Chemists have pursued a complementary goal: encoding topology directly through synthesis. A foundational advance was Dietrich-Buchecker and Sauvage's 1989 molecular trefoil knot[5] in which metal coordination organized molecular strands into the required crossings before covalent closure—proof that topology could be chemically programmed, albeit in a short, structurally defined backbone unlike the long, fluctuating chains studied by polymer physicists. To date, metal-template synthesis remains among the most successful routes to synthesize molecular knots, as it embeds the requisite crossing information within open-tangles.[6] The work of Du et al.[7] generalizes this approach with an elegant idea: repurposing a molecular knot as a topological synthon (Figure 1A). Building on Hunter's prior idea of a kinetically locked overhand-knot motif,[8] Du et al. recognized that such a metal-templated tangle could serve as a *general* topological synthon. An iron(II)-coordinated overhand knot kinetically fixes the strand crossings needed for a trefoil, and two telechelic polystyrene (PS) chains are attached to the synthon through click chemistry, after which double strain-promoted azide-alkyne cycloaddition closes the polymer, locking in the topology. The second cycloaddition is approximately 180-fold faster than the first, strongly favoring intramolecular closure and giving the metallated trefoil polymer in 98% yield. Demetallation then releases the knotted polymer without changing its topology.

The power of the approach lies in its precision and modularity. The synthon predetermines the resulting knot topology. The yield of the product is high, avoiding lengthy purification steps or confounding results from a mixture of linear and knotted polymers. The same synthon can be appended with chains of the same chemistry and varying molecular weights to produce chemically identical knots with varying chain contours. The synthesized products have narrow dispersities, making it possible to study how knot geometry changes with chain length without broad molecular weight distributions obscuring the comparison. Alternatively, the synthon can be appended with chemically distinct chains —demonstrated here for PS, poly(ethylene glycol) (PEG), and a PS-PEG block copolymer. This separation between topological programming and polymer composition is one of the important conceptual advances of this article. Importantly, the method allows for the synthesis of matched controls, which is critical for isolating the role of topology in material properties. From the same building blocks, the authors assemble three topoisomers of identical chemical composition: a linear chain, an unknotted macrocycle, and a trefoil-knotted ring—the simplest nontrivial knot. This is the experimental holy grail for

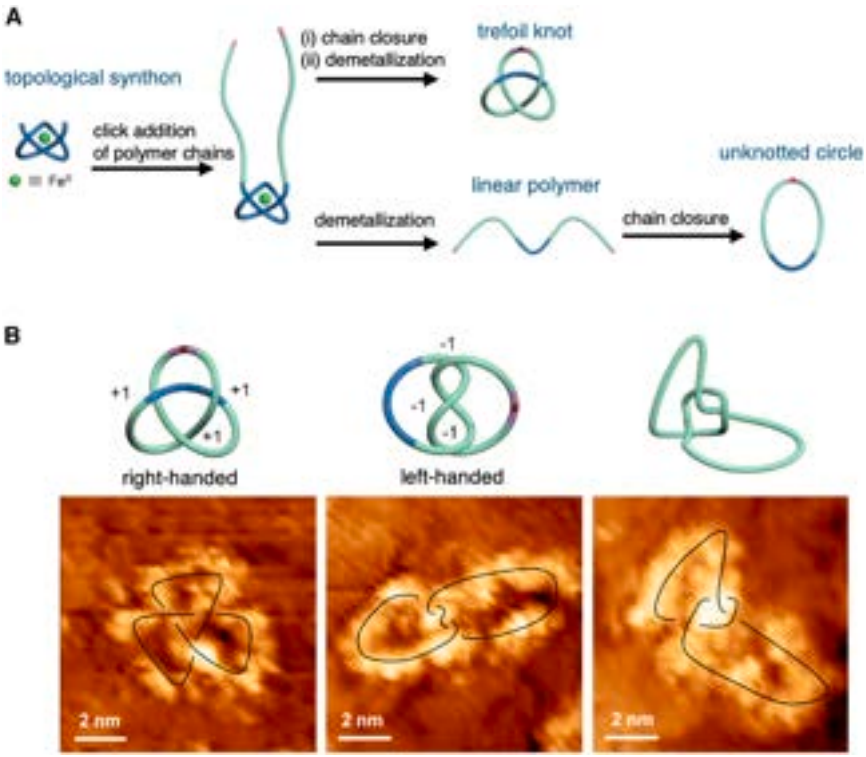

Figure 1. Chemical synthesis of defined polymer topoisomers and STM imaging of knots
(A) Chemical synthesis of precise polymer topologies starting with a metal-stabilized open trefoil-knot synthon.
(B) Single-molecule STM images showing three types of polystyrene conformers: high-, medium-, and low-symmetry trefoil knots (left to right). Reproduced with permission from Du et al.[7]

topology-property studies because it lets one isolate the role of topology.

The matched topological isomers reveal substantial effects of knotting. Trefoil PS has a smaller apparent hydrodynamic radius and lower intrinsic viscosity than the corresponding linear and unknotted cyclic polymers. The intrinsic-viscosity ratio of knotted to linear PS is approximately 0.48, compared with approximately 0.66 for cyclic relative to linear chains. The progression from linear to cyclic to trefoil topology therefore produces increasingly compact hydrodynamic behavior. Topology also alters segmental dynamics. For one matched PS series, the glass-transition temperature increases from approximately 93.0°C for the linear polymer to 99.3°C for the unknotted ring and 101.5°C for the trefoil. A shorter, tighter trefoil exhibits an even higher glass-transition temperature, consistent with increased conformational restriction and reduced free volume. Thermal decomposition, by contrast, is largely unaffected, as expected for a process dominated by chemical bond breaking rather than large-scale chain conformation. Similar trends occur for other backbones. Trefoil PEG and trefoil PS-PEG have smaller hydrodynamic radii and lower intrinsic viscosities than their linear counterparts. Trefoil formation raises the glass-transition temperature of PEG from −36.15°C to 2.18°C and that of PS-PEG from 31.02°C to 61.92°C. These large shifts illustrate how topology can serve as a materials-design variable without changing the polymer repeat units. The extension to PEG and to a PS-PEG diblock is more than a demonstration of scope, as PEG is the workhorse of biomaterials research.

Perhaps the most striking result is visual. Using low-temperature, ultrahigh-vacuum scanning tunneling microscopy (STM), the team images individual knotted PS chains on a silver surface and resolves three distinct trefoil conformers (Figure 1B). A high-symmetry state contains three well-resolved loops with an approximately triangular arrangement of crossings. A medium-symmetry state appears as a two-loop, partly double-helical structure, whereas a low-symmetry state contains strongly unequal loops, with one loop merged into the compact knot region. Their populations depend on polymer length, local stiffness, and deposition solvent. For the longer trefoil deposited from dichloromethane, approximately 33% of the molecules adopt the high-symmetry state. Adding dimethylformamide reduces this fraction to approximately 4%, demonstrating that relatively subtle changes in solvation can strongly reorganize a knot. Rebinding the metal localizes the otherwise diffuse entanglement near the coordination site, providing a chemical means of converting a loose, mobile knot into a tight, positionally defined one. Coarse-grained Langevin simulations then rationalize these populations, showing that the balance of bending energy and conformational entropy—tuned by chain length, backbone stiffness, and solvent quality—dictates which conformer dominates. This feedback between single-molecule imaging and physics-based modeling helps move this field forward.

The knotted synthon of Du et al. is not the first knotted polymer. Its importance lies instead in combining lessons from molecular topology and polymer synthesis into a broadly transferable chemical synthesis platform. A compact molecular structure encodes the crossing sequence, while appended chains independently specify molecular weight, flexibility, solvation, block architecture, and chemical function.

At the single-chain level, the platform offers a rare, well-defined testbed for long-standing predictions about knot size, localization, and metastability that have been explored almost exclusively through simulation studies.[9] At the materials level, the finding that knotting reproducibly lowers viscosity and raises T_g positions topology as an orthogonal design axis, tunable without altering monomer chemistry—of interest for materials processing. Applied to drug delivery, a compact knotted polymer could behave quite differently in physiological flows, be more resistant to *in vivo* degradation pathways and have modified cellular uptake compared to its linear form.

The synthon logic is inherently composable, and future synthons could encode

knots more complex than the trefoil. Joining two trefoil synthons will give composite knots—granny and square knots—whose handedness could be programmed, allowing chirality and its amplification to be studied along a single chain. One can imagine knots placed periodically as designed "topological monomers," or knotted junctions engineered into networks to toughen or reroute stress. Distinct binding sites could potentially tighten, localize, or release different knotted regions in response to chemical stimuli.

Knots have long been the physicist's playground and the chemist's aspiration. By turning a knot into a reagent, Du et al. hand both communities a tool of real generality. Polymer topology is becoming not merely an outcome to observe, but a structural variable that chemists can deliberately program.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Sumners, D.W., and Whittington, S.G. (1988). Knots in self-avoiding walks. J. Phys. Math. Gen. *21*, 1689–1694. https://doi.org/10.1088/0305-4470/21/7/030.
2. Knot Atlas. Main Page. https://katlas.org/wiki/Main_Page.
3. Rybenkov, V.V., Cozzarelli, N.R., and Vologodskii, A.V. (1993). Probability of DNA knotting and the effective diameter of the DNA double helix. Proc. Natl. Acad. Sci. USA *90*, 5307–5311. https://doi.org/10.1073/pnas.90.11.5307.
4. Klotz, A.R., Soh, B.W., and Doyle, P.S. (2018). Motion of knots in DNA stretched by elongational fields. Phys. Rev. Lett. *120*, 188003. https://doi.org/10.1103/PhysRevLett.120.188003.
5. Dietrich-Buchecker, C.O., and Sauvage, J.-P. (1989). A synthetic molecular trefoil knot. Angew. Chem., Int. Ed. Engl. *28*, 189–192. https://doi.org/10.1002/anie.198901891.
6. Ashbridge, Z., Fielden, S.D.P., Leigh, D.A., Pirvu, L., Schaufelberger, F., and Zhang, L. (2022). Knotting matters: orderly molecular entanglements. Chem. Soc. Rev. *51*, 7779–7809. https://doi.org/10.1039/d2cs00323f.
7. Du, C., Chen, Z., Xu, C., Sun, Z., Zhang, Z.H., Liu, X.G., Chen, B., Zhang, C., Li, Z., Rao, Y., et al. (2026). Trefoil polymers from a knotted synthon. Nat. Chem. Published online June 29, 2026. https://doi.org/10.1038/s41557-026-02197-4.
8. Guo, J., Mayers, P.C., Breault, G.A., and Hunter, C.A. (2010). Synthesis of a molecular trefoil knot by folding and closing on an octahedral coordination template. Nat. Chem. *2*, 218–222. https://doi.org/10.1038/nchem.544.
9. Grosberg, A.Y., and Rabin, Y. (2007). Metastable tight knots in a wormlike polymer. Phys. Rev. Lett. *99*, 217801. https://doi.org/10.1103/PhysRevLett.99.217801.