

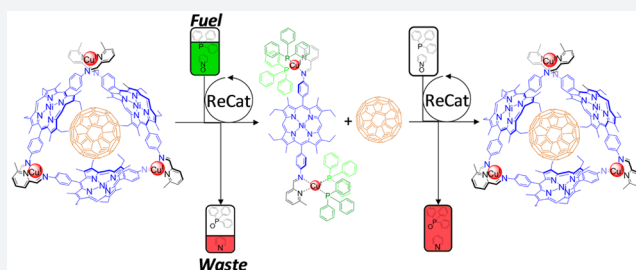
Fuel-Controlled Reassembly of Metal–Organic Architectures

Christopher S. Wood, Colm Browne, Daniel M. Wood, and Jonathan R. Nitschke*

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, U.K.

S Supporting Information

ABSTRACT: Many examples exist of biological self-assembled structures that restructure in response to external stimuli, then return to their previous state over a defined time scale, but most synthetic investigations so far have focused on systems that switch between states representing energetic minima upon stimulus application. Here we report an approach in which triphenylphosphine is used as a chemical fuel to maintain Cu^I-based self-assembled metallocsupramolecular architectures for defined periods of time. This method was used to exert control over the threading and dethreading of the ring of a pseudorotaxane's axle, as well as to direct the uptake and release of a guest from a metal–organic host. Management of the amount of fuel and catalyst added allowed for time-dependent regulation of product concentration.



Self-assembly allows for the construction of functional chemical systems with applications as diverse as catalysis,¹ gas storage,² molecular machinery,³ and ion transport,⁴ as well as being integral to the function of biological molecules such as proteins⁵ and DNA.⁶ Self-assembled complexes have been developed that can respond to stimuli such as light,⁷ pH,⁸ anions,⁹ and electrical potential.¹⁰ Strict self-assembly processes lead to the formation of products that are stable at equilibrium, whereby carefully designed building blocks come together to yield an energy-minimized structure.¹¹ In contrast, biological systems achieve greater complexity of structure and function by utilizing self-assembly in conjunction with the controlled reaction or “burning” of a reactive species or “fuel”, such as ATP, to maintain a system out of equilibrium.¹² The development of artificial chemical systems that can utilize a chemical fuel in such a way is an attractive goal because it would provide a platform for the development of new applications by providing temporal control: a sensor could be programmed to report on its analyte only when fuel was present and being consumed, or a receptor designed to bind or release a chemical signal only for the duration of fuel-burning. To date, few examples of such systems have been reported, with interest focused upon the macro- and mesoscopic scales and upon the use of biological building blocks.¹³

Here we build upon others' recent successes¹⁴ in demonstrating functional out-of-equilibrium systems by establishing a method that allows metal-templated supramolecular structures to reversibly rearrange during a time period when an added phosphine ligand “fuel” is undergoing catalytic “burning”. These structures can be designed to express different functions, such as rotaxane formation or guest binding, establishing our method as a platform for new applications based upon chronological control over metal-templated assembly.

Metal-templated self-assembly has proven to be a versatile method for the design of intricate supramolecular structures.¹⁵ Copper(I) has seen wide use as a template¹⁶ and was found to be suitable for the formation of complexes using subcomponent self-assembly, in which coordinative (N→Cu) and dynamic-covalent (C=N) linkages are constructed together.¹⁷ The labile nature of copper(I) metal centers allows for facile ligand exchange, which is a desirable feature for the design of a fuel-controlled self-assembling system.

Pseudorotaxanes, together with other interlocked architectures, have been shown to have applications in areas as diverse as guest binding,¹⁸ catalysis,¹⁹ and artificial muscles.²⁰ Thus, a Cu^I-based pseudorotaxane, developed from principles established by the Leigh group,²¹ was developed as a model system with which to investigate fuel-controlled self-assembly.

The combination of macrocycle **1**²² with *p*-anisidine, 2-formylpyridine, and Cu^I led to the quantitative formation of pseudorotaxane **2** (Figure 1a). Full characterization data for **2** and all other new compounds are presented in the Supporting Information. Cu^I is known to form [CuN₂P₂]⁺ heteroleptic complexes preferentially when both nitrogen and phosphine ligands are present, as opposed to forming the corresponding homoleptic [CuN₄]⁺ and [CuP₄]⁺ complexes.²³ The addition of triphenylphosphine (PPh₃) to pseudorotaxane **2** resulted in the selective displacement of bipyridine **1** to generate the heteroleptic phosphine complex **3** (Figure 1a).

The oxidation of phosphines is thermodynamically favorable,²⁴ and we hypothesized that if conditions could be developed that led to the oxidation of PPh₃ to triphenylphosphine oxide (OPPh₃), while leaving the components of **2** intact, PPh₃ could be used as a chemical fuel to control the conversion between **2** and **3**. The addition of excess of PPh₃ would bring

Received: August 12, 2015

Published: December 3, 2015

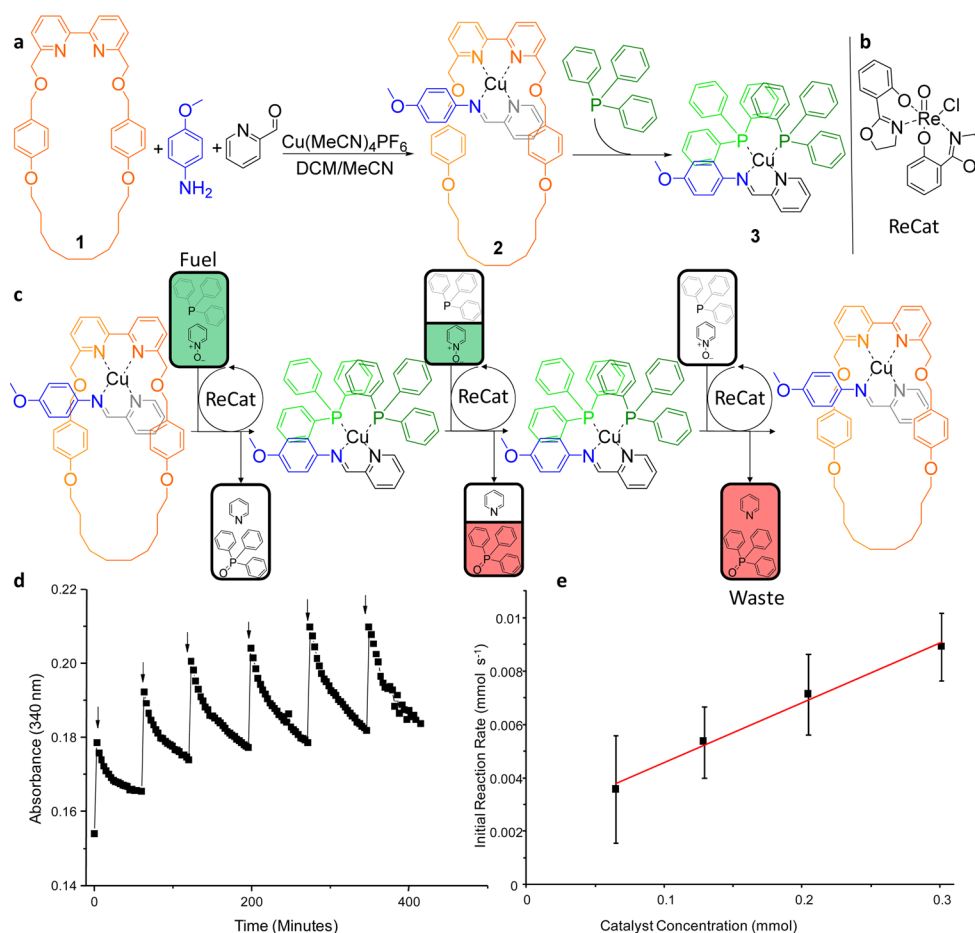


Figure 1. Preparation of a pseudorotaxane, and its time-dependent disassembly and reassembly. (a) Synthetic scheme for the formation of 2 from *p*-anisidine, 2-formylpyridine, and macrocycle 1, and its subsequent conversion to 3 via addition of PPh_3 . (b) Structure of oxo-transfer catalyst (ReCat) used to oxidize PPh_3 . (c) Addition of PPh_3 to 2 led to the formation of 3. Upon complete oxidation of PPh_3 , pseudorotaxane 2 reforms. (d) Reaction progress over time, monitored by UV-vis spectroscopy. Each arrow indicates a point at which 2 equiv of PPh_3 per Cu^{I} were added. (e) Plot showing the linear increase in initial rate with increasing concentration of ReCat; points represent the averages of three runs, with error bars providing ESDs between runs.

about the conversion of 2 into 3, the PPh_3 would then be oxidized over a set time and, as OPPh_3 is a poor ligand for copper(I), the oxidation of all PPh_3 would lead to the destruction of 3, and the reformation of 2 as the system re-equilibrates. The established redox chemistry of aryl phosphines would therefore enable temporal control to be exerted over a metal-organic system via the maintenance of a transient species, moving synthetic supramolecular chemistry closer toward the complexity that has evolved in the biological sphere.

PPh_3 is known to be slow to react with dioxygen, and to gain in oxidative stability once bound to a metal center.²⁴ Unsurprisingly, 3 was found to be air-stable; no reaction was observed between 3 and pyridine *N*-oxide in solution or the solid state over a period of several weeks. An oxo-transfer catalyst was therefore added to the reaction mixture in order to facilitate the oxidation of PPh_3 . The catalyst chosen for this purpose was ReCat (Figure 1b), which has been shown by Abu-Omar and co-workers to efficiently transfer oxygen from pyridine *N*-oxides to PPh_3 .²⁵ ReCat has several benefits, including rapid oxidation of PPh_3 under ambient conditions (the reaction has a second order rate constant $>10^6 \text{ L mol}^{-1} \text{ s}^{-1}$ at 293 K),²⁵ activity in a variety of solvents, and varying

reaction rates depending on the pyridine *N*-oxide derivative used as the terminal oxidant.

To investigate the fuel-controlled conversion between 2 and 3, 2 (1 μmol) was dissolved in 1:1 acetonitrile/dichloromethane (0.5 mL). Upon addition of ReCat (5 mol %) and pyridine *N*-oxide (20 equiv) to this solution, there was no observable color change. NMR, MS, and UV-vis spectroscopy confirmed that 2 remained stable under these conditions. Upon addition of PPh_3 (2 μmol) there was a rapid color change from opaque brown to clear yellow, characteristic of the formation of 3, which was confirmed by ^1H NMR, mass spectrometry, and UV-vis spectroscopy. A single broad resonance corresponding to PPh_3 was observed in the ^{31}P NMR spectrum. The solution regained the dark brown color associated with 2 (Movie 1, Supporting Information) over the course of 30 s; ^1H NMR analysis confirmed that this color change corresponded to the regeneration of 2 (Supporting Information, Figure S13). Further addition of PPh_3 (2 μmol) caused the ^1H NMR signals of 2 to disappear and those of 3 to reappear. NMR spectra also reflected the consumption of pyridine *N*-oxide and the production of pyridine and OPPh_3 . The signals for 2 progressively reappeared and those of 3 disappeared over time. UV-vis spectroscopy also provided insight into processes occurring in the reaction mixture: an increase in absorption at

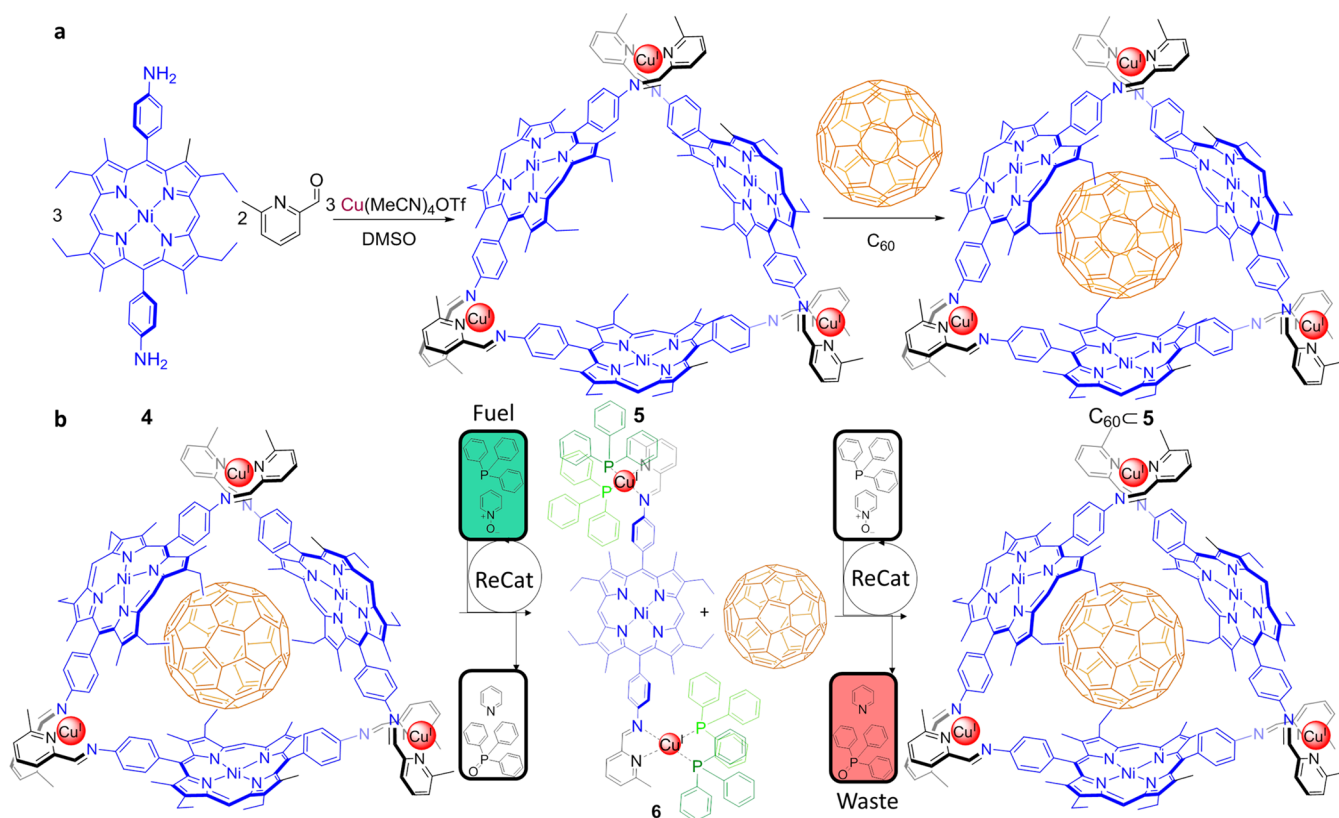


Figure 2. Uptake and release of C₆₀ from 5. (a) Scheme depicting assembly of Cu₃L₃ triangle 5 upon mixing 4, 2-formylpyridine and Cu(MeCN)₄OTf in DMSO, and its binding of C₆₀. (b) Control of the disassembly of homoleptic 5 to heteroleptic 6, and its reassembly, with concomitant release and uptake of a C₆₀ guest in a 1:1 mixture of CD₃CN/DCM.

340 nm was observed following the addition of PPh₃ (2 equiv) to a solution of 2, assigned to the MLCT band of 3. The intensity of this absorption decayed over time as PPh₃ was consumed by the oxidation reaction and 2 was reformed (Figure 1d). It was possible to perform six fuel additions to the solution before the process became difficult to follow due to the increasing concentration of OPPh₃, the intensity of the signals of which obscured the other signals in both UV-vis and NMR spectra.

The rate of fuel burning could be controlled by the amount of catalyst added, with a linear relationship observed between the initial rate of the decay of 3 and catalyst concentration observed using UV-vis spectroscopy (Figure 1e). The system shown in Figure 1 thus establishes the ability to control self-assembly of 2 using a chemical fuel, although no function is achieved beyond the threading and dethreading of a pseudorotaxane.

Chemical fuels are utilized in natural systems to achieve functional ends, such as for controlling the uptake and reactivity of guests. An example of this is the ATP-regulated folding of guest proteins within chaperonins such as GroEL, where the binding of ATP within the chaperone's cavity changes its structure and blocks the binding of substrates, ejecting them postfolding.²⁶ The hydrolysis of the ATP to ADP then allows for the chaperone to regain its shape and facilitate further folding events.²⁶ We envisaged that the dynamic system described above would allow us to build upon the well-developed foundations of static host-guest systems, to enable a guest to be released when fuel was present and rebound once the fuel was consumed; i.e., PPh₃ would have a role analogous to ATP in the example described above. The new triangular

Cu₃L₃ macrocycle 5 was thus prepared as a dynamic, self-assembling host for the fullerene C₆₀. Macrocycle 5 formed when nickel(II)-porphyrin-containing diamine 4, 2-formylpyridine, and Cu^I were mixed in a 1:2:1 ratio (Figure 2a).

The binding of C₆₀ by 5 was followed by NMR spectroscopy. Binding was observed both through shifts in the ¹H signals of the porphyrin subunits of 5 upon addition of C₆₀ and the appearance of a signal for the fullerene in the ¹³C NMR spectrum, similar to that seen for comparable host-guest systems (Supporting Information, Figures S17–18).²⁷ Binding was further confirmed by mass spectrometry experiments (Supporting Information, Figures S22–23). As the electronic absorption spectrum of 5 is dominated by the intense Soret bands of the porphyrin moieties at higher concentrations and the complex dissociates at higher dilutions, UV-vis absorption spectra (Supporting Information, Figure S14) did not allow for the characterization of 5 or for the quantification of its C₆₀ affinity.

PPh₃ thus served again as the system's chemical fuel, disrupting the formation of 5 when present, and controlling the uptake and release of C₆₀ (Figure 2b). Upon addition of PPh₃ to a solution of 5, the brown color of the host-guest complex was observed to disappear, and the solution became red. NMR and mass spectra showed that the host-guest complex was no longer present, and new ¹H NMR signals corresponding to heteroleptic dicopper(I) complex 6 were observed. As was observed in the case of the pseudorotaxane system shown in Figure 1, the presence of ReCat and pyridine N-oxide led the PPh₃ fuel to be burned, in turn allowing the reformation of 5, which subsequently bound C₆₀ once more. This process could

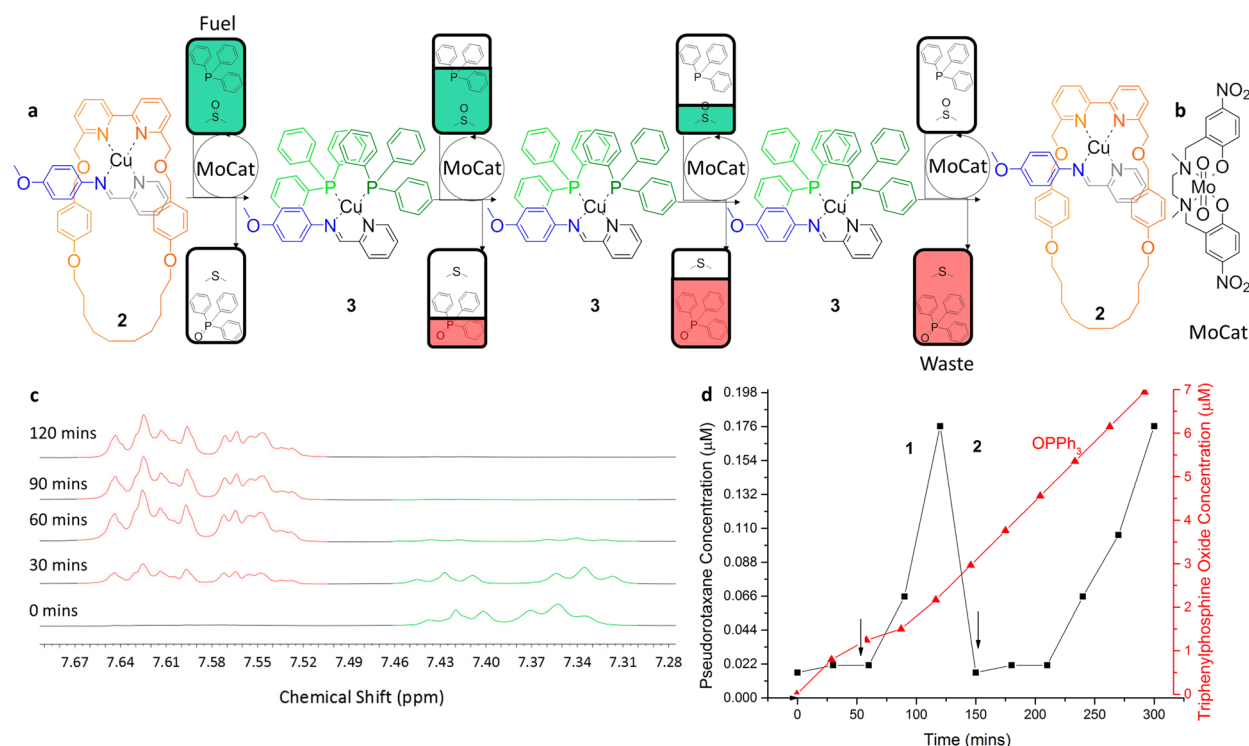


Figure 3. Controlled conversion of **2** to **3** using MoCat. (a) Dethreading of macrocycle **1** from pseudorotaxane **2** upon addition of PPh₃ and subsequent formation of OPPh₃ using MoCat in DMSO. The excess of PPh₃ must be consumed by the oxidation reaction before reformation of **2** can occur. (b) Structure of MoCat. (c) Partial ¹H NMR spectra showing the decrease in concentration of PPh₃ (green) over time and the increase in concentration of OPPh₃ (red) upon heating **3** at 363 K with MoCat (40 mol %) in DMSO. (d) Plot of the concentrations of **2** (black) and OPPh₃ (red) over time. Arrows indicate the points at which PPh₃ (8 equiv) was added. The concentration of **2** remained constant at zero until the excess PPh₃ had been consumed, at which point it began to increase.

also be repeated for multiple fuel addition cycles (Supporting Information, Figure S15).

The system of Figure 2 thus establishes a causal link between fuel consumption, reassembly, and the function of guest binding. Fuel is consumed in steady fashion until a threshold concentration is reached at which point a chemical event then occurs—herein, the disassembly of a pseudorotaxane (Figure 1) or a triangular receptor (Figure 2). In biological systems, the triggered event may be used as a “reset” signal, to introduce more fuel and restart the cycle. This delay/triggered-reset behavior underpins the functioning of the biological clocks that govern such diverse phenomena as the cell cycle and circadian rhythms.²⁸

The generation of a time delay is a useful property, which cannot be provided in a simple static self-assembling system. For example, addition of sufficient acid to protonate macrocycle **1** would lead to the disassembly of **2**, which could be reversed by addition of a suitable base, with both steps requiring a manual signal input (i.e. the system acts as a binary switch). Our dynamic system for controlling the dethreading of **2** allows for the programming of the lifetime of the out-of-equilibrium state.

For a programmed time delay to be of use, the rate of fuel consumption must be matched to the desired delay time scale. In the case of ReCat-mediated phosphine oxidation, however, the oxidation of free PPh₃ in solution occurs rapidly ($t_{1/2} = 30$ s under the conditions of Figure S1),²⁵ while oxidation was observed to slow upon metal coordination. We therefore sought an alternative oxo-transfer catalyst.

The alternate catalyst chosen for this purpose was MoCat (Figure 3b), a molybdenum-containing catalyst with a tetradentate salan ligand developed by White and co-workers.²⁹ This catalyst was chosen because (i) the rate of oxidation is influenced by the Hammett parameters of the substituents on the catalyst ligand, providing tunability; (ii) the catalyst uses DMSO as the source of oxygen to transfer to PPh₃, simplifying the reaction conditions by allowing DMSO to be used as the reaction solvent and eliminating the need to add pyridine *N*-oxide; and (iii) most importantly for our purposes, the rate of oxidation with MoCat, with a first-order rate constant of $7.13 \times 10^{-2} \text{ L mol}^{-1} \text{ s}^{-1}$ at 403 K,²⁹ is much slower than that of ReCat (first-order rate constant $>10^6 \text{ L mol}^{-1} \text{ s}^{-1}$ at 293 K).²⁵

To test the compatibility of MoCat with the Cu^I complexes of this study, MoCat (40 mol %) was added to a solution of **2** in DMSO (1 μM). No changes in the ¹H NMR signals of either compound were observed after 48 h at 363 K, indicating that MoCat and **2** are stable in each others' presence. No reaction was observed between **3** and DMSO over 48 h at 363 K in the absence of catalyst. The addition of PPh₃ (2 equiv per Cu^I) to the reaction mixture resulted in an immediate color change of the solution from deep brown to light yellow, with ¹H NMR analysis confirming the formation of **3**. The solution remained unchanged when kept at room temperature, but upon heating to 363 K the color was seen to change to the dark brown of **2** over the course of several hours. NMR and MS experiments confirmed the reformation of **2** and the formation of OPPh₃ (Figure 3c). As with ReCat, the conversion could be repeated following multiple additions of fuel to the system, with 12

cycles being possible with no notable decrease in the rate of oxidation of PPh₃ by MoCat.

To investigate the ability of the PPh₃ fuel to control the concentration of **2** over a prolonged period, excess PPh₃ (8 equiv per Cu^I) was added to **2**. The conversion to **3** proceeded cleanly, as before, but the concentration of **2** now remained at a steady state even as the concentration of OPPH₃ grew. As the free PPh₃ in solution was consumed, **3** remained stable, with **2** only being observed once there was no free PPh₃ left in solution (Figure 3d). This system thus incorporates an effective time delay, with the lifetime of **3** within the system depending only upon the amount of fuel present and the rate at which it is consumed.

CONCLUSIONS

The addition and oxidation of PPh₃ has thus been used to regulate the timing of responses within complex metallosupramolecular systems: the threading and dethreading of a pseudorotaxane, and the uptake and release of a fullerene guest from a macrocyclic host. The rates of these processes could be controlled both through the choice and concentration of the oxo-transfer catalyst employed, as well as the amount of phosphine fuel present.

The above methods allow time-dependent control over guest binding and rotaxane formation and has the potential to be coupled to yet more complex responses, such as those exhibited by molecular machines.³⁰ The ability to incorporate time delays into complex molecular systems is of importance in the context of designing intricate responses, as highlighted by examples both in natural systems, such as the delicate orchestration of the myriad individual events of the cell cycle,³¹ and in the artificial information-processing systems that make up digital computers, whose signals must be passed in the correct temporal order.³² Future work will aim to utilize the temporal control demonstrated here in order to develop more complex applications within systems chemistry.³³

METHODS

Fuel-Controlled Dethreading of **2 Using ReCat.** **2** (10 mg, 1 μmol) was dissolved in 1:1 CD₃CN/CD₂Cl₂ (0.5 mL) in a NMR tube. Pyridine *N*-oxide (1.93 mg, 0.2 mmol) and ReCat (5 mol %) were added, and the solution was sonicated for 5 min. Triphenylphosphine (5.31 mg, 2 μmol) was added and the tube was shaken and sonicated to ensure complete mixing. The reaction was kept at 298 K and monitored by NMR until complete oxidation of the PPh₃ had occurred, at which point a further 2 equiv of PPh₃ was added. This process was repeated seven further times, beyond which the reaction became difficult to follow by NMR.

Fuel-Controlled Release of C₆₀ from **5 using ReCat.** C₆₀C₅ (4 mg, 1 μmol) was dissolved in 1:1 CD₃CN/CD₂Cl₂ (0.5 mL) in a NMR tube. Pyridine *N*-oxide (1.93 mg, 0.2 mmol) and ReCat (5 mol %) were added, and the solution was sonicated for 5 min. Triphenylphosphine (5.31 mg, 2 μmol) was added and the tube was shaken and sonicated to ensure complete mixing. The reaction was kept at room temperature and monitored by NMR until complete oxidation of the PPh₃ had occurred, at which point a further 2 equiv of PPh₃ was added. This process was repeated seven further times, beyond which the reaction became difficult to follow by NMR.

Fuel-Controlled Dethreading of **2 Using MoCat.** **2** (10 mg, 10 μmol) was dissolved in DMSO-*d*₆ (0.5 mL) in a NMR

tube. MoCat (50 mol %) was added and the mixture was sonicated for 10 min. Triphenylphosphine (5.31 mg, 20 μmol) was added. The tube was heated at 363 K and the reaction process was monitored by measuring NMR spectra every 30 min.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscentsci.5b00279.

Synthetic procedures and spectroscopic data for all newly reported compounds; experimental procedures for the fuel-burning systems reported in Figures 1–3 (PDF) Movie 1 (AVI)

AUTHOR INFORMATION

Corresponding Author

*E-mail: jrn34@cam.ac.uk.

Funding

This work was supported by the European Research Council (259352).

Notes

The authors declare no competing financial interest.

REFERENCES

- (1) Pluth, M. D.; Bergman, R. G.; Raymond, K. N. Proton-Mediated Chemistry and Catalysis in a Self-Assembled Supramolecular Host. *Acc. Chem. Res.* **2009**, *42* (10), 1650–1659.
- (2) Ferey, G. Hybrid Porous Solids: Past, Present, Future. *Chem. Soc. Rev.* **2008**, *37* (1), 191–214.
- (3) Lewandowski, B.; De Bo, G.; Ward, J. W.; Pappmeyer, M.; Kuschel, S.; Aldegunde, M. J.; Gramlich, P. M. E.; Heckmann, D.; Goldup, S. M.; D'Souza, D. M.; Fernandes, A. E.; Leigh, D. A. Sequence-Specific Peptide Synthesis by an Artificial Small-Molecule Machine. *Science* **2013**, *339* (6116), 189–193.
- (4) Davis, J. T.; Okunola, O.; Quesada, R. Recent Advances in the Transmembrane Transport of Anions. *Chem. Soc. Rev.* **2010**, *39* (10), 3843–3862.
- (5) Anfinsen, C. B. Principles that Govern the Folding of Protein Chains. *Science* **1973**, *181* (4096), 223–230.
- (6) Watson, J. D.; Crick, F. H. C. Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid. *Nature* **1953**, *171* (4356), 737–738.
- (7) Han, M.; Michel, R.; He, B.; Chen, Y.-S.; Stalke, D.; John, M.; Clever, G. H. Light-Triggered Guest Uptake and Release by a Photochromic Coordination Cage. *Angew. Chem., Int. Ed.* **2013**, *52* (4), 1319–1323.
- (8) Busschaert, N.; Elmes, R. B. P.; Czech, D. D.; Wu, X.; Kirby, I. L.; Peck, E. M.; Hendzel, K. D.; Shaw, S. K.; Chan, B.; Smith, B. D.; Jolliffe, K. A.; Gale, P. A. Thiosquaramides: pH Switchable Anion Transporters. *Chem. Sci.* **2014**, *5* (9), 3617–3626.
- (9) Riddell, I. A.; Smulders, M. M. J.; Clegg, J. K.; Hristova, Y. R.; Breiner, B.; Thoburn, J. D.; Nitschke, J. R. Anion-Induced Reconstitution of a Self-assembling System to Express a Chloride-Binding Co₁₀L₁₅ Pentagonal Prism. *Nat. Chem.* **2012**, *4* (9), 751–756.
- (10) Liu, Y.; Flood, A. H.; Bonvallet, P. A.; Vignon, S. A.; Northrop, B. H.; Tseng, H.-R.; Jeppesen, J. O.; Huang, T. J.; Brough, B.; Baller, M.; Magonov, S.; Solares, S. D.; Goddard, W. A.; Ho, C.-M.; Stoddart, J. F. Linear Artificial Molecular Muscles. *J. Am. Chem. Soc.* **2005**, *127* (27), 9745–9759.
- (11) Lindsey, J. S. Self-Assembly in Synthetic Routes to Molecular Devices. Biological Principles and Chemical Perspectives: A Review. *New J. Chem.* **1991**, *15*, 153–180.
- (12) (a) Mitchison, T.; Kirschner, M. Dynamic Instability of Microtubule Growth. *Nature* **1984**, *312* (5991), 237–242. (b) Flaherty,

- K. M.; DeLuca-Flaherty, C.; McKay, D. B. Three-Dimensional Structure of the ATPase Fragment of a 70K Heat-Shock Cognate Protein. *Nature* **1990**, *346* (6285), 623–628. (c) Vale, R. D. The Molecular Motor Toolbox for Intracellular Transport. *Cell* **2003**, *112* (4), 467–480.
- (13) (a) Hermans, T. M.; Frauenrath, H.; Stellacci, F. Droplets Out of Equilibrium. *Science* **2013**, *341* (6143), 243–244. (b) Grzybowski, B. A.; Stone, H. A.; Whitesides, G. M. Dynamic Self-Assembly of Magnetized, Millimetre-Sized Objects Rotating at a Liquid-Air Interface. *Nature* **2000**, *405* (6790), 1033–1036. (c) Fialkowski, M.; Bishop, K. J. M.; Klajn, R.; Smoukov, S. K.; Campbell, C. J.; Grzybowski, B. A. Principles and Implementations of Dissipative (Dynamic) Self-Assembly. *J. Phys. Chem. B* **2006**, *110* (6), 2482–2496. (d) Weitz, M.; Kim, J.; Kapsner, K.; Winfree, E.; Franco, E.; Simmel, F. C. Diversity in the Dynamical Behaviour of a Compartmentalized Programmable Biochemical Oscillator. *Nat. Chem.* **2014**, *6* (4), 295–302.
- (14) (a) Boekhoven, J.; Brizard, A. M.; Kowgi, K. N. K.; Koper, G. J. M.; Eelkema, R.; van Esch, J. H. Dissipative Self-Assembly of a Molecular Gelator by Using a Chemical Fuel. *Angew. Chem., Int. Ed.* **2010**, *49* (28), 4825–4828. (b) Debnath, S.; Roy, S.; Ulijn, R. V. Peptide Nanofibers with Dynamic Instability through Nonequilibrium Biocatalytic Assembly. *J. Am. Chem. Soc.* **2013**, *135* (45), 16789–16792. (c) Dambeniaks, A. K.; Vu, P. H. Q.; Fyles, T. M. Dissipative Assembly of a Membrane Transport System. *Chem. Sci.* **2014**, *5* (9), 3396–3403. (d) Semenov, S. N.; Wong, A. S. Y.; van der Made, R. M.; Postma, S. G. J.; Groen, J.; van Roekel, H. W. H.; de Greef, T. F. A.; Huck, W. T. S. Rational Design of Functional and Tunable Oscillating Enzymatic Networks. *Nat. Chem.* **2015**, *7* (2), 160–165. (e) Ragazzon, G.; Baroncini, M.; Silvi, S.; Venturi, M.; Credi, A. Light-Powered Autonomous and Directional Molecular Motion of a Dissipative Self-assembling System. *Nat. Nanotechnol.* **2014**, *10* (1), 70–75. (f) Cheng, C.; McGonigal, P. R.; Liu, W.-G.; Li, H.; Vermeulen, N. A.; Ke, C.; Frascioni, M.; Stern, C. L.; Goddard III, W. A.; Stoddart, J. F. Energetically Demanding Transport in a Supramolecular Assembly. *J. Am. Chem. Soc.* **2014**, *136* (42), 14702–14705.
- (15) (a) Chakrabarty, R.; Mukherjee, P. S.; Stang, P. J. Supramolecular Coordination: Self-Assembly of Finite Two- and Three-Dimensional Ensembles. *Chem. Rev.* **2011**, *111* (11), 6810–6918. (b) Beves, J. E.; Blight, B. A.; Campbell, C. J.; Leigh, D. A.; McBurney, R. T. Strategies and Tactics for the Metal-Directed Synthesis of Rotaxanes, Knots, Catenanes, and Higher Order Links. *Angew. Chem., Int. Ed.* **2011**, *50* (40), 9260–9327. (c) Cook, T. R.; Stang, P. J. Recent Developments in the Preparation and Chemistry of Metallacycles and Metallacages via Coordination. *Chem. Rev.* **2015**, *115*, 7001–7045.
- (16) Dietrich-Buchecker, C. O.; Sauvage, J.-P. A Synthetic Molecular Trefoil Knot. *Angew. Chem., Int. Ed. Engl.* **1989**, *28* (2), 189–192.
- (17) Nitschke, J. R. Construction, Substitution, and Sorting of Metallo-organic Structures via Subcomponent Self-Assembly. *Acc. Chem. Res.* **2007**, *40* (2), 103–112.
- (18) Lee, S.; Chen, C.-H.; Flood, A. H. A Pentagonal Cyanostar Macrocyclic with Cyanostilbene CH Donors Binds Anions and Forms Dialkylphosphate [3]Rotaxanes. *Nat. Chem.* **2013**, *5* (8), 704–710.
- (19) Berná, J.; Alajarin, M.; Orenes, R.-A. Azodicarboxamides as Template Binding Motifs for the Building of Hydrogen-Bonded Molecular Shuttles. *J. Am. Chem. Soc.* **2010**, *132* (31), 10741–10747.
- (20) Bruns, C. J.; Stoddart, J. F. Rotaxane-Based Molecular Muscles. *Acc. Chem. Res.* **2014**, *47* (7), 2186–2199.
- (21) Campbell, C. J.; Leigh, D. A.; Vitorica-Yrezabal, I. J.; Woltering, S. L. A Simple and Highly Effective Ligand System for the Copper(I)-Mediated Assembly of Rotaxanes. *Angew. Chem., Int. Ed.* **2014**, *53* (50), 13771–13774.
- (22) Berná, J.; Crowley, J. D.; Goldup, S. M.; Hänni, K. D.; Lee, A.-L.; Leigh, D. A. A Catalytic Palladium Active-Metal Template Pathway to [2]Rotaxanes. *Angew. Chem., Int. Ed.* **2007**, *46* (30), 5709–5713.
- (23) (a) Jardine, F. H.; Vohra, A. G.; Young, F. J. Copper(I) Nitrate and Nitrate Complexes. *J. Inorg. Nucl. Chem.* **1971**, *33* (9), 2941–2945. (b) Kaeser, A.; Mohankumar, M.; Mohanraj, J.; Monti, F.; Holler, M.; Cid, J.-J.; Moudam, O.; Nierengarten, I.; Karmazin-Brelot, L.; Duhayon, C.; Delavaux-Nicot, B.; Armaroli, N.; Nierengarten, J.-F. Heteroleptic Copper(I) Complexes Prepared from Phenanthroline and Bis-Phosphine Ligands. *Inorg. Chem.* **2013**, *52* (20), 12140–12151.
- (24) Holm, R. H.; Donahue, J. P. A Thermodynamic Scale for Oxygen Atom Transfer Reactions. *Polyhedron* **1993**, *12* (6), 571–589.
- (25) McPherson, L. D.; Drees, M.; Khan, S. I.; Strassner, T.; Abu-Omar, M. M. Multielectron Atom Transfer Reactions of Perchlorate and Other Substrates Catalyzed by Rhenium Oxazoline and Thiazoline Complexes: Reaction Kinetics, Mechanisms, and Density Functional Theory Calculations. *Inorg. Chem.* **2004**, *43* (13), 4036–4050.
- (26) (a) Saibil, H. Chaperone Machines for Protein Folding, Unfolding and Disaggregation. *Nat. Rev. Mol. Cell Biol.* **2013**, *14* (10), 630–642. (b) Xu, Z.; Horwich, A. L.; Sigler, P. B. The Crystal Structure of the Asymmetric GroEL-GroES-(ADP)₇ Chaperonin Complex. *Nature* **1997**, *388* (6644), 741–750. (c) Wang, J.; Chen, L. Domain Motions in GroEL upon Binding of an Oligopeptide. *J. Mol. Biol.* **2003**, *334* (3), 489–499.
- (27) (a) Kishi, N.; Li, Z.; Yoza, K.; Akita, M.; Yoshizawa, M. An M₂L₄ Molecular Capsule with an Anthracene Shell: Encapsulation of Large Guests up to 1 nm. *J. Am. Chem. Soc.* **2011**, *133* (30), 11438–11441. (b) Wood, D. M.; Meng, W.; Ronson, T. K.; Stefankiewicz, A. R.; Sanders, J. K. M.; Nitschke, J. R. Guest-Induced Transformation of a Porphyrin-Edged Fe^{II}L₆ Capsule into a Cu^IFe^{II}L₄ Fullerene Receptor. *Angew. Chem., Int. Ed.* **2015**, *54* (13), 3988–3992.
- (28) (a) Nigg, E. A. Cyclin-dependent Protein Kinases: Key Regulators of the Eukaryotic Cell Cycle. *BioEssays* **1995**, *17* (6), 471–480. (b) Bloom, J.; Cross, F. R. Multiple Levels of Cyclin Specificity in Cell-cycle Control. *Nat. Rev. Mol. Cell Biol.* **2007**, *8* (2), 149–160. (c) Hut, R. A.; Beersma, D. G. M. Evolution of Time-Keeping Mechanisms: Early Emergence and Adaptation to Photoperiod. *Philos. Trans. R. Soc., B* **2011**, *366* (1574), 2141–2154.
- (29) Whiteoak, C. J.; Britovsek, G. J. P.; Gibson, V. C.; White, A. J. P. Electronic Effects in Oxo Transfer Reactions Catalysed by Salan Molybdenum(VI) cis-dioxo Complexes. *Dalton. Trans.* **2009**, *13*, 2337–2344.
- (30) (a) Ballardini, R.; Balzani, V.; Credi, A.; Gandolfi, M. T.; Venturi, M. Artificial Molecular-Level Machines: Which Energy To Make Them Work? *Acc. Chem. Res.* **2001**, *34* (6), 445–455. (b) Coskun, A.; Banaszak, M.; Astumian, R. D.; Stoddart, J. F.; Grzybowski, B. A. Great Expectations: Can Artificial Molecular Machines Deliver on Their Promise? *Chem. Soc. Rev.* **2012**, *41* (1), 19–30.
- (31) Elledge, S. J. Cell Cycle Checkpoints: Preventing an Identity Crisis. *Science* **1996**, *274* (5293), 1664–1672.
- (32) Patterson, D. A.; Hennessy, J. L. *Computer Organization and Design: The Hardware/Software Interface*, 5th ed.; Morgan Kaufmann: Burlington, MA, 2013.
- (33) (a) Ludlow, R. F.; Otto, S. Systems chemistry. *Chem. Soc. Rev.* **2008**, *37* (1), 101–108. (b) Whitesides, G. M.; Ismagilov, R. F. Complexity in Chemistry. *Science* **1999**, *284* (5411), 89–92.