

Endergonic synthesis of Diels-Alder adducts enables non-equilibrium adaptive behaviors in chemical reaction networks

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Abstract: The overwhelming majority of artificial chemical reaction networks respond to stimuli relaxing towards an equilibrium state. The opposite response – moving away from equilibrium – can afford the endergonic synthesis of molecules, of which only rare examples have been reported. Here, we report six examples of Diels-Alder adducts accumulated in an endergonic process and use this strategy to realize adaptive phenomena. Indeed, systems respond to repeated occurrences of the same stimulus by increasing the amount of adduct formed, with the final network distribution depending on the number and frequency of stimuli received. Our findings indicate how endergonic processes can contribute to the transition from responsive to adaptive systems.

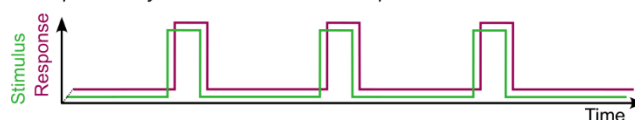
Inspired by the dynamics of living systems,^[1–3] research on soft matter systems is evolving from responsive systems to adaptive ones, a step that seems necessary to develop intelligent materials.^[2,4–6] When exposed to a chemical stimulus, responsive systems evolve towards a new equilibrium, according to Le Chatelier's principle (Figure 1a).^[5] In contrast, systems that adapt away from equilibrium can absorb energy from the stimulus, evolving against the thermodynamic drive – an endergonic process.^[7,8] The state formed upon stimulus removal depends on the ability to absorb and "store" energy from the source. As a result, a subsequent stimulus may induce a different response (as the initial point will be different), bringing the system to a new state in a path-dependent manner.^[9,10] An example of adaptive behavior is the progressive accumulation of a given high-energy species upon multiple exposures to a stimulus, illustrated in Figure 1b,c. Realizing molecular mechanisms that can give rise to such training phenomena is desirable, and has been explicitly identified as a future challenge for the development of responsive systems.^[5]

Molecular ratchet mechanisms,^[11–15] developed in the context of molecular machines, can promote endergonic processes.^[13,16–18] This area has been historically associated with interlocked molecules and light-driven systems,^[14,19] but is increasingly exploring catalytic processes to alter the behavior of small molecules and self-assembling systems.^[17,18,20,21] This approach is particularly interesting in light of the parallel with biological processes, which leverage chemical catalysis to perform elaborated functions.^[18,21,22] When catalyzed by acids, carbodiimide hydration results in the transient formation of covalent bonds,^[23–25] and this phenomenon proved versatile to

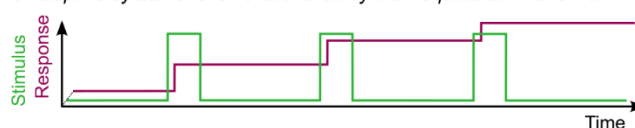
drive non-equilibrium processes, being fruitfully used in relation to both molecular machines and self-assembly.^[26–31]

Ratchet mechanisms can be designed to promote the accumulation of a certain species at concentrations not compatible with equilibrium,^[20] a process referred to as endergonic synthesis.^[18] It implies the presence of a "driving" reaction, which shifts the target "driven" reaction away from equilibrium thanks to the underlying ratchet mechanism. The reagent of the driving reaction has been often identified as a chemical fuel.^[29,32] Besides molecular machines,^[28,33–37] examples in this area are essentially limited to few deracemizations^[38–40] and mostly individual cases of dynamic-covalent reactions.^[18,41–45] Usually, such systems exploit a templating agent that is removed to afford a metastable distribution.^[42–44] In a recent example of this type, a hydrazone with catalytic properties could be over-accumulated (from 47% to 83%).^[44] During the preparation of this manuscript, a preprint presented the formation of a Diels-Alder adduct (up to 15%) with high regio- and stereoselectivity, by using carbodiimide to tether two reactants transiently.^[45]

a Responsive systems: evolve towards equilibrium



b Adaptive systems: evolve further away from equilibrium - this work



c Strategy: endergonic synthesis

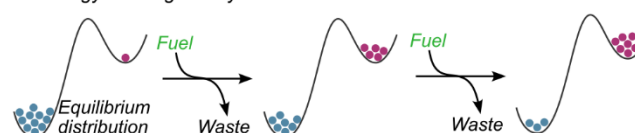


Figure 1. Illustration of the difference between how a) a responsive and b) an adaptive system respond to time-dependent changes in the amount of a chemical stimulus. c) Strategy explored to achieve adaptivity: the repeated addition of a chemical fuel progressively shifts the reaction interconverting two species represented as blue and purple dots, to over-accumulate one of them, here the purple ones.

ⁱ The term "adaptive" is used herein to describe a chemical reaction featuring progressive shifts of species distribution further away from equilibrium upon repeated additions of a chemical stimulus. Our use is consistent with ref. [5],

while we acknowledge that other uses are present in the literature, for example in ref. [4].

ⁱⁱ Version 2 of this preprint – online few days before the submission of this manuscript – includes also a 2-step adaptation experiment.

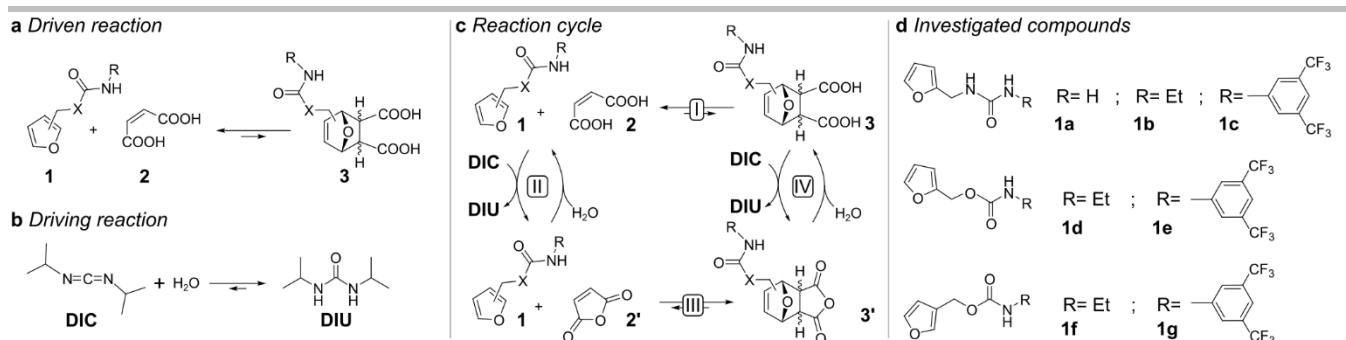


Figure 2. a) Driven reaction: the target reaction to be shifted away from equilibrium, with X and R specified for the investigated compounds in panel d. b) Driving reaction, providing energy to the system. c) Reaction cycle coupling the driven reaction **I** to the driving one – carbodiimide hydration – which can be catalyzed via either steps **II** or **IV**; the cycle is completed by reaction **III**, which is both kinetically and thermodynamically favored with respect to reaction **I**. d) Investigated compounds, in addition to 3-methylfuran (**1h**, *vide infra*).

Here, we leverage endergonic synthesis driven by chemical catalysis to realize adaptive responses in small-molecule networks. In particular, we use carbodiimide hydration to power the endergonic formation of multiple Diels-Alder adducts, producing the adaptive response illustrated in Figure 1b,c upon repeated addition of a chemical fuel.

We focused our attention on furan-based dienes of type **1** (Figure 2a), which barely react with maleic acid **2** to form only small amounts of adduct **3** under the employed experimental conditions. This is the reaction to be driven away from equilibrium. As the driving reaction we employed the hydration of *N,N*-diisopropylcarbodiimide (**DIC**) to give the corresponding urea (**DIU**, Figure 2b). Indeed, activation of acid **2** with **DIC** affords maleic anhydride **2'**, which is more activated towards Diels-Alder reactions, both kinetically and thermodynamically.^[46] The resulting reaction network is shown in Figure 2c. The change in reaction properties between steps **I** and **III** may already install a ratchet effect under alternating conditions. Yet, hydrogen bond donors in **1** may also produce kinetic differences in carbodiimide hydration and anhydride hydrolysis, steps **II** and **IV**, providing an additional information ratchet effect.^[28,47] On this ground, a screening of several derivatives bearing hydrogen bond donors brought us to focus on dienes **1a-g**, having pendant urea or carbamate moieties (Figure 2d). These compounds are readily available upon reaction of the corresponding isocyanates with aminomethylfuran or hydroxymethylfuran (see SI sections 1-3 for synthetic details). 3-methylfuran (**1h**), lacking hydrogen bond donors, was used as a control compound.

After a screening of temperatures and solvents, we selected as operating conditions a temperature of 40 °C and the mixed solvent CD₃CN:D₂O 85:15. Under this condition, the half-life of maleic anhydride **2'** is about 4 hours. This time scale should be compatible with reaction **III**; therefore, we tested the reaction of **2'** with dienes **1**. Mixing these compounds in CD₃CN at 100 mM affords new NMR peaks consistent with the formation of the corresponding Diels-Alder adducts. The identity of the new species was confirmed by bidimensional NMR, HPLC coupled to high-resolution mass spectrometry analysis, and computational modeling (see SI section 4). As the data in Table 1 indicates, the reaction proceeded in fair yields for most compounds in 48 h, with a marked preference for the formation of *exo*-**3'** over *endo*-**3'**. The extent of reaction at 48 h was considered unsatisfactory only for compounds **1d** and **1e**, the carbamate derivatives of 2-

hydroxymethylfuran, and these compounds were not further studied. In contrast, the best results were obtained with carbamates **1f** and **1g**, prepared from 3-hydroxymethylfuran.

The same species observed in pure acetonitrile form also when mixing the starting materials in the target aqueous solvent, with the newly formed species disappearing after some time. The experimental observations are consistent with the hydrolysis of Diels-Alder adducts **3'** to give **3**, as the same species could also be detected (albeit just in traces in most cases) when equilibrating a mixture of **1** and **2** under the same conditions (SI section 4). For example, mixing 100 mM of **1f** and **2'** in the aqueous mixed solvent afforded *exo*-**3f'**, with its concentration peaking at ca. 15 mM after 7 h, to then form *exo*-**3f** (Figure S63). Importantly, *exo*-**3f** slowly reverted towards the separated components **1f** and **2**, confirming that reaction **I** is not thermodynamically favored.

These preliminary studies indicated which of the selected compounds have suitable thermodynamic and kinetic properties for reactions **I** and **III**. The outlined premises are sufficient to approach the endergonic formation of adducts *exo*-**3**, *i.e.*, their synthesis in conditions when they are not thermodynamically

Table 1. Yields of the Diels-Alder reaction (**III**) between furan-based dienes **1** and anhydride **2'**, both 100 mM in CD₃CN at 40 °C, monitored at 48 h.

Diene	Yield ^[a] (% of <i>exo</i> -adduct)	<i>exo:endo</i>
1a	20	96:4
1b	20	96:4
1c	21	96:4
1d	7 ^[b]	95:5
1e	5	96:4
1f	46	>99:1
1g	32	>99:1
1h	72	99:1

^[a] NMR yields of the major adduct, obtained using an internal standard. ^[b] Data obtained at 42 h.

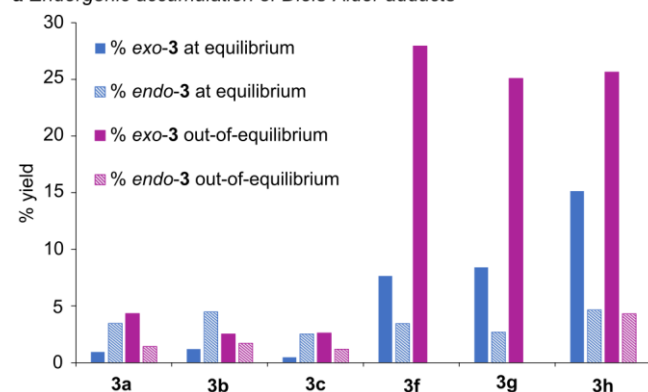
stable.^[18] To this aim, we pre-equilibrate mixtures of **1a-c,f-h** and **2**, and then added three equivalents of **DIC**. In all cases we could observe the counterclockwise sequence of reactions **II**→**III**→**IV** shown in Figure 1c: first anhydride **2'** formed, followed by adduct *exo-3'*, which then hydrolyzed to give *exo-3*. To compare a non-equilibrium state with the corresponding equilibrium we considered the moment in time when anhydrides **2'** and **3'** had completely hydrolyzed (usually $\leq 1\%$ residue). The results are reported in Figure 3a and SI section 5. In all cases the successful endergonic synthesis of Diels-Alder adducts was achieved, with yields ranging from 3 to 28%.

The non-equilibrium nature of the observed phenomena was further confirmed by the fact that mixtures slowly evolved towards the initial equilibrium distribution. Control experiments excluded a role of accumulation of **DIU** in promoting the observed accumulation of adducts **3**; in fact, its presence shifts the equilibrium distribution of reaction **I** even slightly more towards the separated components (see SI section 6). Interestingly, for all the 2-substituted derivatives (**1a-c**) the *endo*-/*exo*- selectivity was inverted. For example, **1a** formed preferentially the *endo*-adduct under thermodynamic control, while the *exo*-adduct was majorly detected under non-equilibrium conditions. On the other hand, 3-substituted furans afford the best selectivity, with *exo-3f* and *exo-3g* being the sole detected isomers. These observations corroborate the idea that endergonic synthesis can be used to control selectivity.^[45]

Based on the population of **1**, **2**, *endo-3*, and *exo-3* species at equilibrium and upon fueling, we calculated the energy stored in the non-equilibrium distributions (Figure 3b, see SI section 7 for details). Dividing the stored energies by the energy supplied by the driving hydration reaction, we also calculated the corresponding thermodynamic efficiencies (Figure 3b, values in parenthesis).^[17,48,49] Among the six species investigated, **f** and **g** showed the highest stored energy, reaching 49 and 40 J/L, respectively. Comparing these values with other chemically-fueled systems, we observe that the present ones are comparatively high among chemically driven systems. Previous reports of stored energy range from 0.49 J/L in the ATP-driven formation of a catalytic hydrazone,^[44] to 3.0–4.4 J/L in a range of interlocked structures,^[50,51] and 14 J/L in a Diels-Alder adduct (see SI section 7).^[45] One of the reasons for the higher energies stored in the present case is that the employed concentrations are higher herein (high vs low mM). The amount of stored energy is even comparable with the one estimated for a polymer chain entanglement produced by a light-driven molecular rotor, greater than 72 J/L (see SI section 7).^[52]

Having established the endergonic formation of a family of Diels-Alder adducts, we attempted the realization of a multistep non-equilibrium adaptation process. To this aim, we focused on the best-performing dienes, **1f** and **1g**. In the key experiment, the addition of **DIC** is repeated before the system returns to equilibrium, yet after anhydrides **2'** and **3'** have hydrolyzed. When performing this experiment with **1f**, by adding 1.6 equivalents of **DIC** twice, the amount of adduct *exo-3f* increases from its equilibrium value of 7% to 24% after the first addition, further increasing to 27% after the second one, before evolving towards the equilibrium distribution (Figure 4a and SI section 5).

a Endergonic accumulation of Diels-Alder adducts



b Energy "stored" in the non-equilibrium distribution (% efficiency)

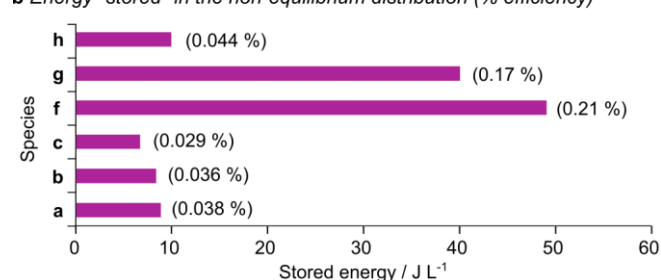


Figure 3. a) Comparison between the % yield of Diels-Alder adducts **3** at equilibrium (blue bars) and away from equilibrium (purple bars), the latter obtained upon adding 3.0 equivalents of **DIC** to an equilibrated mixture of **1** and **2**, and allowing subsequent hydrolysis of formed anhydrides **3'**. Full and striped bars refer to *exo*- and *endo*-adducts, respectively. No *endo*-adduct is observed for **3f** and **3g**. b) Calculated stored energy for non-equilibrium distribution in panel a, with the corresponding % efficiencies shown in parentheses. Conditions: CD₃CN:D₂O 85:15 at 40 °C; 100 mM of both **1** and **2**.

An analogous behavior is observed with compound **1g**, for which the amount of adduct *exo-3g* increases from 7% at equilibrium to 18 to 24% when subject to the same sequence of additions (Figure 4b).

Performing the same type of experiment but adding 1.0 equivalent three times affords a multistep response. For example, in the case of **1f**, the amounts of *exo-3f* accumulated are 18, 23, and 24% compared to 10% at equilibrium (Figure 4c, lighter bars and SI section 5). Fueling **1g** three times affords a similar profile response, with 23% of **3g** accumulated upon the third cycle (Figure 4c, darker bars and SI section 5). Such multistep profiles are qualitatively analogous to those of synthetic polymers able to undergo irreversible mechanochemical strengthening upon cross-linking, a training behavior.^[53,54] However, the endergonic essence of non-equilibrium adaptation enables reversibility, as the reaction network returns to equilibrium.

The observed progressive increase in the concentration of *exo-3f* and *exo-3g* observed in multi-cycle experiments also corresponds to an increase in the stored energy. The values of stored energy and corresponding thermodynamic efficiencies were calculated for all multi-cycle experiments (Figure 4d and SI section 7). Using as an example the 3-step adaptation experiment performed with **1f**, after addition of 1.0 equivalent of **DIC** for three times, the stored energy increases by 21, 9.5, and 2.5 J/L. This

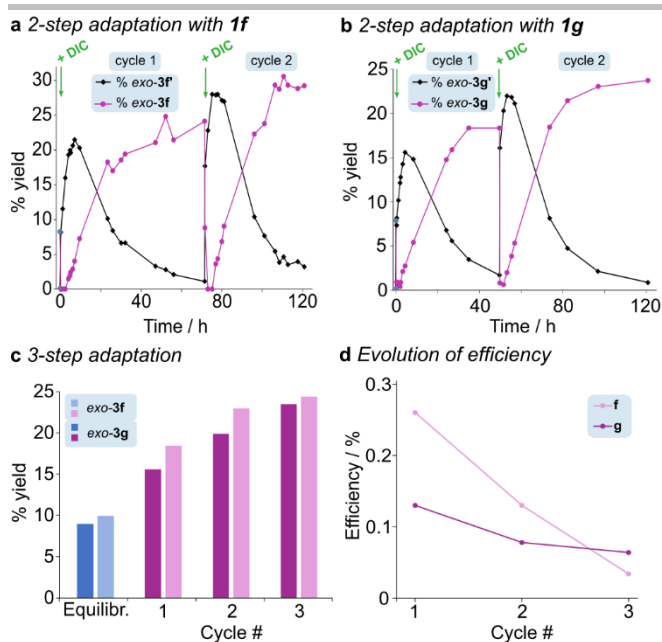


Figure 4. Evolution in time of the % yield of a) *exo-3f* (purple) and *exo-3f'* (black) or b) *exo-3g* (purple) and *exo-3g'* (black) adducts, upon repeated additions of 1.6 or 1.5 equivalents of **DIC**, respectively, performed in correspondence of the arrows. The experiment starts from the equilibrium distribution of **1f** or **1g**, **2**, and **3f** or **3g** (blue circle/diamond at $t=0$), with concentrations monitored by ^1H NMR. c) % yield of *exo-3f* (pale-colored bars) and *exo-3g* (deep-colored bars), obtained upon repeated additions of 1.0 equivalent of **DIC**. d) Evolution of efficiency of energy storage with respect to **f** (pale purple line) and **g** (deep purple line), upon repeated additions of 1.0 equivalent of **DIC**. Conditions: $\text{CD}_3\text{CN}:\text{D}_2\text{O}$ 85:15 at 40 °C, 100 mM of both **1f** or **1g** and **2**.

means that the efficiency of the energy storage process decreases with subsequent fueling cycles, going from 0.26% in the first cycle to 0.034% in the third one (Figure 4d). A similar behavior was observed with compound **1g**. Upon adding 1.0 equivalent of **DIC** three times, the overall stored energy increased, while the efficiency dropped, albeit less abruptly, from 0.13% to 0.064% (Figure 4d).

The experiments presented in Figures 3 and 4 allow us to compare three situations in which a total of 3 equivalents of **DIC** were added, albeit in one, two, or three portions. In all these cases, the overall composition of the system is the same, yet, the amount of *exo-3f* varies between 24 and 28% in the three cases. This scenario reflects a non-equilibrium response to the frequency of addition, another adaptive effect indicated by Walther^[5] as one of the desirable phenomena to engineer *via* precise molecular mechanisms, for developing advanced systems.

Multiple effects contribute to the observed multistep adaptive response. A key design element is that reactions **II** and **IV** (anhydride formation and hydrolysis) are faster than reaction **III**, with reaction **I** being the slowest. As a result, when anhydrides have hydrolyzed, reaction **III** has not reached equilibrium yet, and pulses of **DIC** can lead to different outcomes, depending on the initial conditions. This behavior differs from the classical description of energy ratchet effects, where equilibration of reaction **III** is typically assumed. Information ratchet effects rely on differences in the rates of reaction **II** and **IV**, leading to kinetic asymmetry.^[55] Here, the adaptive response would be favored by

a faster hydrolysis of **3'** to **3**, compared to the hydrolysis of **2'** to **2**, possibly promoted by the carbamate group introduced in the investigated compounds.

To gain insights on this effect, we attempted the adaptation experiment adding three times one equivalent of **DIC** to control compound **1h**, which is an analog of **1f** lacking any hydrogen bond donor in its structure. The product of the endergonic process, *exo-3h*, reached 24% after the addition of 1.0 equivalent of **DIC** (vs 16% under equilibrium conditions), yet a similar amount of *exo-3h* was observed also in subsequent cycles (Figure S66b). The lack of multistep adaptation may be due to the fact that the half-life of anhydride *exo-3h'* (20 h in the presence of 3 equivalents of **DIC**) is longer than that of anhydrides *exo-3f'* and *exo-3g'* (ca. 16 h), which suggests that introducing a carbamate group leads to a sufficient kinetic asymmetry. Clearly, in the presented systems the carbamate group is necessary to observe an adaptive response.

In conclusion, in this communication we have shown that a family of Diels-Alder adducts can be formed under thermodynamically unfavored conditions, powered by the catalysis of carbodiimide hydration. The endergonic reactions take place with yields up to 28%, and diastereoselectivity up to 99:1. We leveraged endergonic assembly to realize non-equilibrium adaptation processes, focusing on the progressive accumulation of target species, which occurred with a frequency-dependent response. The observed behavior is reminiscent of the Venus flytrap, where subthreshold responses are transiently accumulated so that only a close sequence of multiple stimuli induces the target response.^[56] Overall, this study provides concrete examples of how endergonic processes can contribute to the transition from responsive to adaptive systems.

Supporting Information

We cited additional references within the SI.^[57–60]

Acknowledgements

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Keywords: non-equilibrium systems • endergonic processes • systems chemistry • dynamic covalent chemistry • catalysis

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