Endergonic synthesis driven by chemical fuelling

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Abstract

Spontaneous chemical reactions proceed energetically downhill to either a local or global minimum, limiting possible transformations to those that are exergonic. Endergonic reactions do not proceed spontaneously and require an input of energy. Light has been used to drive a number of deracemisations and thermodynamically unfavourable bond-forming reactions, but is restricted to substrates that can absorb, directly or indirectly, energy provided by photons. In contrast, anabolism involves energetically uphill transformations powered by chemical fuels. Here we report on the transduction of energy from an artificial chemical fuel to drive a thermodynamically unfavourable Diels–Alder reaction. Carboxylic acid catalysed carbodiimide-to-urea formation is chemically orthogonal to the reaction of the diene and dienophile, but transiently brings the functional groups into close proximity, causing the otherwise prohibited cycloaddition to proceed in modest (12%) yield and with high levels of regio- (>99%) and stereoselectivity (92:8 *exo*:*endo*). At the chemically fuelled steady state, kinetic asymmetry in the fuelling cycle ratchets the Diels–Alder reaction away from the equilibrium distribution of the Diels–Alder:retro-Diels–Alder products. The driving of the endergonic reaction away from equilibrium occurs through a ratchet mechanism, reminiscent of how molecular machines directionally bias motion. Ratcheting synthesis has the potential to expand the synthetic chemistry toolbox, offering new paradigms in reactivity, complexity and control.

Main

Biological anabolism is the construction of large, often functional-group-rich, molecules from simple and abundant building blocks. These structurally complex products typically have a higher chemical potential than the starting materials,[1] meaning that 'contra-thermodynamic'[2] transformations need to be coupled to exergonic processes to satisfy the conservation of energy.[3–5] Many synthetic schemes in biology involve the energy-demanding reaction being chemically orthogonal to the energy-releasing reaction that drives it.[5–9] This ubiquitous 'chemical fuelling' strategy allows both the synthesis of adenosine triphosphate (ATP) from chemically unrelated redox reactions,[6,7] and the subsequent use of ATP as a universal energy currency to drive numerous transformations[9] in biological metabolism. Energy transduction between two unrelated chemical reactions becomes possible when the endergonic process is a catalyst[3,10] for the exergonic process. In this way a ratchet mechanism[11–20] provides the means of transducing an energy input into the chemical work necessary for endergonic synthesis.[3,4,10,20] In molecular-level machinery, ratchet mechanisms rectify stochastic fluctuations to accomplish directional motion.[10–14] Here we demonstrate that an autonomous chemical reaction that proceeds through thermal activation back-and-forth across transition states[21–23] can also be rectified by a ratchet mechanism to enable a thermodynamically unfavourable reaction outcome (Fig. 1b).[3]

Light energy has been used to power a number of endergonic chemical transformations,[2,24] including deracemisations[25–27] and double bond isomerisations[28–30] (Fig. 1a). However, light-driven endergonic reactions are restricted to substrates that can interact with light, generally through energy transfer or photoredox interactions,[2,24] and the transduction of energy to the driven reaction is invariably inefficient (a typical blue-light deracemisation requires only + 1.7 kJ mol^{-1} of energy[2] yet consumes ~250 kJ mol^{-1} per photon). Even the most exquisite example of light-driven endergonic synthesis, photosynthesis, has an energy efficiency of just 3–6%.[31]

Chemical fuelling[15–20,32] (Fig. 1b) mediates many synthetic processes in biology,[5–9,33,34] can be energy efficient[20] and scalable, and is amenable to many different classes of substrates. However, aside from a small number of deracemisation reactions,[35–37] and a stepwise synthesis of a hydrazone using ATP,[38] artificial autonomous chemically fuelled endergonic synthesis has remained elusive. We sought to explore whether an endergonic example of a classical chemical transformation, the Diels–Alder reaction,[39] could be driven by chemical fuelling. The transduction of chemical energy from carbodiimide hydration through catalysis has recently been used to deracemise atropisomeric 1-(6′-substituted-phenyl)pyrrole 2,2′-dicarboxylic acid derivatives (and directionally drive rotation of the corresponding 6′-unsubstituted molecular motor).[35] Transient tethering of the two carboxylic acids of the biaryl catalyst to form an anhydride enables atropisomer interconversion, with kinetic asymmetry[10,13–20] in the fuelling cycle (generated by the use of a chiral carbodiimide and chiral hydrolysis promoter) driving the endergonic deracemisation.[35] We hypothesised that similar transient tethering could be used to bring a diene and dienophile into close proximity, promoting an otherwise endergonic Diels–Alder reaction by organising the reactants for the cycloaddition and substantially increasing the effective molarity. Transiently organising the reactants in this way also has the potential to exert regio- and/or stereocontrol in the driven reaction.[40]

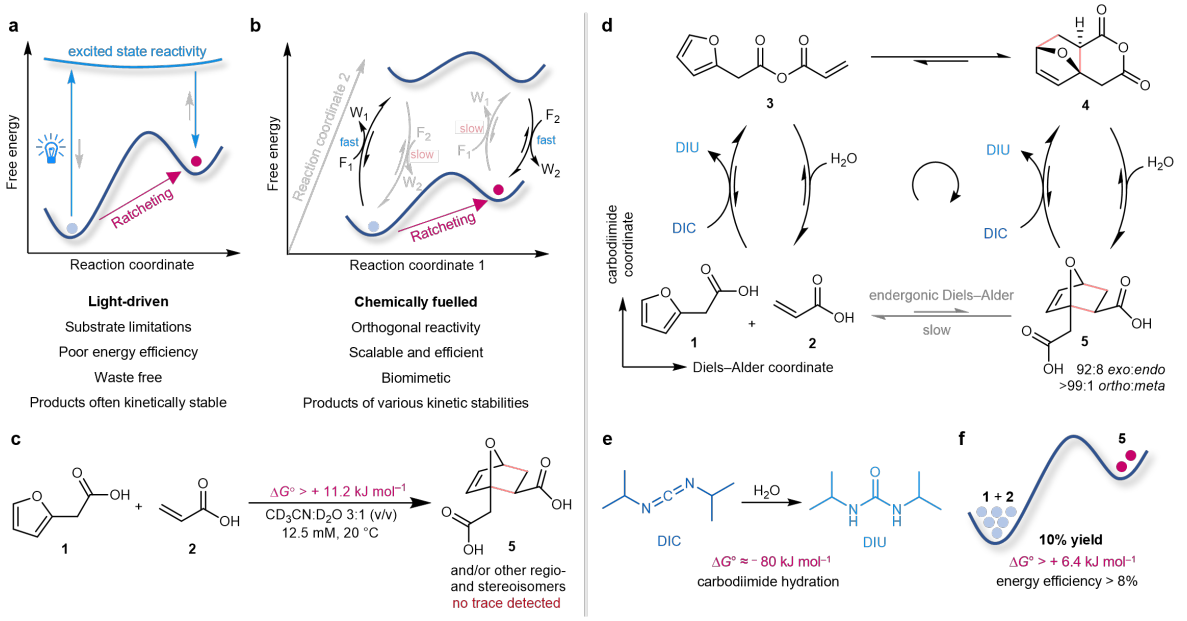

Fig 1 | Endergonic synthesis using a ratchet mechanism. a A typical endergonic chemical transformation, for example a deracemisation or isomerisation reaction, driven by light. Differences in the rates of photon absorption and excited-state relaxation lead to kinetic asymmetry in the reaction cycle, driving the system away from equilibrium. **b** Chemical fuelling of an energetically uphill chemical transformation. An endergonic process in reaction coordinate 1 can be driven by orthogonal chemical fuelling along reaction coordinate 2. In a continuous process, energy transduction is driven by an information ratchet mechanism which relies on kinetic asymmetry in the rates of the fuel-to-waste reactions ($F_1 \rightarrow W_1$ and $F_2 \rightarrow W_2$). **c** An endergonic Diels-Alder reaction between 2-furanacetic acid and

acrylic acid. No Diels–Alder adducts (neither **5** nor other possible regio- and stereoisomers) were detected by ^{1}H NMR or mass spectrometry, indicating an equilibrium constant, K, < 0.01 M^{-1} for **1**+**2**⇌**5**. **d** Driving the endergonic Diels-Alder reaction of **1** and **2** thermodynamically uphill under autonomous chemical fuelling. DIC = diisopropylcarbodiimide, DIU = diisopropyl urea. **e** Fuel-to-waste reaction (hydration of diisopropylcarbodiimide) and the energy released by it.[52] **f** Efficiency of energy transduction from the fuel-to-waste reaction to the ratcheted Diels–Alder reaction.

Results and Discussion

The Diels–Alder reaction is a synthetically important transformation in which six-membered rings are formed with up to four new stereocentres.[39] The cycloaddition can be accelerated and the stereochemical outcome controlled by catalysts,[41] however the yield and regio- and stereoselectivity of the reaction can all be limited by unfavourable thermodynamics.[40,42] Temporary tethering groups have been used to improve the regio- and stereochemical outcome of Diels-Alder reactions, but adding and removing the tether requires an additional two or three synthetic steps.[40] The intermolecular Diels–Alder reaction of furans and acrylates often favours the diene and dienophile, leading to low levels of the Diels–Alder adduct at equilibrium.[43,44] Furthermore, the symmetry of the furan offers little electronic polarisation, leading to poor regioselectivity in reactions that do proceed.[43,44] Carrying out the reaction at elevated temperatures is also problematic due to the propensity of furans to thermally decompose. As such, this class of substrates provides a good testing ground to explore the effects and efficacy of chemical fuelling on a challenging endergonic reaction.

We chose 2-furanacetic acid (**1**) and acrylic acid (**2**) as diene and dienophile respectively (Fig 1c). Each building block contains a carboxylic acid for forming an intermolecular anhydride, and molecular modelling suggested that the length between the diene and dienophile when tethered would not be strained when adopting the tricyclic transition state required for the cycloaddition. (Indeed, in preliminary experiments chemical fuelling of analogous acid pairs with one fewer or one additional carbon atom in the chains did not cause the formation of Diels-Alder adducts.) The transient formation of anhydrides and esters by carbodiimides in the presence of water has been exploited in nonequilibrium and systems chemistry,[45–48] and we have previously proposed[3] that such a fuelling reaction could be suitable for driving coupled reactions out-of-equilibrium.

Mixing **1** and **2** in CD_3CN:D_2O 3:1 (v/v) at 12.5 mM, led to no detectable (by ^{1}H NMR spectroscopy or mass spectrometry) Diels–Alder adduct **5** after 21 days at either 20 °C or 100 °C, indicating a substantial thermodynamic or kinetic barrier to the cycloaddition under the reaction conditions (Fig 1c; Supplementary Information, Section S2). ^{1}H NMR spectroscopy showed that, should the lack of cyclisation be because the reaction is thermodynamically unfavourable, the equilibrium constant (K) is < 0.01 M^{-1} at 20 °C. (Note: This was subsequently confirmed by thermal equilibration of the Diels–Alder adduct **5** to **1** and **2**, starting from a pristine sample of **5** isolated from chemical fuelling, see Supplementary Information, Sections S3 and S4).

Addition of diisopropylcarbodiimide (DIC, 1 equiv.) to the non-reacting mixture of **1** and **2** led to the rapid formation of both symmetrical and mixed (**3**) anhydrides (Fig. 1d, e). Over the course of several hours, the Diels–Alder adduct **4** was observed to form, presumably from intramolecular cycloaddition of the mixed anhydride, **3**; the cycloaddition that did not proceed between the two carboxylic acids (**1** and **2**) under the same conditions of solvent, temperature and concentration. Concomitant hydrolysis of the anhydrides led to Diels–Alder adduct **5** in 10% yield (Fig. 1f). The structure of **5** was confirmed by two-dimensional NMR and high-resolution mass spectrometry (HRMS) (Supplementary Information, Section S3.5). Addition of 2 equivalents of DIC improved the yield of **5** to 12%. Retro-Diels–Alder of the adduct **5** to reform **1** and **2** occurred spontaneously after the consumption of fuel, with a half-life of 16 days at 20 °C, confirming the endergonic nature of the Diels-Alder cycloaddition of **1** and **2** in the

absence of chemical fuelling, and the kinetic stability of the Diels–Alder cycloadduct **5**. Refuelling (1 equiv. DIC) following thermal relaxation reformed **5**, albeit with a reduced yield (7%) due to *N*-acyl urea formation[50] (Fig 2a-d; Supplementary Information, Section S4.3).

Having confirmed that the cycloaddition of **1** and **2** was thermodynamically unfavourable at this concentration (without fuelling), we compared the unfuelled equilibrium constant ($K < 0.01$ M^{-1}) and the reaction quotient (Q) following chemical fuelling (at t = 70 h, $Q = 0.13$ M^{-1}). Like the equilibrium constant K, the reaction quotient Q is also defined as [**5**]/[**1**]×[**2**], but can be computed at any point during the reaction. Quantitative comparison of Q and K (Supplementary Information, Section S5) indicates that the endergonic Diels–Alder reaction is ratcheted thermodynamically uphill by $\Delta G > +6.4$ kJ mol^{-1} (and the upper bound of 0.01 M^{-1} for K is a conservative estimate). As the energy released by the hydration of DIC is ~80 kJ mol^{-1}, >8% of the energy input is transduced into chemical work in the chemically fuelled cycloaddition to form **5**. The amount of work done, and the efficiency of energy transduction, compares favourably to light and chemically fuelled deracemisations.[24,35]

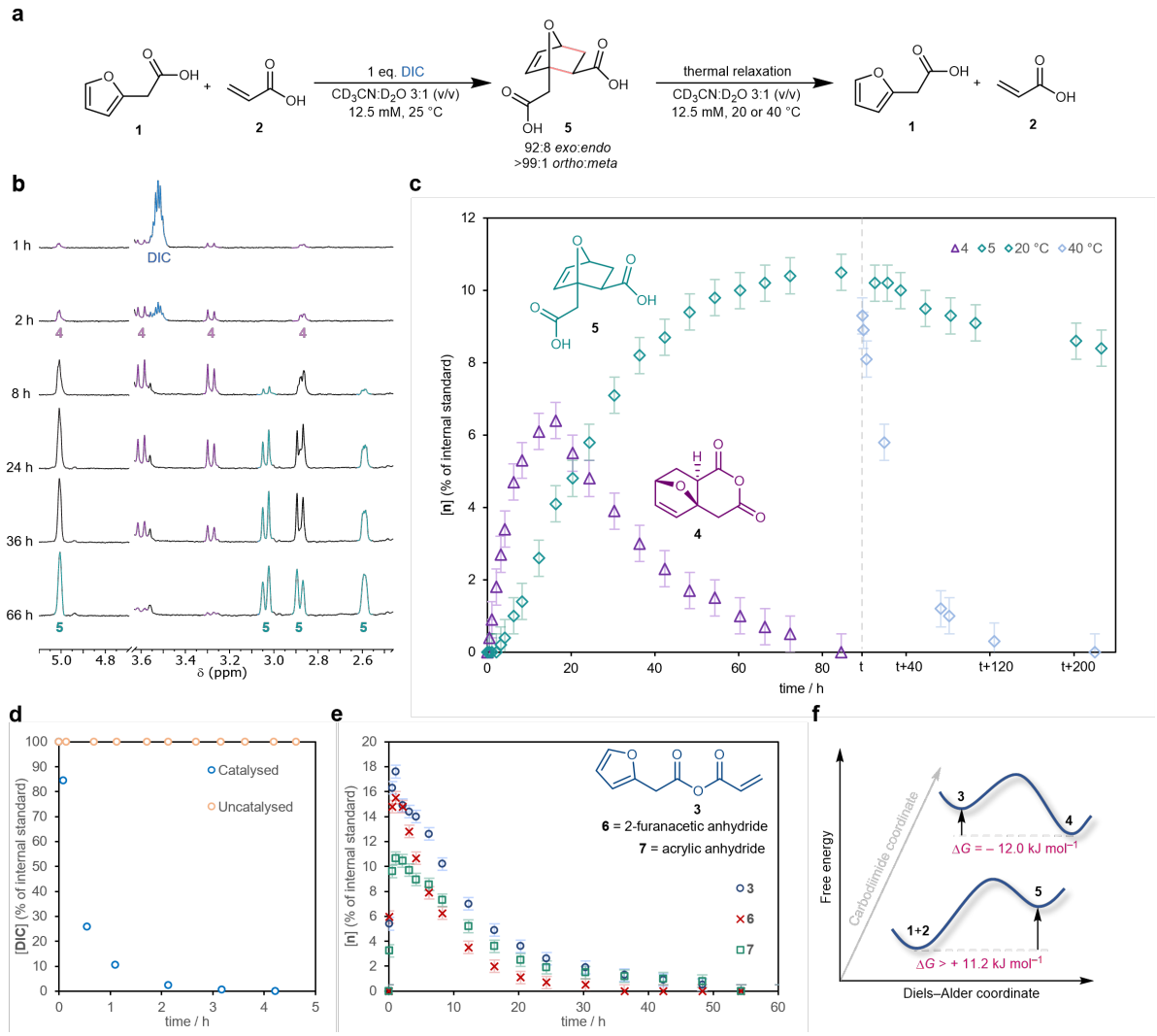

Fig 2 | Ratcheted synthesis of 5. a Ratcheted synthesis of **5** and, in the absence of the chemical fuel, its relaxation to the equilibrium distribution under the same conditions in the absence of fuel. **b** Partial ^{1}H NMR (600 MHz, CD_3CN:D_2O 3:1 (v/v), 298 K) stackplot showing the consumption of DIC (blue) and the formation of **4** (purple) and **5** (teal) over time. **c** Kinetics of the formation of **4** (triangles) and **5** (diamonds) and the subsequent retro-Diels–Alder of **5** to **1** and **2** at 20 °C or 40 °C beginning at time t. **d** Kinetics of carbodiimide hydration catalysed by the endergonic reaction **1**+**2**⇌**5** (blue) and the uncatalysed background (orange). The catalysed consumption of DIC does not fit pseudo-first order

kinetics. **e** Kinetics of mixed (**3**, circles) and symmetrical (**6**, crosses and **7**, squares) anhydride formation and hydrolysis. **f** Free energy profile of ground state species of the anhydride chemical state calculated using (B3LYP/6-31+G(d,p)/GD3BJ) level of theory with corrections for solvation (PCM in acetonitrile (ε = 35.688)). Free energy profile of the diacid chemical state based on experiment. Energies in kJ mol^{-1}. Error bars refer to the measurement of ratios of NMR integrals (±0.5% relative to starting materials).

In addition to being thermodynamically uphill, the ratcheted synthesis of the Diels–Alder adduct **5** also proved to be both regio- and stereoselective (Fig. 3a). We could not detect the formation of either *meta* regioisomer of **5** by ^{1}H NMR, indicating that the ratcheted synthesis is >99% regioselective for the *ortho*-adduct. Furthermore, we found that **5** is formed under fuelling with 92% stereoselectivity for the *exo*-adduct (Supplementary Information, Section S3.6). Molecular modelling suggests that the high selectivity of the ratcheted synthesis for the *exo*- and *ortho*- isomer result from anhydride ring-strain disfavouring the *endo* and *meta* Diels–Alder transition states.

To confirm that one of the effects of fuelling is to increase the effective molarity of the diene and dienophile, we heated a neat mixture of **1** and **2** in the absence of solvent at 40 °C for 7 days (Fig. 3a; Supplementary Information, Section S7). This resulted in a mixture of the four possible isomeric (*endo*-/*exo*-/*ortho*-/*meta*-) Diels-Alder adducts, in 39% total yield (Supplementary Information, Section S8). However, ^{1}H NMR indicated that the thermal solvent-free reaction afforded poor regio- and stereoselectivity, with only 10% of the cycloaddition products formed corresponding to the *exo* and *ortho* isomer **5**, a 4% yield from **1** and **2**. The substantial increase in the regio- and stereoselectivity of **5** under chemical fuelling compared to the neat thermal synthesis demonstrates that ratcheting can also be used to distinguish between energetically similar reaction outcomes.

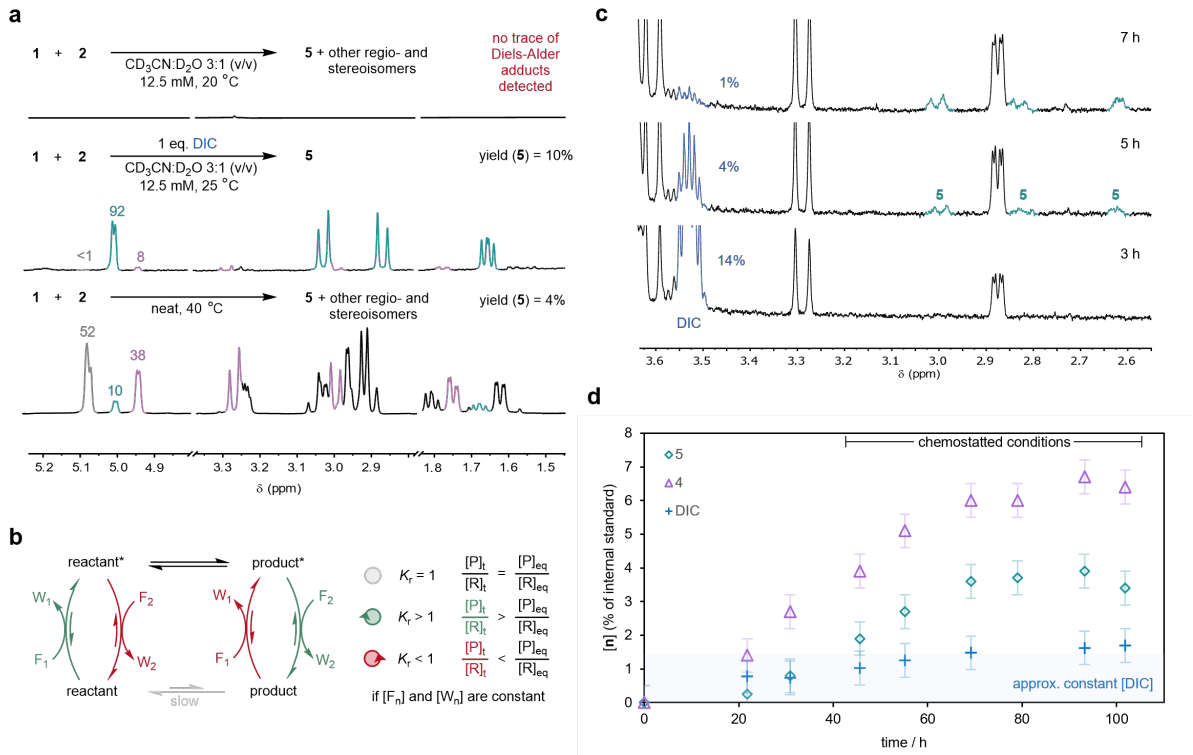

Fig 3 | Reaction selectivity and mechanistic insights. a Partial ^{1}H NMR stackplot (600 MHz, CD_3CN:D_2O 3:1 (v/v), 293 K) showing the regioselectivity, stereoselectivity and yield of the unfuelled reaction (top) and the ratcheted synthesis under the same conditions (middle), in comparison with a thermal synthesis (bottom). Numbers denote the relative proportions (%) of the *exo*-*ortho* (**5**, teal), *endo*-*ortho* (purple) and *meta*- (grey) isomers. **b** Ratcheting synthesis through an information ratchet

mechanism. An orthogonal fuel ($F_1 \rightarrow W_1$ and $F_2 \rightarrow W_2$) reacting along reaction coordinate 2 can drive an endergonic reaction in reaction coordinate 1, so long as there is kinetic asymmetry ($K_r > 1$) in the fuelling cycle. A thermodynamic preference in the 'fuelled' state (a power stroke) is insufficient to drive the reaction. Kinetic asymmetry is present if the ratio of [R]:[P] varies from the equilibrium distribution under chemostatted conditions (constant fuel and waste concentrations).[15,16] K_r = ratcheting constant,[15,16,53] R = reactant, P = product, t = time. **c** Partial ^{1}H NMR stackplot (600 MHz, CD_3CN:D_2O 3:1 (v/v), 293 K) after addition of 2 equiv. DIC showing the formation of **5** before the complete consumption of both fuels (DIC and D_2O). Times are approximate; percentages refer to [DIC] relative to $[DIC]_0$; reaction conditions: [**1**] = [**2**] = 12.5 mM, [DIC] = 25.0 mM, CD_3CN:D_2O 3:1 (v/v). **d** The formation of the Diels–Alder adduct **5** under chemostatted conditions. DIC added continually at 0.7 equiv. per day; reaction conditions: [**1**] = [**2**] = 12.5 mM, CD_3CN:D_2O 3:1 (v/v). The concentration of **5** increases over time before reaching a steady state (4%), indicative of an information ratchet mechanism.[15,16] Error bars refer to the measurement of ratios of NMR integrals (±0.5% relative to starting materials).

Under the reaction conditions, the rate of hydrolysis of the anhydride is rate-limiting for the carbodiimide-to-urea reaction. This results in a fuelling regime in which the system is globally dehydrating for the initial phases of the reaction, followed by globally hydrating once little or no DIC remains. Varying the global conditions of a system over time in order to perform work is characteristic of an energy ratchet mechanism.[11] As carbodiimides can also drive information ratchet mechanisms,[35,47–49] we explored whether the carbodiimide fuelling cycle in Fig. 1d possessed kinetic asymmetry and could therefore promote the formation of **5** at a steady-state under fuelling (Fig. 3b).

Maintaining a constant concentration of fuel to **1** and **2** by continual addition of DIC to the reaction at a rate of 0.7 equiv. per day led to a steady-state of **5** (~4%) in the presence of DIC (Fig. 3d; Supplementary Information, Section S9). This is effectively a chemostatted[15,16,51] regime, since the concentrations of DIC and D_2O are kept constant and the presence of DIU does not affect the rate of any of the other processes. As the amount of **5** is below the NMR detection limit at equilibrium (Fig. 1c; Supplementary Information, Sections S2 and S4), but is formed under chemostatted conditions, the fuelling cycle must[15,16] possess modest kinetic asymmetry and proceed through an information ratchet[11,13] mechanism (see Supplementary Information, Section S10). Under non-chemostatted conditions where the chemical fuel is all added at time zero, the slow hydrolysis step means that the majority of **5** is produced after the consumption of fuel, effectively through an energy ratchet[11] mechanism.

Conclusions

The use of ratchet mechanisms to directionally bias stochastic processes is a key principle that underpins the operation of molecular machines.[11–14,35,47–49] The endergonic synthesis of **5** demonstrates how autonomous chemically fuelled ratchet mechanisms can also modulate and direct the outcome of organic chemical transformations, just as they do in biology.[3] The chemically fuelled transformation of **1** and **2** to **5** involves a transiently formed tether between the reactants, which favourably organises them to bring about the desired transformation. The chemically fuelled yield of **5** is only 12%, but the key to a higher yield (for autonomous chemically driven ratcheted syntheses in general) is to generate as large a kinetic asymmetry in the fuelling cycle as possible. This is achieved by maximising the differences in the reaction rates through Curtin-Hammett-type[53] principles. Despite the modest yield of the chemical fuelling cycle that forms **5**, the energy transduced from the carbodimide-to-urea reaction by the cycle is >3× greater than that required for a deracemisation process,[24] and it proceeds with an energy efficiency >10× greater[24] than photo-deracemisations driven by blue light. In addition to making the endergonic transformation possible, the steric and chemical constraints necessary for ratcheting also result in improved regio- and stereochemical control in the chemically fuelled Diels–Alder synthesis of **5**.

Like ATP, **5** is thermodynamically unstable under the conditions of its chemically fuelled synthesis. However, the kinetic stability of **5** is higher than that of ATP ($t_{1/2}$**^{5}** = 16 days vs.

$t_{1/2}^{ATP}$ ~ 6 h).[20] We note that catalysis of the exergonic retro-Diels–Alder reaction of **5** could allow a suitable molecular machine to harness the chemical energy generated by the ratcheted synthesis to do useful work, rendering **5** a regenerable chemical fuel. However, even though every step of the thermally activated chemically fuelled cycle that makes **5** from **1** and **2** is subject to microreversibility, that does not mean that the products of chemically fuelled endergonic synthesis must necessarily have modest kinetic stability. That simply depends on whether the fastest (fuelled or non-fuelled) reverse pathway has a sufficiently high activation barrier. Such is the case, for example, for the chemically fuelled deracemisation of 1-(6′-substituted-phenyl)pyrrole 2,2′-dicarboxylic acid derivatives, where the $t_{1/2}$ of enantiomers of the 6′-ethyl biaryl system is ~22,000 years.[35] As such, chemically fuelled ratcheted synthesis should prove useful for the endergonic synthesis of products with a range of kinetic stabilities, as well as recyclable fuels,[20] in sequence-specific synthesis,[33,34,54,55] dissipative materials[15,16] and endergonic supramolecular structures[17–19]. The simplicity of the reactants and fuelling cycle of **5** provides a minimalist demonstration of chemically fuelled ratcheted synthesis that aids its understanding in biology and potential utility in synthesis.

Data availability

The data that support the findings of this study are available within the paper and its Supplementary Information.

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Author contributions J.M.G. conceived the project. E.O., J.M.G., A.B and T.W.M designed and carried out the experiments. D.A.L. directed the research. All authors contributed to the analysis of the results and the writing of the manuscript.

Competing interests The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at xxxxx

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