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Ratcheting Synthesis

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Abstract | Synthetic chemistry has traditionally relied on reactions between reactants of high chemical potential and transformations that proceed energetically downhill to either a global or local minimum (thermodynamic or kinetic control). Catalysts can be employed to manipulate kinetic control, lowering activation energies to influence reaction outcomes. However, such chemistry is still constrained by the shape of one-dimensional reaction coordinates. Coupling synthesis to an orthogonal energy input can allow ratcheting of chemical reaction outcomes, reminiscent of the ways that molecular machines ratchet random thermal motion to bias conformational dynamics. This fundamentally distinct approach to synthesis allows multi-dimensional potential energy surfaces to be navigated, enabling reaction outcomes that cannot be achieved under conventional kinetic or thermodynamic control. In this Review we discuss how ratcheted synthesis is ubiquitous throughout biology, and consider how chemists might harness ratchet mechanisms to accelerate catalysis, drive chemical reactions uphill, and program complex reaction sequences. Molecular ratcheting has the potential to expand the chemist's toolbox, offering new paradigms in reactivity, complexity and control.

Introduction

Chemical reactions most commonly proceed under either thermodynamic or kinetic control (Fig. 1a).[1] Under thermodynamic control the product distribution is determined by the differences in the free energies of all the accessible chemical species.[2] Supplying a reaction with sufficient heat allows exploration of the potential energy surface and equilibration to the thermodynamic minimum. Kinetic control causes reactions to proceed to local minima, favouring the product(s) formed fastest.[3] Catalysts can modify reaction outcomes by lowering the activation energy of a particular pathway to bias the formation of a product by kinetic selection,[4] a feature exploited in asymmetric catalysis (Fig. 1b). In this Review, we focus on a third way to manipulate product outcomes: ratchet mechanisms.[5–12] These processes harness an additional energy input (e.g., light (Fig. 1c),[13] chemical[14] (Fig. 1d), electrochemical,[15] mechanical[16] energy, etc.) that occurs orthogonally with respect to the targeted transformation and allows the navigation of complex potential energy landscapes.[17,18] In this way, reaction outcomes can be realised that are not achievable with pathways under conventional kinetic or thermodynamic control.

Some reaction mechanisms reminiscent of ratchets are familiar to chemists, without necessarily attaching the moniker of 'ratchets' to them. A simple example is the photoisomerization of azobenzenes, in which the formation of the *Z*-isomer is 'ratcheted' in an endergonic synthesis powered by light (Fig. 1c).[13] What is less well-known is that the ratcheting of synthesis can also be achieved by coupling chemically orthogonal processes together such that a 'fuel-to-waste'[14] transformation is catalysed by a process that also includes conversion of substrate to product in the same catalytic cycle/cyclic reaction scheme (Fig. 1d).[6,19] In such systems, the free energy

released from the fuel-to-waste reaction through catalysis can be used to drive the second reaction or process. This is fundamentally different to the use of high energy reagents to activate functional groups that are directly involved in a synthetic transformation (e.g. triphenylphosphine and diethyl azodicarboxylate which activate carboxylic acid groups in the Mitsunobu reaction or sacrificial oxidants in metal-catalysed oxidations or cross-coupling reactions). The latter reagents provide an alternative pathway for a chemical transformation but the reactions still proceed under classic thermodynamic or kinetic control (Fig. 1a). Rather, a ratcheted synthesis harnesses energy by rectifying a process that does not directly involve functional groups transformed in the fuel-to-waste reaction (Fig. 1d), with the energy released along reaction coordinate 2 (fuel-to-waste) biasing the distribution of the chemical transformation along reaction coordinate 1. Actual non-biochemical examples of this that are as simple as the photoisomerization of azobenzene (Fig. 1c) are scarce (or, at least, as yet unrecognised). However, a hypothetical minimalist system that illustrates the necessary features of such a process could be a Diels-Alder/retro-Diels-Alder reaction driven away from the equilibrium distribution of diene-dienophile:Diels-Alder-adduct by coupling the reaction to carbodiimide hydration (Fig. 1e). Kinetic asymmetry, arising from differences in the rates of anhydride formation and hydrolysis between the left and right cycles (Fig. 1e), would cause a change in the distribution of the components within the overall cycle,[6,19] driving the amount of Diels-Alder adduct present away from its equilibrium value in favour of the diene and dienophile carboxylic acid products. The energy from the carbodiimide-to-urea reaction rectifies the dynamic equilibrium for the Diels-Alder/retro-Diels-Alder reaction. We chose this simple, but hypothetical example, to illustrate the concept in this Review because it shows the process clearly. It is evident from Fig. 1e exactly how and why the energy from a fuel-to-waste reaction can be transduced to drive a coupled chemical reaction away from equilibrium. For the use of a closely related mechanism to drive directional rotation of the components of a motor-molecule, see section on catalyst dynamics and molecular ratchets.

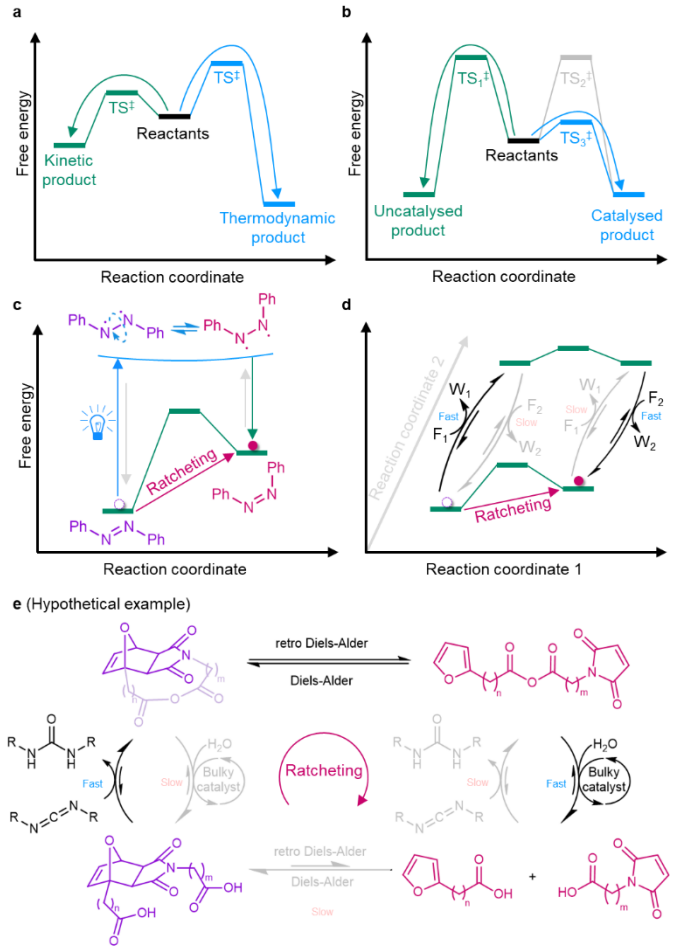


Figure 1| **Ratcheting synthesis. a**, Kinetic vs. thermodynamic control in determining reaction outcomes.[1] The blue pathway results in a product with a lower free energy, while the green pathway occurs faster due to the lower activation barrier. **b**, Catalysis enables the manipulation of activation barriers, allowing reaction outcomes to be altered.[4] As illustrated, in the absence of a catalyst the green and grey pathways are equally kinetically favoured, while addition of an asymmetric catalyst instead favours the blue pathway. Nonetheless, the reaction must remain thermodynamically downhill. **c**, Ratcheting enables product distributions to be biased by harnessing energy from orthogonal sources. A familiar example is the photoisomerisation of azobenzene,[13] where preferential photoexcitation of the *E*-isomer enables it to undergo stochastic free rotation around the N–N single bond and subsequently relax to the *Z*-isomer. The less thermodynamically stable *Z*-isomer becomes kinetically trapped in the ground state and therefore persists in the reaction mixture. In this way, the formation of the *Z*-isomer is 'ratcheted' in an endergonic synthesis powered by light. **d**, A generalised example of the transduction of chemical energy through catalysis to drive chemically orthogonal synthesis. Kinetic asymmetry[22–24] in the catalytic cycle (black arrows = fast, grey arrows = slow) creates a chemical engine[19] to ratchet synthesis. Energy from the fuel-to-waste reaction (F⟶W, reaction coordinate 2)[14] drives synthesis out of equilibrium along reaction coordinate 1. **e**, Hypothetical example of a Diels-Alder reaction that could, in principle, be ratcheted by continuous catalytic hydration of a carbodiimide fuel. Chemical gating (i.e. the kinetics of different pathways) in the formation and hydrolysis of the anhydride, with or without strain induced by intramolecular cyclisation, generates kinetic asymmetry in the reaction cycle, which would drive the ratio of diene-dienophile:Diels-Alder-adduct away from the lowest free energy (i.e. equilibrium) value.

Ratcheting is the fundamental mechanism for driving Markovian[20] systems (that is, stochastic dynamic processes, such as thermally activated chemical reactions or Brownian motion[21–25]) away from equilibrium.[5–12] While artificial nanoscale ratchets are best known for controlling movement[5] (in the context of molecular motors[15,25–34] and pumps[35–44]), they can be used to control other types

of stochastic processes,[6,7,11,16–18,21,45] including chemical synthesis.[46–48] Biomolecular synthesis relies on ratchets to accelerate catalysis and perform endergonic, programmable and sequence-specific transformations.[49] Rectification of stochastic processes requires an energy input,[5,6,14] for which biology uses photons,[50] fuel-to-waste reactions[14,51] or the dissipation of transmembrane gradients.[52] Molecular machinery, such as the ribosome (Fig. 2a),[53,54] deoxyribonucleic acid (DNA)[55,56] and ribonucleic acid (RNA) polymerases[57,58] (Fig. 2b), fatty acid synthase[59,60] (Fig. 2c) and adenosine triphosphate (ATP) synthase[22,61] (Fig. 2d) all use ratchet mechanisms in their functions as molecular synthesizers. Such is the importance of biological ratchets for synthesis that, by some estimates, the cell expends 30–50% of its energy on synthesising, operating, and maintaining just the ribosome.[62,63]

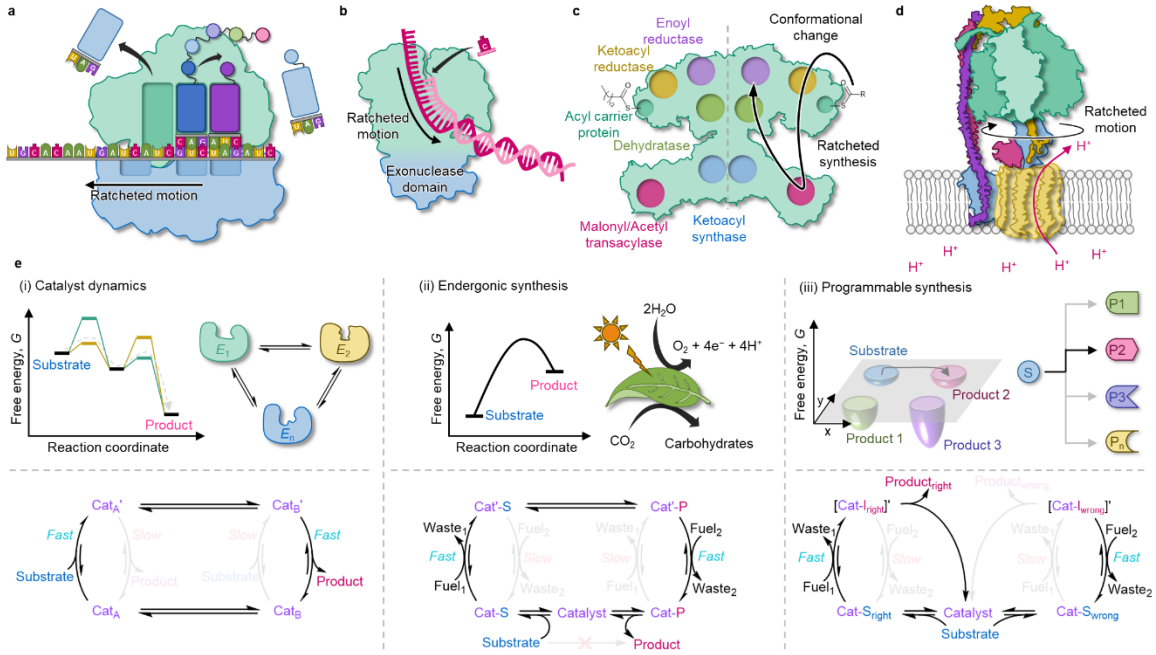


Figure 2| **Ratchets for synthesis (biology and artificial systems). a**, Ribosomes translate information stored in mRNA to synthesise polypeptides.[53,54] A ratchet mechanism is used to move directionally along an mRNA strand and achieve greater fidelity of translation than a passive process. **b**, DNA polymerase replicates DNA.[55,56] Ratcheted motion moves the DNA strand directionally through the machine. The exonuclease domain error checks the transcribed strand, removing incorrectly added bases. **c**, Fatty acid synthase synthesises fatty acids as long-term energy-dense storage molecules.[59,60] Large-amplitude conformational changes allow the acyl carrier protein to sample the reactive sites of the machine, while kinetic gating ensures the correct order of reactivity. **d**, ATP synthase harnesses proton gradients to synthesise ATP from ADP and phosphate, an energetically unfavourable reaction under physiological conditions.[22,61] **e**, Elements of ratchet mechanisms can be identified in a range of biological and artificial synthetic processes. Kinetic asymmetry[24] in the reaction cycles[19] (below) introduces control over the rates of reactions and selection of products. (i) Switching a catalyst (Cat, purple) between two (or more) states allows slow steps of a catalytic cycle to be avoided (grey), accelerating catalysis. Spontaneous enzyme dynamics during a catalytic cycle has been hypothesised to increase the catalytic rate.[170–190] (ii) Endergonic synthesis (e.g. photosynthesis), where products (P, pink) of a reaction have a higher free energy than the substrates (S, blue), can be produced through a ratchet mechanism. Energy from light, electricity, gradients, or a fuel-to-waste reaction[14] offsets the energetic cost of the uphill reaction.[124] In designing such mechanisms, it is important to recognise that light-driven systems are not constrained by microscopic reversibility in the same way that ground state processes are. (iii) Programmable synthesis is required to make specific products from a common pool of reagents or to store information in biological polymers.[231] A catalyst binds the 'right' and 'wrong' substrate with a preference governed by the native thermodynamic bias (horizontal equilibrium arrows). An energy input ($Fuel_1 \rightarrow Waste_1$ process) raises the bound substrates to an excited intermediate [Cat-I]' state, which can either decay back to the initial state ($Fuel_2 \rightarrow Waste_2$ process) or to the product. Kinetic gating of these processes allows for both kinetic selection of the desired product and error correction of an incorrectly bound substrate.[227]

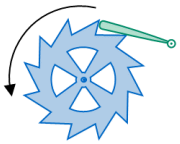
Different ratchet mechanisms (energy ratchets and information ratchets, see Box 1) operate by fundamentally different principles. For ground state ratchets driven by catalysis of a fuel-to-waste reaction, kinetic asymmetry (i.e. the ratio of forward to backward cycles) in the chemical engine cycle is key. In contrast, ratchet mechanisms that rely on transitioning between ground states and excited states, such as those driven by light, are based on different underlying physics, and unlike ground state processes are not constrained by microscopic reversibility. For more detailed discussion of these distinctions, we direct readers to other publications.[22,64,65]

Biomolecular ratchets transduce energy through catalysis of spontaneous processes (typically chemical reactions or the dissipation of transmembrane gradients) to kinetically select reaction pathways.[8,14,22–24,66–68] During catalyst turnover, a catalytic cycle is inherently out of equilibrium due to the input of energy from the substrate-to-product reaction,[14,69,70] as has been explicitly noted for enzyme catalytic cycles.[71,72] This energy input can be harnessed to drive a coupled stochastic process away from equilibrium, even if that process is chemically orthogonal. For example, triphosphate hydrolysis is not directly linked to either directional movement along a track or sequence-specific synthesis, yet it enables both these behaviours to occur in polymerases and the ribosome.[54,56] This transduction of energy between sources that are only coupled indirectly, through a chemical engine cycle, is fundamental to ratchet mechanisms.

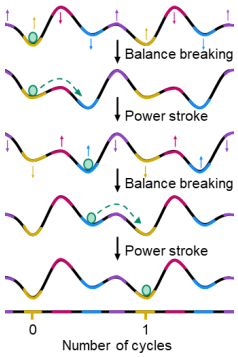
Over the past two decades, molecular energy ratchets and information ratchets (see Box 1)[5] capable of exhibiting directional motion have begun to be developed.[25–44] The earliest artificial molecular motors[9,25–34] and pumps[35–44] provided a framework that established the requirements and designs for molecular ratchet mechanisms.[5–9] The potential of exploiting ratchet mechanisms to control reaction outcomes has been discussed in principle, notably by Astumian in terms of enzymes in 1993[17] and Leigh in terms of systems chemistry in 2010.[18] However, the application of ratchet mechanisms to chemical synthesis has only recently begun to be explored. A small number of artificial molecular machines capable of performing synthesis and enhancing catalysis have been reported.[73–84] These display some aspects of ratchet mechanisms but lack the autonomy and functionality of their biological counterparts.[24,54–63] More general recognition, and subsequently application, of ratchet mechanisms could be transformative for synthesis, offering new paradigms in reactivity, complexity and control. Advances in fields such as molecular biology,[85–95] heterogeneous catalysis,[96–107] synthetic methodology[108–137] and artificial photosynthesis,[138–146] where the underlying ratchet mechanisms sometimes remain unrecognised, have the potential to impact the development of molecular ratchets for synthesis. Here, we discuss the evolution of ratchets for synthesis including the development of dynamic catalysts, endergonic synthesis and programmable and sequence-specific synthesis (Fig. 2e). We draw connections from advances in seemingly disparate fields and consider the common ratchet mechanisms that have been exploited to drive synthesis. Finally, we outline some goals and opportunities for the field.

Main text

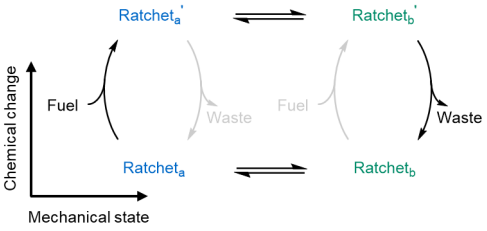
Box 1 | Ratchet mechanisms.



Ratchet mechanisms rectify stochastic processes, and were originally recognised in the context of directionally biasing Brownian motion. An energy input is required to preserve the Second Law of Thermodynamics, allowing ratchets to perform work and progressively move a system away from equilibrium. There are four fundamental characteristics of molecular ratchets: They must be repetitive (in principle), progressive (that is, multiple operations of the ratchet do work cumulatively), processive (that is, take steps in sequence), and directionally biased. Two different classes of ratchet mechanisms that have been explored in artificial molecular machinery:[5]



Energy ratchets involve a repetitive (either stochastic or periodic) change in a potential energy surface, irrespective of the position of a particle on that surface. In its simplest form, this mechanism consists of a periodic series of two different minima and two different maxima along which a Brownian substrate can be directionally transported by repetitively alternating the relative heights of the maxima and depths of the minima. The diagram to the right shows the directionally biased transport of a Brownian particle (green circle) by switching between two potential energy surfaces. Switching of the potential energy surface is termed 'balance breaking' (as the change momentarily means the particle is no longer in the lowest minima), while the subsequent statistically driven directional relaxation of the Brownian particle is termed a 'power stroke'.[5]



Information ratchets drive directional motion by differentiating the relative reaction rates for forward and backward processes dependent on the mechanical state (i.e., conformation or co-conformation in molecular terms) of the machine, known as kinetic gating. Directionality is achieved through the communication of information between a dynamic stochastic process and the coupled dissipative process that provides the energy input. This mechanism does not require modulation of external conditions and instead autonomously transduces a source of energy to drive directional motion. This is the mechanism by which the vast majority of biological machines are believed to operate.[5]

Catalyst dynamics and molecular ratchets

Virtually all biological molecular machines are catalysts, drawing their ability to power processes from their catalysis of fuel-to-waste reactions (often ATP hydrolysis). The importance of catalysis in driving molecular ratchets is a key design principle for synthetic ratchets.[5–8,14,19,24,25,27,36–38] Recently, this idea been inverted, harnessing dynamics through ratchet mechanisms to drive catalysis and allow an escape from the constraints imposed by a static reaction profile.

Driven oscillations in heterogeneous catalysis

In heterogeneous catalysis reactions often exhibit a 'volcano-shaped' rate dependence with respect to the binding strength of the reactants and the products to the surface.[147,148] Strong binding leads to rate-limiting product dissociation, while weak binding leads to a rate-limiting surface reaction . The point at which these rates match (the peak of the volcano) corresponds to the maximum rate of the reaction, known as the Sabatier limit. Metal catalysts may be selected, alloyed, electrified, strained, and magnetised to optimise the catalyst,[100] but once the Sabatier

limit is reached the rate cannot be further improved. The Sabatier limit is the limiting rate of heterogeneous catalysis in many industrial processes.[98,99,103]

However, the Sabatier limit can be overcome through a ratchet mechanism. Dauenhauer and co-workers have shown[96,103] that continuously switching states between potentials on each slope of the volcano allows both a fast surface reaction in one state and fast product dissociation in the other (Fig. 2a), bypassing the rate-limiting processes of each state. To effectively enhance the rate, the oscillation frequency must approximate the rate of the individual chemical steps, which the Dauenhauer team have termed 'catalytic resonance'. (We note that this is not a true resonance, but rather a windowing effect in which a maximal effect is observed in a range defined by the kinetics of the heterogeneous catalysis.[149,150] We use the term in this Review as it is common parlance in the field.) Applying an oscillating voltage at an appropriate frequency across a platinum surface has been shown to enhance the rate of formic acid oxidation by over an order of magnitude above the Sabatier limit.[96] The energy input onto the catalytic surface can be diverse, as long as it elicits a temporary change in surface binding energy: oscillations of light intensity have been shown to enhance the rate of platinum-catalysed methanol decomposition;[100] rapid temperature oscillations have been used to increase selectivity in methane pyrolysis and accelerate ammonia synthesis;[105] and resonant crystal strain has been modelled as a means of enhancing the rate of ruthenium-catalysed ammonia synthesis.[102] The switching between energy profiles used to bring about the accelerated catalysis is characteristic of an energy ratchet mechanism[5] (see Box 1). Indeed, similar windowing effects were recently observed in a synthetic DNA molecular motor driven by an alternating electric potential.[32]

Energy ratchets typically function by repetitively 'flashing' (i.e. switching) between two discrete energy profiles (see Box 1).[5] However, it is also possible to increase the complexity of the number and pattern of the energy profiles with respect to time. Manipulation of the input wavefunction (for example, changing amplitude, frequency, and waveform) can provide a variety of different energy profiles, allowing for greater control than simply switching between two states.[106,154,155] Theory indicates that this should be able to select either pure A or pure B from a reaction that, without energy input, forms A and B as a mixture (Fig. 3a(iv)),[99,107] the choice of products being provided by the wavefunction of the energy input; for example, voltage.[106]

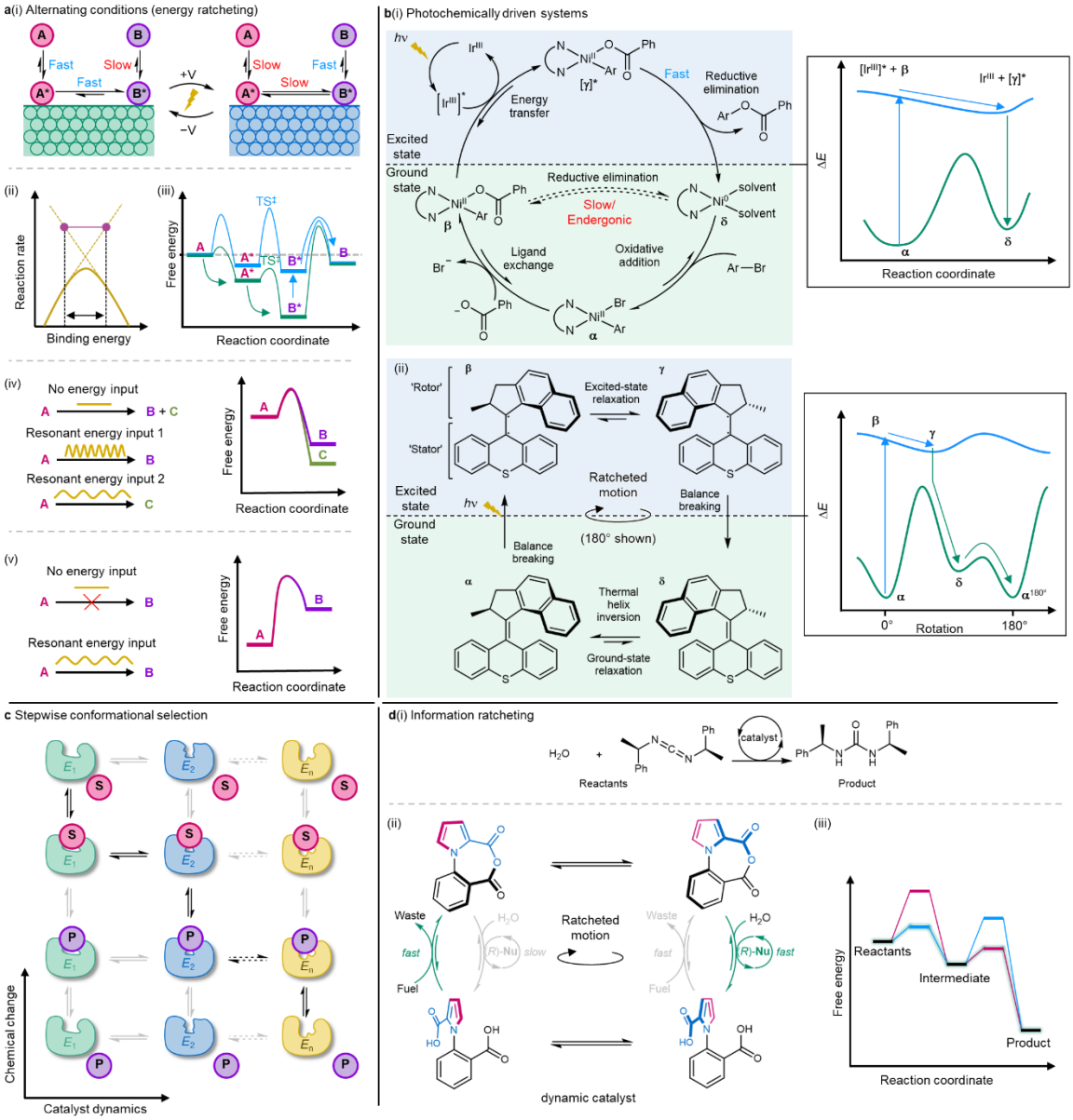


Figure 3| **Driven and spontaneous catalyst dynamics can accelerate the rate of catalysis. a**, Dauenhauer's 'catalytic resonance',[96–107] in which (i) the surface of a catalyst is switched between two potentials at a frequency related to the rates of the catalytic process, (ii) enables heterogeneous catalysts to exceed the Sabatier limit[147] by (iii) accessing fast adsorption, reaction, and desorption processes via an energy ratchet mechanism.[5] (iv) This allows selectivity between possible products and (v), in principle may be able to drive endergonic reactions. **b**, (i) Continuous irradiation gives access to a photoexcited state in MacMillan's Ni-catalysed cross-coupling,[108] so that the catalytic cycle bypasses a slow reductive elimination step. (ii) This mechanism is analogous to that of Feringa light-driven motors,[30,31] where the excited state is used to bypass kinetically inaccessible rotation around a double bond.[224] **c**, Stochastic conformational dynamics can allow enzymes to sample multiple conformations along the reaction coordinate, allowing slow steps (grey arrows) in particular conformations to be bypassed.[170–185] Different conformations (green, blue, yellow) are 'optimised' to favour specific processes (black arrows) within the catalytic cycle. **d**, (i) Similar catalytic rate acceleration by conformational selection is explicit in the catalysis of chiral carbodiimide hydration by an artificial molecular motor.[27] (ii) Chemomechanical cycle for autonomous chemically fuelled rotation of the motor. The grey arrows indicate slower transformations than the corresponding transformations indicated by green. (*R*)-Nu is a chiral nucleophilic catalyst for anhydride hydrolysis. (iii) Energy profile for catalysis of the fuel-to-waste reaction[14] by the dynamic motor catalyst. Fast pathways are accessible for both steps due to spontaneous catalyst dynamics.

Since an increase in reaction rate does not constitute thermodynamic work,[6] the energy transduced by such ratchet mechanisms is dissipated as heat. The choice of a particular wavefunction may allow some of this lost input energy to be transduced into chemical energy, exploiting the energy ratchet mechanism to perform chemical work. Such a system could bias the distribution of a chosen reaction energetically uphill in favour of the product, or open the door to novel reactivity that is typically inaccessible, all while operating at an increased rate (Fig. 3a(v)).[98,99] Indeed, the transduction of input energy into chemical energy using an energy ratchet mechanism has been demonstrated experimentally by Nocera and co-workers,[141] who used a spatially (rather than temporally) separated energy ratchet[156] to perform the endergonic synthesis of H_2 from H_2O in their 'artificial leaf' (see section on Endergonic Synthesis).

The potential of such ratchet-based technology is obvious: numerous heterogeneous catalysis processes[107,157] require high temperatures and/or pressures to be economically viable.[158] By applying a frequency matched potential to the catalysts, reaction temperatures might be lowered without compromising rate,[159] and by transduction of the input energy into chemical energy, the pressure required may also be lowered without compromising conversion. Applying a particular wavefunction might also enable byproducts to be minimised.

Ratchet mechanisms in homogeneous catalysis

Homogeneous catalytic cycles involving reactions with oppositely sloping scaling relations may also be constrained by Sabatier rate profiles (Fig. 3a(ii)).[157–159] Examples of volcano plots in homogeneous catalysis include metal-catalysed cross-couplings, where oxidative addition and reductive elimination form the rate-limiting slopes of the volcano.[157] As electronic modifications that promote reductive elimination hinder oxidative addition, in these reactions a balance must be found, often with palladium (Pd^0/Pd^{II}).[157] Despite lower overall rates, other metals provide attractive alternatives to palladium due to their earth-abundance and superior rates in challenging steps—for example, copper (Cu^I/Cu^{III}) offers the potential for rapid reductive elimination but is constrained by an 'oxidative addition problem', while nickel (Ni^0/Ni^{II}) typically provides rapid oxidative addition but slow reductive elimination.

Rather than attempting to move either copper (Cu^I/Cu^{III}) or nickel (Ni^0/Ni^{II}) towards the Sabatier limit (by exploitation of different ligands to change the metal's frontier orbital energies), ratchet mechanisms can be harnessed to counter rate-limiting, and even endergonic, chemical steps (see Endergonic Synthesis section).[99] As with catalytic resonance,[96–107] this energy input allows access to two distinct catalytic energy profiles on either slope of the Sabatier volcano (Fig. 3a(ii)), creating a catalyst that can exhibit both nickel-like oxidative addition and copper-like reductive elimination.

For example, MacMillan has demonstrated[108] a photochemical nickel (Ni^0/Ni^{II}) catalysed cross coupling reaction, in which rapid oxidative addition can occur in the ground state, while rapid reductive elimination can occur in an electronically excited state, providing access to a kinetically inaccessible C–O bond forming reaction (Fig. 3b(i)). Similarly, Ritter has demonstrated[113] copper (Cu^I/Cu^{II}) catalysed ether formation, in which the copper oxidative addition problem is avoided by photoexcitation of the aryl halide starting material. In the excited state, the starting material forms high energy radical species that relax to undergo a formal oxidative addition to Cu^I, a reaction that is both kinetically and thermodynamically inaccessible in the ground state.[109]

Clear parallels exist between MacMillan's light-driven excited-state catalysis[108] (Fig. 3b(i)) and Feringa's rotary motor[30,31] (Fig. 3b(ii)), which is driven by a light-fuelled energy ratchet mechanism. In both cases progression of the ground-state cycle is impeded by a large kinetic barrier. Following photoexcitation to the triplet state, conformational rearrangement occurs such that electronic relaxation takes place across the ground-state barrier. These examples illustrate how very similar types of energy ratchet mechanism can be applied to drive either directional movement or rate acceleration of a catalysed reaction.

Energy transfer allows access to excited electronic states, however, other means of oscillation between energy profiles may be exploited in a similar manner.[5] Baran has employed[111] electrochemical single electron transfer to reversibly switch between a Ni^{0}/Ni^{II} catalytic cycle and a higher energy Ni^{I}/Ni^{III} cycle. Transitioning between these two energy profiles allows a kinetically unfavourable amine coordination to be overcome, greatly increasing the rate of a Buchwald-Hartwig-like coupling. Moreover, as oxidation occurs at the anode and reduction at the cathode, the catalytic cycle is able to transition between the two states autonomously, functioning as what researchers working in supramolecular assembly have termed a spatially-separated energy ratchet.[153] Such a mechanism has recently been employed for deracemization[123,160] (see section on Endergonic Synthesis), and postulated as a means to autonomously drive a molecular motor.[15] Baran has also begun to explore[111] the wavefunction of the energy input,[151,152] demonstrating how 'rapid alternating polarity' can ratchet synthesis by electrochemically reducing a complex molecule with nonequilibrium chemoselectivity.[112] Again, parallels exist here to the methodology being investigated in catalytic resonance.[99]

Harnessing ratchet-like mechanisms to access excited-state energy profiles is increasingly being explored as a means of avoiding what would otherwise be rate-limiting or endergonic steps[114] (see section on Endergonic Synthesis). In general, catalysis may be driven by selectively exciting the catalytic intermediate (or starting material) immediately preceding an unfavourable step, either in the form of direct excitation, energy transfer or single-electron transfer. This input of energy can be transduced by a ratchet mechanism[5,6] to enhance the rate of the catalysed reaction or to perform work chemically by ratcheting synthesis. The development of such processes is expanding the chemical toolbox, either with entirely novel reactions or by usefully extending existing methods (e.g. to use earth-abundant elements rather than precious metal catalysts).

Enzyme dynamics

Enzymes are capable of extraordinary reaction rate accelerations, some of which far exceed even the fastest artificial catalysts.[161,162] Pauling's model of transition state stabilisation[163,164] has largely stood the test of time, but the presence of seemingly crucial conformational dynamics in some systems[165] led to the induced fit[166] and conformational selection[167,168] models of enzymatic rate acceleration being proposed.[169] These concepts have evolved into a more complex 'stepwise conformational selection' notion for enzyme mechanisms,[170–180] but precisely how dynamics cause rate acceleration in enzymes, and the extent to which observed structural changes instead occur incidentally as coupled motions, remains the subject of debate.[181–185]

Enzymes exist in an incessantly interconverting ensemble of conformational states[175,176,178,180] ranging from small-amplitude vibrational modes to global changes in tertiary structure[169] with timescales extending over many orders of magnitude.[175,179,184] Each of the conformational states can exhibit a different energy profile along the catalysed reaction coordinate due to differences

in catalytic residue positioning,[186] electrostatics,[181,182,187] solvation[175,187] and substrate orientation.[187] Thus, enzyme catalysed reactions can be represented by a two-dimensional energy landscape, where conformational dynamics occur orthogonally to the reaction coordinate (Fig. 3c).[178,179] Stepwise conformational selection proposes that the fastest pathway for a reaction may involve the sampling of different conformational states while traversing the reaction coordinate, exploiting the lowest conformationally dependent kinetic barrier for each step.[178] Rate acceleration may therefore occur with mechanistic similarity to catalytic resonance,[96–107] i.e. by the sampling of different reaction coordinates during catalysis. Unlike the driven oscillations that give rise to catalytic resonance,[96–107] enzyme dynamics occur spontaneously through random thermal motion.[169] However, forced conformational oscillations within enzymes have also been proposed to ratchet the catalysed reaction.[17] The dependence of the reaction rate on the conformational state of the enzyme directly parallels the mechanically dependent kinetic gating that drives information ratchet mechanisms (see Box 1).[4–9,27]

The prevention of particular conformational dynamics, for example by cooling[188,189] or mutagenesis,[181,190,191] has been shown to significantly inhibit turnover in some enzymes. The inferior rate-accelerations of artificial enzymes compared to their biological counterparts is often speculated to arise (at least in part) from the lack of evolved conformational dynamics.[190] Indeed, directed evolution of a conformationally dynamic network in an artificial enzyme has been shown to enhance its catalysis.[190,192] While the occurrence of mid-reaction conformational dynamics is uncontroversial, whether these dynamics are causal in enzyme rate accelerations (or whether, like solvent rearrangement, they occur simply as a consequence of the reaction) is the subject of debate.[183,184] However, since (ground-state) biomolecular machines appear to operate through information ratchet mechanisms,[5,22] which necessarily exhibit conformationally dependent kinetic gating (i.e. the fastest pathway for the reaction necessarily involves movement),[4–8] the potential for conformational dynamics to affect the rate of catalysis is evident.

Smaller dynamic catalysts

The importance of conformational dynamics in small-molecule and transition-metal-complex-based catalysis is also increasingly being recognised.[193–196] Historically, catalyst selectivity often relied on steric hindrance of unwanted pathways, rendering catalyst rigidity an important design element.[196,197] In exploring the role of attractive noncovalent interactions in catalysis,[198,199] the benefits that catalyst flexibility can afford[197] in terms of stereoselectivity[200–205] and rate[200] have become apparent. Yet these benefits may arise solely from the ability of flexible catalysts to adopt a single favourable conformation, meaning that the effects of conformational dynamics that actually occur during catalysis remain largely unexplored. Dynamics have been shown to occur during catalysis,[206–212] including in some well-known ligand scaffolds,[213–215] but to date no experimental study has demonstrated a causal link between conformational dynamics and enzyme-like rate accelerations.[197,209]

In the field of artificial molecular machines, the exploitation of large-amplitude conformational changes is a well-understood feature of machine design.[5,9] In recent years the incorporation of catalytic sites into conformationally dynamic molecular machines has given rise to the first artificial chemically fuelled autonomous motors[14,27] and pumps.[36,37] These information ratchets catalyse fuel-to-waste reactions in a conformationally dependent manner (kinetic gating), such that the fastest pathway for the reaction necessarily includes conformational changes orthogonal

to the reaction coordinate.[5–9,19] Such a mechanism is responsible for asymmetry in the molecular dynamics (kinetic asymmetry), driving the system directionally away from equilibrium.

An autonomous chemically fuelled single-bond rotary motor was recently synthesised[27] by our group (Fig. 3d). The motor-molecule exhibits spontaneous conformational dynamics between two enantiomeric conformations and is a catalyst for carbodiimide hydration (Fig. 3d(i))[14] in a four-step catalytic cycle. Each of the two chemical steps of the cycle occurs at a different rate depending on the conformation of the motor, resulting in double kinetic gating.[37] Static versions of the catalyst can be generated by sterically blocking axial rotation (i.e. forming atropisomers). It is implicit from the chemomechanical cycle[19] of the motor that conformational dynamics allows access to both fast reaction pathways (Fig. 3d(ii), (iii)), while related static atropisomer catalysts must necessarily follow one slow pathway. Only the modest kinetic gating of current versions of the artificial motor-molecule prevents experimental confirmation of the causal connection between conformational dynamics and rate.

Although conformational dynamics likely already operate in some artificial catalysts,[206–215] their effects likely often remain unrecognised.[197] Catalyst dynamics based on ratchet mechanisms should enable rate acceleration by conformational selection. Such designs have the potential to exploit dynamics to allow faster reaction rates (without the need for an energy input),[178] improve stereocontrol and substrate selectivity (without drastically increasing catalyst complexity),[197] and allow the energy of catalysed reactions to be transduced[68–70] to achieve different outcomes and be used for task performance beyond synthesis.

Ratchet mechanisms and the origins of life

The mechanistic link between dynamic rate accelerations and ratchet mechanisms[6] has other broad implications. As faster catalysis leads to selection and amplification in self-replicating systems,[216] primitive dynamic catalysts following the type of minimalist mechanism shown in Fig. 3d(ii) would have had an 'evolutionary' advantage on pre-biotic earth because of the accelerated catalysis that dynamic conformational selection causes. Mechanical gating[14] in such a dynamic catalyst would lead to a directional molecular ratchet, i.e. a molecular motor.[5] In other words, a molecular motor might initially evolve not because of its ability to perform work, but rather because its fundamental mechanism can be a means by which catalysis is inherently accelerated. Unlike other molecular systems, such a ratchet, fuelled by the catalysed reaction, would be capable of progressively and repetitively performing mechanical (and other) work, which early proto-cells could then repurpose and exploit (exaptation[217]) when tasks such as synthesis, information processing, transport and force generation became useful.[49,218,219] It seems to us that this may be how life's first molecular machines evolved.

Endergonic synthesis

Endergonic synthesis refers to chemical reactions that produce molecules that have a higher chemical potential than the starting materials.[114] The endergonic (energy consuming) reaction must be coupled to an exergonic (energy releasing) process to offset this energy requirement.[68] The energy releasing process can include fuel-to-waste reactions, the dissipation of concentration gradients, electrochemistry, mechanical work or the absorption of photons.[6,7,14–16,19,49]

Traditional synthetic methods are largely based on the use of high chemical potential reagents to form products of lower chemical potential, with reactions progressing towards a local (kinetic control) or global (thermodynamic control) energy minimum. For example, while the synthesis of 'high energy' acid chlorides from 'low energy' carboxylic acids can be achieved, it must be done at the expense of an even higher energy reagent, such as thionyl chloride.[220] Kinetic control can be used to transiently generate 'high energy' species, for example the formation of esters under hydrolytic conditions, a feature commonly exploited in transient self-assembly.[6,7,19,220] Biology makes extensive use of this strategy, for example in glycolysis, where the activation of glucose by phosphorylation leads to the net production of two molecules of ATP.

The introduction of kinetic asymmetry to such systems results in chemical engines[19] that can dissipatively maintain nonequilibrium product concentrations using a ratchet mechanism.[6] The ratcheted approach to endergonic synthesis provides a number of benefits; ratchets can transduce energy between otherwise unrelated systems,[19,66–69] allowing endergonic reactions to be thermodynamically offset by a non-chemical or chemically unrelated exergonic process. It also allows the use of a general energy input for a variety of different chemistries and processes,[51] enabling a reduction in the number of specific reagents needed and thus reducing off-target reactivity in complex environments such as cells. Moreover, the approach can enable greater levels of control, as energy inputs can be more closely matched with energy requirements, reducing wasted energy and reagents.[14,221] Although artificial molecular ratchets have to date largely focussed on mechanical processes, there is no fundamental requirement for energy transduction to be mediated by motion, and other ratchet-based processes (chemical, photochemical, etc.) can in principle be used in similar ways.[96–146]

Biology employs ratchet-based approaches for endergonic synthesis, often using mechanical motion (i.e. conformational and co-conformational changes) as a convenient mediator between different forms of energy.[22,49] This is illustrated by F_oF_1-ATP synthase,[61] which is a Brownian ratchet motor that rotates in one direction as it dissipates a proton gradient, and in the opposite direction as it catalyses the hydrolysis of ATP.[22] Although these processes are chemically unrelated, as the ratchet is strongly coupled to the energy source,[14] driving the ATPase part of the motor backwards (through the proton gradient providing a sufficiently strong driving force) forces the endergonic synthesis of ATP.[22] The motion of ATP synthase allows spatial coupling of processes that occur in different domains of the molecular machine, while enabling transduction of energy from the proton gradient into chemical energy. Motion in fatty acid synthase[59] is also used as a mediator, transducing energy from ATP hydrolysis and reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidation to achieve the selectivity required to synthesise the desired fatty acid over various statistically possible alternative products.[60]

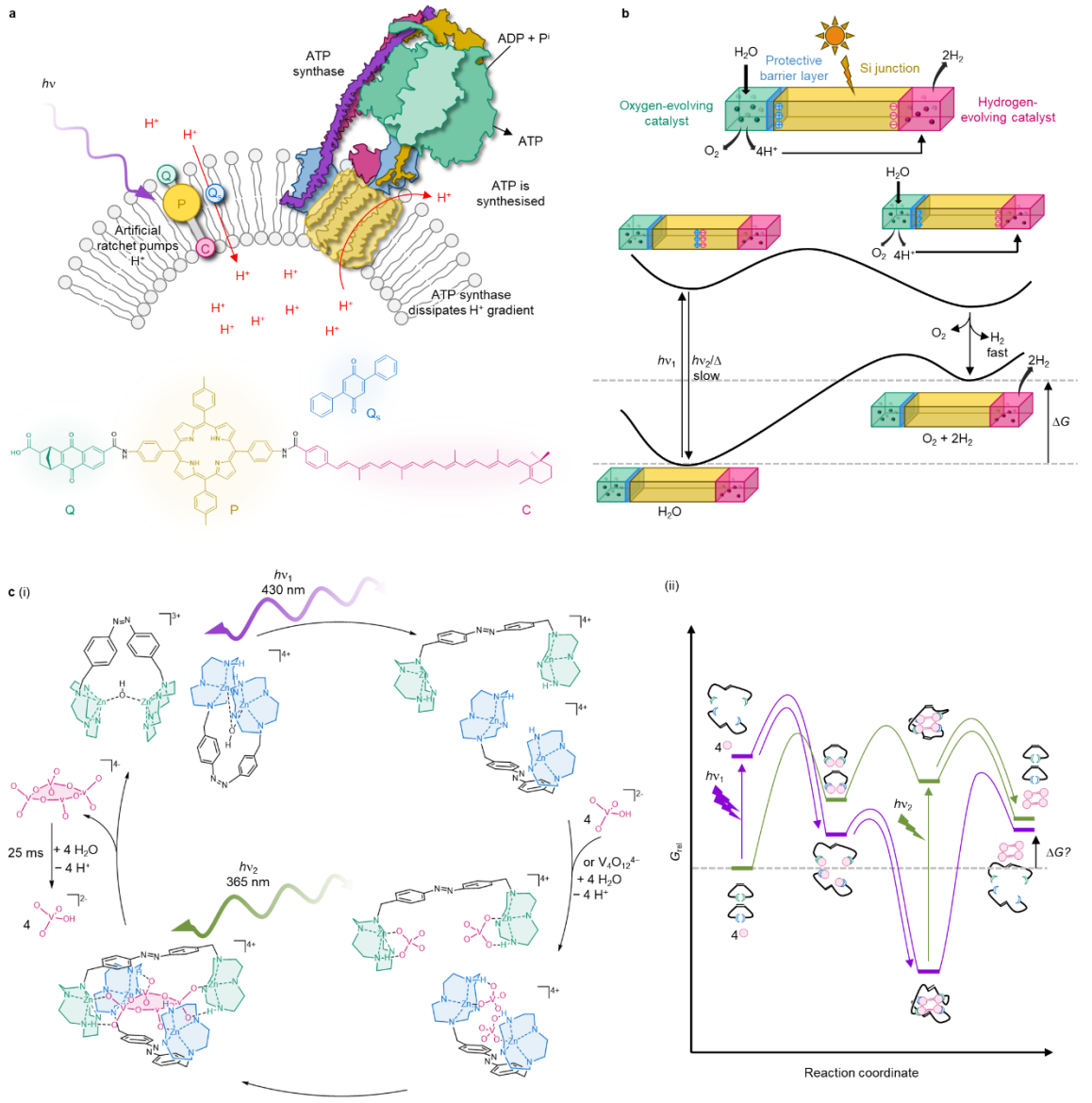


Figure 4| **Ratchets in endergonic synthesis. a**, Gust and Moore used their light-driven artificial proton pump[222] to generate a transmembrane proton gradient, which was dissipated to drive ATP synthase and thus synthesise ATP through the transduction of light energy into chemical energy.[223] **b**, Nocera's artificial leaf is powered by light to split water into O_2 and H_2.[139–141] Irradiation of a silicon junction forms pairs of electrons and holes that migrate to different ends of the device where electrons are used to oxidise water to O_2 and H^+, while the holes reduce H^+ to H_2. **c**, Herges attempt to create a molecular synthesiser to drive the formation of tetravanadate ions when powered by light.[83] The synthesisers template tetravanadate formation when in the *E*-form, making this the system energy minimum (purple energy profile). Switching the synthesiser to the *Z*-form was envisaged to expel tetravanadate from the template, increasing its concentration above the expected equilibrium value (green energy profile). However, this energy profile is speculative and was not probed experimentally.

Artificial photosynthesis

Gust and Moore developed[222] an artificial light-driven proton pump inspired by biological electron transport chains (Fig. 4a). Photoexcitation of the directionally membrane-embedded pump results

in excitation to a diradical charge-separated state, creating an excited state with spatially separated redox potentials. Radical recombination is most efficiently accomplished by the transfer of a proton from the exterior of the membrane to the interior by a freely diffusing quinone (Q_S, blue, Fig. 4a), which pumps a transmembrane proton gradient through a light-driven ratchet mechanism. This gradient may then be dissipated by ATP synthase, resulting in autonomous semi-artificial endergonic ATP synthesis driven by light.[223] Gust and Moore's light driven ATP synthesis is a rudimentary version of what biology achieves through photosynthesis.[50]

One of the most investigated examples of artificial endergonic synthesis is photocatalytic water splitting. This is exemplified by Nocera's 'artificial leaf' technology,[139–141] which seeks to emulate the structures involved in the water oxidation phase of photosynthesis, where the incoming light energy is first transduced (Fig. 4b).[50] In the artificial leaf process, low chemical potential water is split into a high chemical potential mixture of hydrogen and oxygen. Although structurally this solid-state device may appear very different to solution-phase molecular ratchets,[5–9] its ratchet mechanism is clearly identifiable (Fig. 4b). Photo-irradiation causes charge separation in a silicon junction (yellow) which relaxes within the photoexcited state as the electrons and holes migrate directionally to opposite sides of the device (determined by the p/n doping of the silicon).[139] Once electron and hole pairs are separated, the most expedient way for the device to return to the ground state is for the holes to oxidise water at the oxygen-evolving catalyst (green) and for the electrons to reduce protons at the hydrogen-evolving catalyst (pink). Oxygen and hydrogen are evolved as gases, further driving the cycle. As the device is not a single molecule, multiple cycles occur contemporaneously so that the process appears continuous. However, just as with solution-phase ratchets, kinetic control of the dissipating excited state is used to perform work,[5,6] here in the form of splitting water into oxygen and hydrogen.

Endergonic synthesis with artificial molecular machines

Despite the use of molecular dynamics to couple an endergonic reaction to an energy source by ATP synthase,[22] to date there has only been one explicit attempt to use an artificial small-molecule machine to synthesise a high energy product in a comparable catalytic manner. Herges linked[83] two Zn^{2+}-based vanadate-binding units via an azobenzene photoswitch, which could be photoisomerized to regulate the distance between them (Fig. 4c). When in the *Z*-form, the distance between the zinc centres is too small to accommodate vanadate, the complex instead binding only water. When isomerised to the *E*-isomer, however, a dimer forms out of two assemblers, stabilising the formation of a tetravanadate anion, which on its own is less stable than the respective monovanadate anions. The idea was that by switching the assembler from *E*-to-*Z* once tetravanadate had been formed, the ion would be expelled, increasing the concentration of tetravanadate in solution above what would be expected at equilibrium.[73,83] This would constitute endergonic synthesis, as the energy from light would have been transduced to form a high energy vanadate species, driving the distribution of vanadate anions out of equilibrium. The modulation of the assembler affinities for substrate binding and product release is closely related to the reasoning behind catalytic resonance in heterogenous catalysis (Fig. 3a).

Unfortunately, while the assembler-template synthesis of tetravanadate was observed, unbound tetravanadate is too short-lived under the reaction conditions to be observed experimentally. Therefore, it is impossible to tell whether the vanadate was expelled when the templating assemblers were isomerised from *E*-to-*Z*, before subsequently hydrolysing to monovanadate in solution, or whether tetravanadate was disassembled along with the template. This distinction is

important, as while the former example functions as an energy-ratchet-based endergonic synthesiser, the latter merely stabilises the bound tetravanadate species.[6] Further studies and designs are needed to distinguish between these two possibilities.

Photochemically driven artificial endergonic synthesis

Strategies for endergonic synthesis that do not rely on ratcheted conformational changes have also been explored. MacMillan[108–110] (Fig. 3b(i)), Baran,[111,112] and others[113–132] have coupled photochemical and electrochemical energy inputs to chemical synthesis, relying on transitions between ground state and excited state energy surfaces, as opposed to mechanical/conformational changes (see section on Endergonic synthesis with artificial molecular machines). Access to an excited state can be used to overcome a slow step in a catalytic cycle,[108–110] but transitioning between different energy surfaces can also be used to perform an endergonic reaction (Fig. 5a).[98,99] This process is similar to Feringa's overcrowded alkene motors (Fig. 3b(ii)),[30,31] which exploit a similar change in energy profile to achieve photoinduced directional rotation.[224] Various groups have demonstrated endergonic syntheses in a mechanistically similar manner,[114,124] harnessing light-fuelled ratchet mechanisms to make,[116,117] break,[118] and isomerise[115,119–123] chemical bonds (Fig. 5b). These ratchet mechanisms have been used to perform up to 60 kJ mol^{-1} of chemical work,[116] double that required for the synthesis of ATP from adenosine diphosphate (ADP) and phosphate *in vivo*,[225] albeit with a thermodynamic efficiency[14] significantly lower than ATP synthase. The 'uphill' nature of these processes is well-established[114,124] and Knowles has noted[118] that such mechanisms are analogous to the ratchet mechanisms used to design[5] molecular machines.

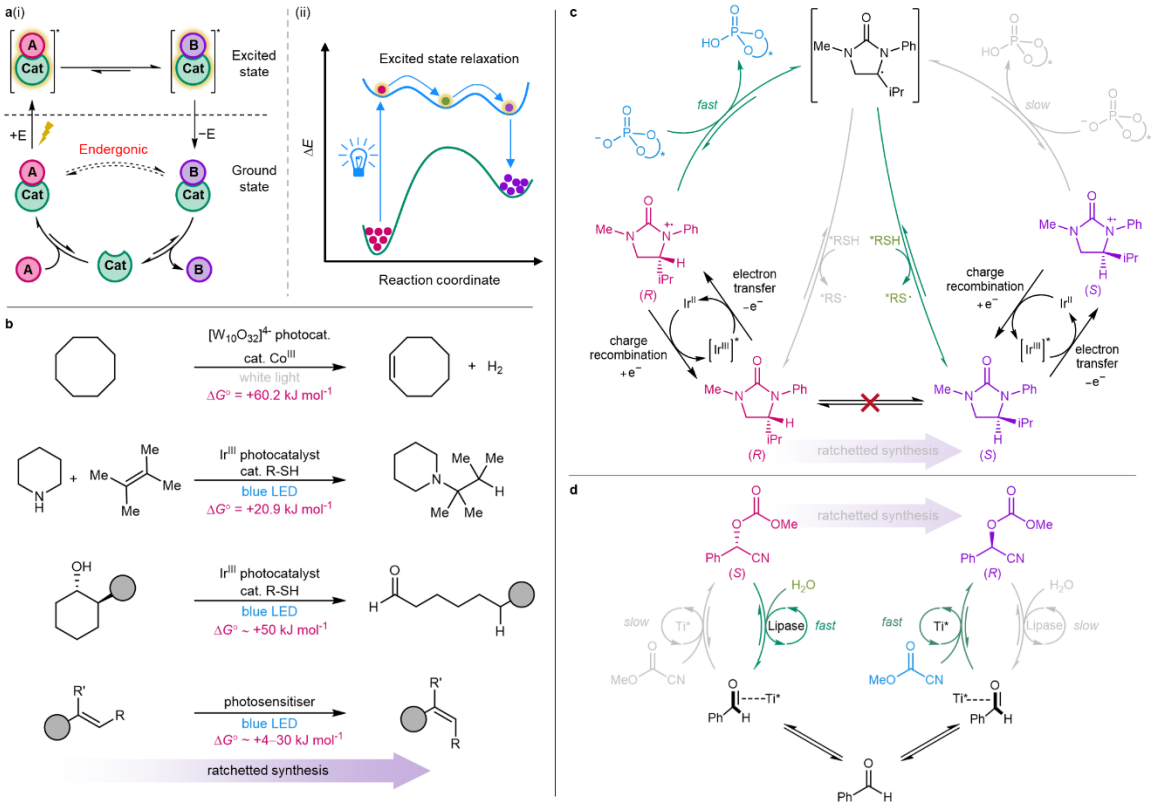


Figure 5| **Endergonic synthesis in synthetic methodology. a**, General scheme of endergonic synthesis by accessing excited energy states, e.g. by photoexcitation (i) A catalytic cycle for the conversion of A⟶B cannot proceed due to an endergonic step. Excitation of the catalytic intermediate preceding the endergonic allows access to an excited state, where the conversion of A⟶B can readily occur. Relaxation results in the endergonic formation of B. (ii) General energy landscape for photochemically driven endergonic synthesis. Excitation is followed by excited state relaxation and subsequent relaxation to the ground state for form the endergonic product. **b**, Selected examples of photochemically driven endergonic oxidation, addition, ring-opening and isomerisation reactions.[114] **c**, Knowles's photochemically driven deracemization.[129] Iridium photoredox catalysis creates a nitrogen-centred radical cation. Enantioselective deprotonation with a chiral phosphine base (blue) forms an sp^2 carbon-centred radical (black), which selectively abstracts a hydrogen atom from a chiral thiol (light green) to regenerate the ground state molecule. Differences in rates of the two enantioselective reactions (deprotonation and hydrogen atom abstraction) result in kinetic asymmetry in the overall cycle, kinetically driving the endergonic deracemization. **d**, Moberg's minor enantiomer recycling[133–137] improves the enantiomeric excess of a titanium-catalysed enantioselective cyanation of a prochiral aldehyde by recycling the incorrect enantiomer through a kinetic proofreading process. The incorrect cyanohydrin (pink) is enantioselectively hydrolysed by a lipase to re-form the aldehyde, which can subsequently enter the cycle to enantioselectively form the desired enantiomer (purple), driving the deracimisation through kinetic asymmetry.

Kinetic proofreading, deracemization, and minor enantiomer recycling

Oxidative phosphorylation (particularly required for respiration) and photosynthesis are prominent examples of ratchet-driven endergonic synthesis in organisms.[50] However, almost all biological processes involve the input of energy at some level. High-fidelity replication of information polymers requires an energy input to prevent sequence scrambling as a result of entropy (see section on Programmable and sequence-specific synthesis). In addition to biasing sequence fidelity using ratchet-based polymerases (Fig. 2a),[55,57] biology uses error checking mechanisms. Topoisomerases[226] and the exonuclease domain of DNA polymerases are able to recognise 'incorrect' structures and kinetically promote a reaction that leads to their removal or

repair, a process termed kinetic proofreading[227] (Fig. 2e(iii)). These ratchets perform endergonic synthesis by ensuring a replication accuracy significantly greater than would otherwise be possible. Although a significant amount of energy is wasted in futile cycles (proofreading the correct sequence also costs energy),[227] such a mechanism is fundamentally necessary for high-specificity genetic heredity[228] and to avoid death by error-catastrophe,[229] highlighted by the ubiquity of kinetic proofreading in all forms of life.[227]

A basic form of kinetic proofreading is apparent in synthetic deracemization reactions.[123–132] Deracemization reactions are a form of endergonic synthesis, converting a lower energy, equilibrium mixture (the racemate) to a higher energy (enantio-enriched) form, mediated by a catalyst and driven by an external energy source. Knowles,[129] Bach,[128] and others[114,123,124,131] have demonstrated a number of photoderacemizations. In a typical example (Fig. 5c),[129] photo-induced single electron transfer promotes a chiral molecule to an excited radical cation state. Deprotonation by a phosphate generates an achiral radical intermediate, which can regenerate the chiral starting material by the transfer of a hydrogen atom from a thiol. If a chiral phosphate and chiral thiol are appropriately matched, chemical gating can be introduced to kinetically drive the molecule towards a single enantiomer through a doubly kinetically gated[37] information ratchet mechanism. Thus, the molecule is effectively kinetically pumped from one enantiomer to the other, with relaxation to the ground state kinetically trapping the steady state distribution. The ratio of enantiomers is determined by kinetic asymmetry arising from chemical gating in the deprotonation and hydrogen atom transfer steps. The phosphate and thiol act as fuels,[14] which are continuously regenerated by the energy input from light. Knowles has noted[118] that such deracemizations must be driven by the same type of ratchet mechanisms introduced to drive molecular machinery. Indeed, the deracemization (kinetically driven by different reaction rates of enantiomers, in the case of deracemization, or enantiomeric conformations in the case of a rotary motor) mirrors the chemically fuelled operation of the rotary molecular motor shown in Fig. 3e.[27]

The deracemization principle has been adapted and extended by Moberg,[133–137] who developed the concept of minor enantiomer recycling to increase the enantiomeric excess of stereoselective reactions (Fig. 5d). Following an enantioselective reaction, the undesired enantiomer reacts faster with an additional reagent to re-enter the catalytic cycle, allowing it to be converted to the desired enantiomer. In this case, the energy input is provided by additional chemical reagents, which again essentially act as chemical fuels for the deracemization process (a chemical fuel is a species where the energy released from a fuel-to-waste reaction is used to drive a different process[14,19]), while kinetic asymmetry is introduced through chiral catalysts. Moberg has explicitly recognised the governing principle of microscopic reversibility for understanding such reaction networks,[137,230] which map perfectly to the chemical engine cycle of ratchet-driven processes.[14,19] This complex ratcheted synthesis, which consumes chemical energy to recycle the 'incorrect' product, is conceptually directly related to the kinetic proofreading carried out by biological polymerases.[55–58]

Programmable and Sequence-Specific Synthesis

The programming of reactions to occur in a specific order, or the assembly of different building blocks in a sequence-specific manner, is fundamental to biology.[53–60] This energetically-demanding process requires the use of ratchet mechanisms to process an information and energy input to override the native thermodynamic and kinetic preferences of a reaction in order to form

a non-statically defined distribution of products. Almost all proteins are made from just twenty-two canonical amino acids, while the instructions for their sequences are encoded in the order in which any of the four nucleotides appear in a DNA/messenger RNA (mRNA) strand.[231,232] While complementary base pairing provides a thermodynamic statistical bias to synthesise the correct protein sequence from an RNA template, this passive approach alone is insufficiently accurate.[227,229] Biology instead employs ratchet mechanisms for information processing, rather than relying on a purely thermodynamic preference for the correct sequence.[54,56,58,60,226,227] Additionally, error checks are actively made on sequences as they are written,[227] expending energy in order to ensure writing fidelity is maintained through ratchet-based kinetic proofreading (see section on kinetic proofreading, deracemization, and minor enantiomer recycling).

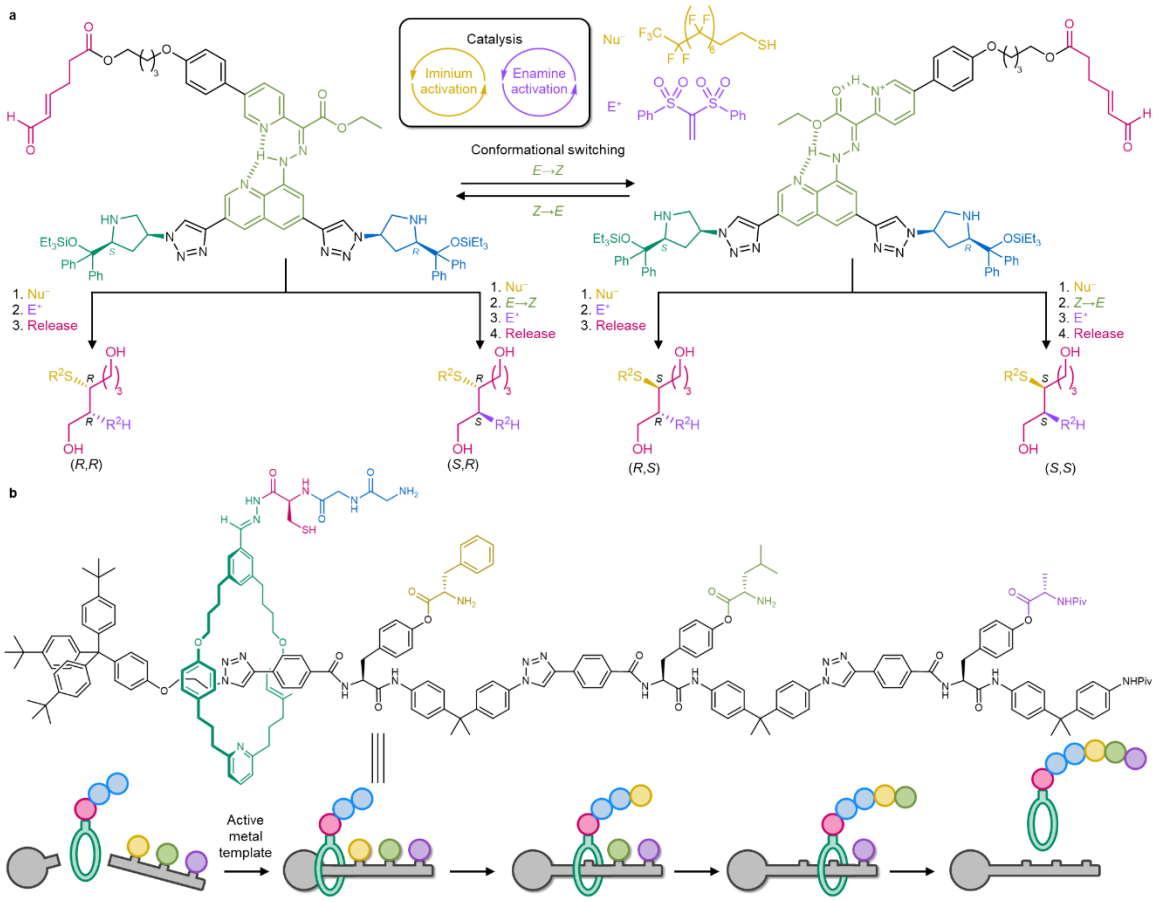


Figure 6| **Small-molecule machines for programmable synthesis. a**, Leigh's programmable synthesis machine.[82] Acid/base is used to control the orientation of a hydrazone switch, which positions a substrate close to one of two oppositely-handed proline-based organocatalysts for a tandem iminium/enamine reaction. Inputting a different series of operations allows controlled access to all four possible diastereomers of the product. **b**, Leigh's rotaxane-based pre-programmed synthesiser.[76] The rotaxane is threaded using an active metal template approach,[237] which traps the macrocycle in a high energy (low entropy) state. The macrocycle has an appended cysteine residue, which allows it to pick up and add the amino esters to its peptide chain through native chemical ligation,[238] thereby removing a barrier to macrocycle shuttling and allowing access to the subsequent residue. The macrocycle can move along the thread, driven by the increasing entropy as each new compartment is accessed, picking up each amino ester in turn to create a predetermined polypeptide sequence. Once the last barrier is added to the chain, the macrocycle dethreads, providing an entropic driving force for the process.

The archetypal example of a biomolecular ratchet performing programmable synthesis is the ribosome,[53,54] which reads the information encoded in a strand of mRNA and translates it into the corresponding peptide sequence. Complementary base pairing between codons on the information bearing mRNA strand and the cargo-carrying transfer RNA (tRNA) allows accurate addition of the correct amino acid residue to the growing chain. Once an amino acid has been added, the ribosome then moves directionally along the template thread in quantized steps. Similarly, DNA and RNA polymerases[55–58] interpret the information contained in a DNA/RNA strand to transcribe it, with complementary base pairing between an activated monomer (a nucleoside triphosphate) and the template thread again driving recognition. Once the correct nucleotide has been added, the polymerase then moves directionally to the next position on the template. Both the ribosome and DNA/RNA polymerases are promiscuous, able to synthesise practically any sequence they encounter, and contain in-built error-checking mechanisms, kinetically favouring the replacement of the incorrect monomer (Fig. 2e(iii)).[54,56,58] Like many rudimentary artificial molecular machines, the ribosome and DNA/RNA polymerases take advantage of pseudo-mechanically interlocked structures[5,9] to ensure processivity, aiding the reading of the input strand sequence in the correct order.

While the ribosome and polymerases are programmable, in that they can be instructed to synthesise a particular sequence, there are other biomolecular machines that perform sequence-specific synthesis based on information inherent to their own structure. One such example is fatty acid synthase,[59] a super enzyme complex that predominantly synthesises a single type of fatty acid (the 16-carbon palmitate). Fatty acid synthase carries out a set series of six reactions, mediated by transport of the substrate around different active sites. The growing fatty acid cargo stochastically samples all of the catalytic sites, with kinetic gating inducing a kinetic preference for reactions at the correct site, so that steps occur in the correct order.[60] This energetically demanding process enables the growth of the fatty acid in a defined sequence, extending the chain by two carbons each time. Elongation stops when the growing chain becomes too big for the reaction channel.[233] In combination with the kinetic control of the reaction sequence, the enzyme contains the full set of synthetic instructions within its own structure. While this strategy is less versatile than the more generally programmable molecular synthesisers,[53–58] it represents a robust and reliable strategy for performing complex reaction cascades, with individual machines/catalysts having structures specialized at producing their intended product.

Both programmable[53–58] and non-programmable[59,60] sequence-specific synthesis requires an information input, whether from an instruction strand or built into the structure of the synthesiser, which is then translated into the product. Translating or copying information is an energetically demanding process (as entropy drives scrambling of information),[21,232] with the ratchet mechanism helping to ensure fidelity by kinetically controlling the desired output, overriding the native thermodynamic and kinetic preferences of a reaction. This differs from simple reaction cascades, where the structure of the substrates controls the reaction outcome through conventional kinetic or thermodynamic control (Fig. 1a). The first steps have been taken along the path to ultimately create artificial molecular machines that perform synthesis in a comparable manner.[73–84] The early generations of such systems fall well-short of matching the functional complexity and synthetic ability of biomolecular machines.[5,22,53–59] Nevertheless, ratchet-like elements have been incorporated within their mechanisms.

Small-molecule programmable synthesisers

The Leigh group have reported a programmable molecular machine capable of performing stereodivergent synthesis (Fig. 6a).[82] By changing the sequence of chemical inputs, the machine changes the configuration of a hydrazone rotary switch in order to move a substrate between two chiral organocatalytic sites of opposite handedness, in a process reminiscent of substrate transport by fatty acid synthase (Fig. 2c).[58,59] Consequently, the enantioselectivity of iminium-enamine mediated reactions could be selectively programmed to favour any one of four possible diastereomeric products. The machine builds on an earlier small-molecule robotic transporter,[234] which uses an energy ratchet mechanism to move a cargo directionally between sites on a track, akin to a molecular walker.[235] Inputs of acid and base switch the transporter between different energy surfaces to control the directional transport of the molecular cargo. This mode of operation is mirrored in the stereodivergent synthesis machine[82] (Fig. 6a), where acid/base switching kinetically defines each step of the reaction pathway by moving the substrate into close proximity to the organocatalytic site of the required handedness for each particular step.

Although the movement of the substrate between multiple active sites is reminiscent of fatty acid synthase,[60] unlike fatty acid synthase the artificial molecular machine can be externally programmed (by adding acid/base in different orders) to produce different products, a feature associated with the ribosome and polymerases.[54,56,58] Programmable synthesis in biology must be performed autonomously, which generally requires an information ratchet mechanism,[5] while the first generation artificial molecular machine[82] controls stereodivergent synthesis through step-wise manipulations as part of an energy ratchet mechanism.

Finding ways to program the assembly of building blocks in a specified order leads to the generation of sequence-specific oligomers and polymers,[53–58] allowing the encoding of information.[231,232,236] The Leigh group have described a series of rotaxane-based machines that synthesises oligomeric peptides[76–79,81] (and other types of monomer[80]) with a predetermined sequence (Fig. 6b). The machines typically feature a cysteine-derivatised macrocycle, threaded onto a rigid track (through active template synthesis[237]) that features a series of amino acid phenolic ester barriers in a particular sequence.

Under the conditions of machine operation, when the macrocycle encounters a barrier, the amino acid residue is removed from the track (by formation of a thioester with the cysteine residue appended to the macrocycle) and then transferred onto the *N*-terminus of the growing oligomer chain through native chemical ligation.[238] The removal of the barrier allows access to more of the track (and thus the next amino acid) and the transfer of the acyl group to the oligomer regenerates the nucleophilic cysteine thiol group for native chemical ligation of the next barrier. Once all of the barriers have been removed, the macrocycle dethreads and the sequence of the new oligomer can be read by tandem mass spectrometry. Iterations of such machines have demonstrated the sequence-specific synthesis of β-amino acids,[78] the use of Wittig chemistry to form sequence oligomers connected by C=C bonds,[80] the tandem operation of two machines in the same reaction vessel,[81] and the machine-mediated assembly of a polyleucine oligomer of narrow polydispersity that spontaneously folds to form an asymmetric epoxidation catalyst.[79]

The rotaxane architecture of these artificial molecular machines is crucial to their function. Like the ribosome[53,54] and DNA/RNA polymerases,[55–58] the mechanically interlocked structure ensures processivity, as the macrocycle is unable to dissociate from the thread to bind to and add monomers out of sequence. However, processivity alone is insufficient for sequence-specific synthesis[239,240] as the sequence must be 'read' directionally for the transformations to proceed in the correct order.[241,242] The dynamics in these artificial machines are not (yet) directionally ratcheted as they are in their biological counterparts. Rather, assembly of the rotaxane structure uses kinetic control of active metal template synthesis[237] to trap the macrocycle on a short section of the thread. Removing the barriers allows the macrocycle to access more of the thread (and eventually to dissociate), providing an entropic driving force that is, in part, transduced into sequence information.[21,68,69] Despite not operating repetitively, the raising of the macrocycle energy followed by directional relaxation is reminiscent of the balance breaking and power stroke steps of energy ratcheting.[5] Another issue with these early generations of artificial molecular synthesisers is that by removing each building block from the track, the original information encoded in the strand is destroyed once it is translated elsewhere. However, the directional non-destructive 'reading' of a sequence of stereochemical information encoded in a strand was recently achieved in a rotaxane system.[241] Coupling of such a ratcheting system to a 'writing' process (i.e. sequence-specific synthesis) would achieve the translating of sequence information encoded on a synthetic molecular strand, in a manner reminiscent of biomolecular machinery but in a wholly artificial system.

Despite the proven utility of solid-phase peptide synthesis (especially when automated), as with the artificial programmable stereodivergent synthesiser, this mechanism renders it fundamentally incompatible with a general multi-component system. A more complex and life-like 'systems chemistry' approach[2,243] must rely on the autonomous operation of each component so that, just as in biological cells, sophisticated system-level behaviour can be performed under the same global conditions. The advantage of autonomous operation in complex systems has been demonstrated by operating two differently programmed rotaxane-based synthesisers in tandem,[81] which each independently generate a specific sequence.

Oligonucleotide-based programmable synthesisers

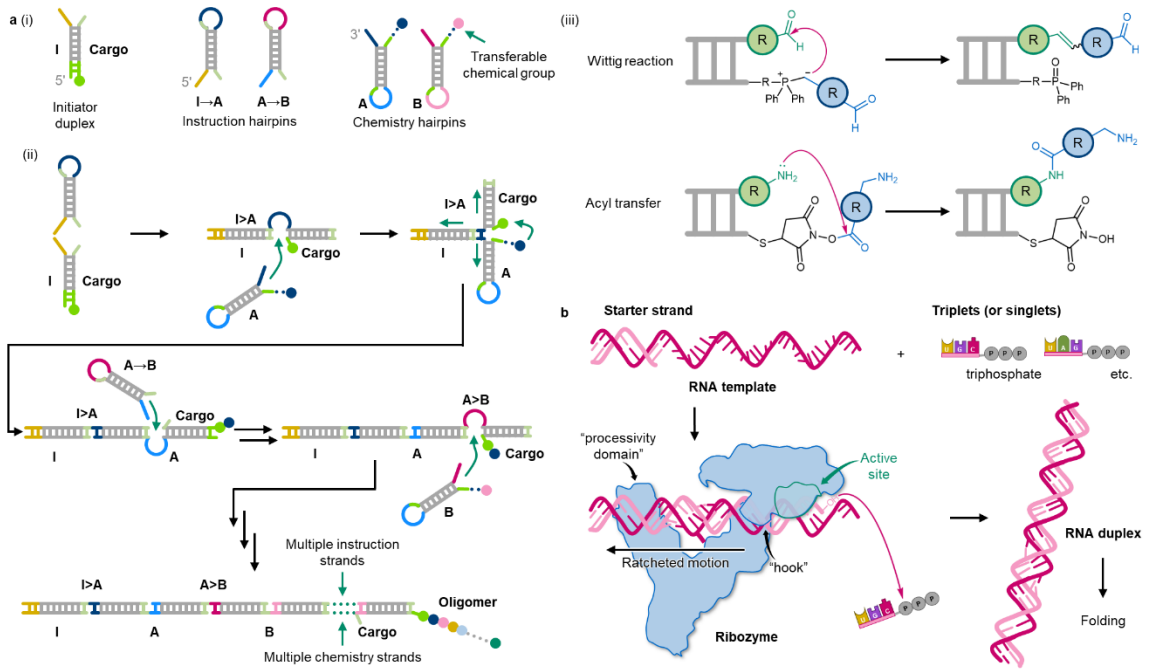


Figure 7| **Oligonucleotide-based sequence-programmable synthesis. a**, Turberfield and O'Reilly's DNA-based autonomous synthesiser.[84] (i) The instructions for the synthesis are programmed onto DNA hairpin strands, including the initiator, instruction hairpins (which contain sequence information), and chemistry hairpins (which carry reactive monomers). The order of monomer addition is determined by the series of unsatisfied complimentary toeholds and regions of DNA hidden in the fold of each hairpin (shown as matching colours). (ii) Toehold mediated strand displacement[248] between the initiator strand and the first instruction hairpin reveals a section of unpaired DNA complementary to the toehold on the first chemistry strand (both dark blue), which is inserted by a second toehold-mediated strand displacement. This brings the cargo (green) and the transferable group close enough to react, revealing the next unpaired region for the complementary toehold of the second instruction hairpin. These steps are repeated until the sequence is terminated, or until reagents run out if repeating instructions are used. (iii) The synthesiser has been used for both Wittig chemistry and polypeptide formation. **b**, An artificial ribozyme, which can synthesise an RNA sequence complementary to a template strand.[95] The ribozyme moves directionally along the template strand and extends a short complementary starter strand by catalysing the reaction of the terminal alcohol with the 'correct' activated nucleobase triplet. A 'hook' creates a pseudo-mechanically interlocked structure around the active site, which ensures processivity, while another region of the ribozyme is proposed to act as a 'processivity domain' guiding directional ratcheting.

The complexity of artificial small-molecule machines, such as those in the previous section, often means that their construction requires lengthy synthetic schemes.[76–82] This difficulty is circumvented by DNA nanotechnology, where the synthesis of artificial structures is routinely carried out by commercial automated DNA synthesis. The highly specific and predictable nature of DNA/RNA base pairing allows very large structures to be produced[244] that fold with high fidelity using techniques such as DNA origami.[245] This has been explored in numerous DNA motors,[32] walkers (linear motors)[246] and in the field of DNA computing.[247] Drawbacks of this approach include that DNA molecular machines generally need to be as big or even bigger than motor proteins (small-molecule machines are typically ~1/1000th of the size by volume/mass) and that DNA is more limited in terms of chemical functionality and compatibility than wholly artificial small-molecule systems.

The groups of Turberfield and O'Reilly have developed an oligonucleotide-based system that performs sequence-specific synthesis (Fig. 7a).[84] Information is encoded through instruction hairpins, which kinetically gate binding of the correct monomer, and chemistry hairpins, which carry a specific monomer as a cargo (Fig. 7a(i)). A series of toehold-mediated strand displacements first bind the correct instruction hairpin, followed by the correct cargo, and finally bring each monomer in sufficiently close proximity to the end of the growing oligomer to promote their reaction (Fig. 7a(ii)). Toehold-mediated strand displacement is exergonic[248] and thus acts as the necessary energy input[14] to translate the sequence information. The order is encoded into the nucleotide sequence, with base pairing between different regions of the instruction and chemistry hairpins defining a series of reactions that can either be terminated at a defined point or cycled indefinitely. The DNA-based synthesiser has been used to perform both amidation reactions and Wittig chemistry (Fig. 7a(iii)).[84] The ratchet mechanism of the design leads to progressive, processive and repetitive reactions performed in a specified order.

As with the small-molecule track-based synthesisers (Fig. 6b),[76–81] information translation is destructive, as each input hairpin is incorporated into a growing duplex 'waste' strand. Each instruction and chemistry hairpin are required to be sufficiently large to drive toehold-mediated strand displacement and affect high-fidelity recognition. As such, the synthesiser suffers from poor atom economy and is reminiscent of the 'burnt bridges' walker mechanisms[5] commonly employed in DNA nanotechnology.[246] Structurally pre-programming the order of reactions quickly becomes unwieldy, with the number of unique structures required scaling linearly with polymer length, leading to high levels of complexity and waste even for small to medium length sequences. Thus it becomes more efficient to read the instruction on an input strand with a promiscuous ratchet such as the ribosome.

An RNA-based catalyst (a ribozyme) capable of replicating a template RNA strand is fundamental to the RNA world theory.[249] Given a ready supply of nucleoside triphosphates, this ribozyme is posited to have been one of life's first molecular machines. The vestiges of this chemistry may remain in the ribosome, which contains solely RNA (and thus no proteins) in the immediate vicinity of its active site.[250] Lost to the evolutionary past, however, studies into the RNA world have focussed on synthetic ribozymes.[85–95]

In the early 1990s, an RNA sequence was isolated from a random pool and shown to be a catalyst for the ligation of two non-specific RNA strands.[85] Over the next decade, directed evolution of this sequence led to ribozyme catalysts capable of extending a non-specific RNA template with high fidelity by up to 14 nucleotides, using nucleoside triphosphates as a fuel.[86–95] Directed evolution has led to artificial ribozymes that are highly effective polymerases, with one example capable of replicating non-specific templates of a greater length (206 nucleotides) than itself (202 nucleotides),[92] with potential implications for the Eigen paradox and the origin of life.[216,228] Artificial ribozyme polymerases have been shown to be capable of synthesising other catalytically active ribozymes,[90,91] synthesising their own building blocks[94] (which may then, separately, spontaneously self-assemble[93]), and demonstrating polymerase activity with trinucleoside triphosphates.[94] A primitive self-replicating ribozyme functioning by an A + B mechanism has also been created,[89] yet self-replication by single-nucleotide strand extension still remains an elusive goal in this field.

Averaging around ~60,000 Da,[92] these artificial polymerase ribozymes are large and complex molecular structures (although only ~2% of the size of the ribosome).[53] As such, elucidating the mechanisms through which they operate is challenging. Regions conserved, lost, or added during

directed evolution, and recently X-ray[90,92] and electron diffraction structures,[95] have allowed the function of particular regions of the ribozyme to be inferred. However, due to their ability to transduce chemical energy (from nucleoside triphosphate hydrolysis) to generate information, to move directionally along a strand, and catalyse reactions repetitively and processively, these ribozymes clearly function by an information ratchet mechanism.[5] Diffraction studies reveal a semi-interlocked active site, with an exterior processivity domain that may be responsible for ratcheting the catalyst along the thread.[92] Both features are reminiscent of biological polymerases (Fig. 2b).[55–58]

Conclusions/Outlook

While general programmable synthesis by artificial nanoscale machines[82,251,252] remains elusive, biology performs atomically precise synthesis aided by ratchet mechanisms.[22,54,56,58,60] As chemical reactions are stochastic processes,[20,46–48] the exploitation of Brownian ratchets can control reaction outcomes irrespective of the thermodynamic or kinetic preference of a 1D reaction coordinate, mirroring Parrondo's paradox[45] in which controlled switching between two losing games can produce an overall winning outcome. This Review has sought to bring together various recognised, and some previously unrecognised, examples of ratchet mechanisms in synthesis, together with summaries of how molecular synthesisers transduce energy through ratchet mechanisms to control synthesis in biology. Our goal has been to provide an explanation of how ratcheting works, how it is different to conventional kinetic and thermodynamic control of chemical reactions, and how going forward it can be useful for chemical synthesis.

Increasingly, different fields are converging on the use of (what turn out to be) ratchet mechanisms to solve what might superficially appear to be unrelated challenges in synthesis. While a ratcheting strategy may be a logical extension from a 'molecular machines'[5] perspective (e.g. artificial small-molecule synthesisers (Fig. 6)),[76–83] in other areas they have been found as a mechanistic solution to particular problems. Ratchets mechanisms are evident in photovoltaics (Fig. 4b),[138–146] and in heterogeneous catalytic resonance, where they allow the Sabatier limit to be exceeded (Fig. 3a).[96–107] In synthetic methodology,[108–137] ratchet mechanisms enable endergonic synthesis[118] and unfavourable steps in catalytic cycles to be overcome (Fig. 3b(i) and 5).[108–114] The diversity of perspectives from different fields is valuable, and mirrors the early development of molecular motors, where Kelly's explicit quest for a molecular ratchet[253,254] contrasted with Feringa's serendipitous discovery of a motor when developing chiroptical switches.[30,255] The subsequent translation of the physics literature by Astumian and the Leigh group into fundamental design principles for molecular ratchets[5,17,18,23-25,28,35,36,66,68] has driven the understanding of ratchet mechanisms for chemistry. In a similar manner, an understanding based on the physics and physical chemistry of ratcheted synthesis may help establish new and general design principles in synthetic methodology, which could prove transformative for various processes in synthesis.

Some intriguing questions can already be considered. It is striking that many artificial systems described in this review use light to access excited states in order to freely traverse potential energy surfaces and transduce energy.[108–110,113–132] In contrast, biological synthesising machines make extensive use of conformational dynamics,[22,54–60] either between components to dictate the sequence of reactions,[59,60] or as a convenient way of transducing energy from one form to

another.[22] Employing movement to transduce energy, rather than accessing excited potential energy surfaces, may simply relate to the limited availability of light in biology or to other factors such as increased efficiency and the problems of excited state degradation pathways.[14,250] Paralleling the way that turbines are used as an intermediary between heat gradients and electrical energy on the macroscopic scale, biology may have evolved to harness movement as the key mediator between different forms of energy. The ability of movement to influence, and to be influenced by, different forms of energy may also have been crucial to the evolution of biological ratchets and life on earth.[216–218] Evolutionary selection of simple dynamic catalysts may have chanced upon mutations leading to directional motion, and subsequently the emergence of life's first functional molecular machines.[27]

A number of challenges remain in the growing use of ratchets for synthesis. Firstly, progress has occurred across a broad range of largely unrelated fields, and as such chemists have yet to develop general principles for the transduction of different energy sources to drive synthesis. We hope that this review helps towards this goal by highlighting the underlying theory and through the use of a consistent terminology across the various fields. Secondly, ratcheting necessarily increases the complexity of the reaction pathway, which may hinder mechanistic elucidation (and subsequent reaction development) in already complicated systems. Thirdly, the efficiency of energy transduction in artificial ratchets is typically very low,[14] and consequently the development of strongly coupled ratchets, which can perform synthesis in the same manner as ATP synthase,[19] remains a key goal for the field. Advances in artificial molecular machinery are leading to improved control over molecular motion,[5–9,14] which may soon enable the biomimetic use of conformational dynamics as an efficient energy transducer. Finally, high-fidelity programmable synthesis may require ratchets with complexities beyond the limit of those currently synthetically achievable. Ultimately, however, the use of ratchet mechanisms will lead to increased levels of control over reaction outcomes, novel synthetic methods, better selectivity, faster reaction rates, and higher synthetic efficiencies—fundamentally changing the way chemists think about and carry out synthesis.

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Author contributions

All authors contributed equally to the preparation of this manuscript.

Competing interests statement

The authors declare no competing interests.

Glossary terms

Brownian ratchet – A mechanism for rectifying stochastic motion on an asymmetric potential energy surface in response to an energy input.

Catalytic resonance – The exploitation of periodic changes in binding energy to enhance the rate and control the outcome of heterogeneous catalysed reactions.

Catalyst dynamics – Consequential conformational changes in a catalyst that occur during the catalytic cycle.

Chemical engine cycle – Catalytic cycle for the fuel-to-waste reaction encompassing different chemical and orthogonal dynamic (e.g. mechanical) states of a molecular ratchet.

Chemical fuel – The reactants in a fuel-to-waste reaction that release free energy that is transduced to drive a nonequilibrium process, either continuously (via an information ratchet mechanism) or through pulsed or sequential operations (often via an energy ratchet mechanism).

Endergonic synthesis – The synthesis of a molecule that, under the reaction conditions, has a more positive free-energy (higher chemical potential) than the starting materials.

Energy ratchet – A Brownian ratchet that transitions between two (or more) potential energy surfaces allowing a particle to relax directionally to a local minimum, driving the system away from the global equilibrium.

Fuel-to-waste reaction – The exergonic (i.e. free-energy-releasing) conversion of chemical fuel into waste products that provides the chemical potential gradient necessary to drive chemical systems away from equilibrium.

Information ratchet – A Brownian ratchet where differences in the rate of an energy dissipating process dependant on a stochastic process (e.g. dynamics) kinetically drive the system out of equilibrium.

Kinetic asymmetry – The overall kinetic bias in a chemical engine cycle, characterised by the ratcheting constant, K_r, which represents the number of forward cycles divided by the number of backward cycles.

Kinetic gating – The kinetic bias in a process depending on the state of a ratchet, usually represented as a ratio of rates, corresponding to the relative activation energies.

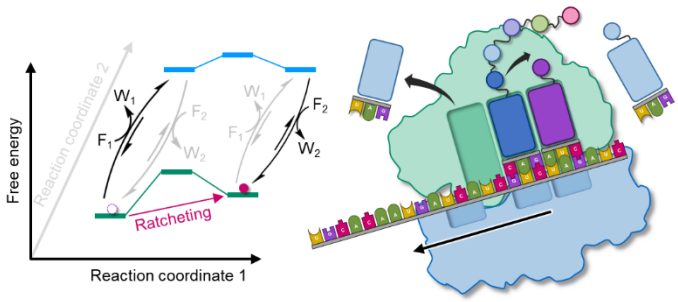
Kinetic proofreading – Kinetic selection of incorrect products for removal, resulting in selectivities exceeding the native thermodynamic preference.

Markov process – A stochastic process where the probability of an event does not depend on the history of events in the system.

Programmable synthesis – The translation of external inputs into a controlled sequence of reactions.

Ratcheted synthesis – The exploitation of a Brownian ratchet to control reaction pathways and outcomes.

Graphical abstract



Short summary

Various stochastic processes, including chemical reactions, can be driven away from—rather than towards—thermodynamic equilibrium through ratchet mechanisms. This Review explores how biology uses ratchets to achieve remarkable levels of control over synthesis, and discusses the recognition of, and early progress in, ratchet-like synthesis in artificial systems.