

Metabolism-inspired chemical reaction networks for chemically driven dissipative oligoesterification

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Abstract: Metabolism is a complex network of chemical reactions in which transient biomolecules are continuously produced and degraded. Mimicking this dynamic process in synthetic systems poses a considerable challenge, as it requires designs that enable the exchange of energy and matter among transient molecules. In this study, we explored a chemically driven oligoesterification process operating within a highly intricate reaction network and constructed a dynamic library of transient oligoesters. Our kinetic analysis uncovered an intriguing phenomenon: oligoesters undergo parasitic exchanges, consuming one another to sustain the system's dynamics before reaching thermodynamic equilibrium. This discovery opens new opportunities for designing synthetic systems that replicate the complexity and self-sustaining behavior of metabolic processes.

Cells, the basic units of life, are open systems that operate far from equilibrium.^[1] Their survival relies on a constant influx of nutrients from the extracellular environment, which triggers a cascade of chemical reactions that assimilate energy, produce transient molecules, and remove waste.

This collective process, known as metabolism, represents a core characteristic of life and functions through a highly interconnected chemical reaction network (CRN).^[2] When the nutrient supply is disrupted, the entry points of the CRN shut down, eventually driving the system to thermodynamic equilibrium, signifying biological death. The complexity of metabolism has long fascinated synthetic chemists, inspiring efforts to develop artificial CRNs that mimic its dynamic processes. These synthetic networks aim to emulate key metabolic principles, advancing the frontier of systems chemistry by creating chemically driven CRNs that echo the intricate events occurring within living cells.^[3–14]

A key feature of metabolism is the dynamic interplay of metabolites consisting the CRN. For instance, cells continuously produce adenosine triphosphate (ATP) through cellular respiration, which functions as a universal energy currency.^[15] ATP, in turn, powers the synthesis of other high-energy molecules. In addition to these unidirectional transformations, metabolic pathways also include reactions that proceed in opposing directions. One example is the paired process of glycolysis and gluconeogenesis, known as a futile cycle, which consumes ATP while dissipating energy as heat.^[16] Similarly, protein degradation releases energy (via gluconeogenesis) and yields amino acid monomers (catabolism), which can be reused to synthesize new proteins (anabolism).^[17] These processes—where the functional components and energy stored in the transient species are consumed to produce new ones of the same kind—are well-established in natural metabolism yet remain less explored in synthetic systems.^[18,19]

In many studies of synthetic (supra)molecular systems operating far from equilibrium, chemical fueling drives the formation of transient bonds between monomeric building blocks, leading to the creation of dynamic oligomer libraries and increasing the systems' complexity.^[20–27] Within these libraries, oligomers compete for limited fuel, undergo reversible exchanges, and degrade over time according to their dynamic kinetic stabilities.^[28] To replicate the dual nature of metabolism—where catabolic and anabolic processes occur simultaneously—in synthetic systems, out-of-equilibrium designs should allow transient oligomers to serve as their own fuel. This approach creates a short-lived, self-sustaining system, where an interruption in fuel supply can unveil the underlying parasitic competition within the network.

In this study, we report on an interesting parasitic behavior observed in dynamic oligoester exchange, identified through a kinetic investigation of chemically driven,

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dissipative oligoesterification. The formation of temporary oligoesters from hydroxy acid building blocks is essentially a competitive interplay between chain-elongating condensation and hydrolytic degradation, which at first glance may appear as simple reversible reactions (Figure 1a). However, our analysis reveals that the system operates within an unexpectedly intricate CRN, involving many unobservable species and their reactions. Furthermore, we demonstrate that transient oligoesters with distinct monomer sequences exhibit significantly varied lifetimes and decay dynamics (Figure 1b).

First, we set out to find the optimal experimental condition for carbodiimide-driven dissipative oligoesterification.^[29–32] Leveraging the hydrolytic lability of *ortho*- and *para*-nitrophenyl esters,^[33–35] we selected 3-bromo-4-hydroxy-5-nitrobenzoic acid (**A**) as the primary building block to promote linear oligomerization and mitigate concerns about the folding or macrocyclization of the oligomers. We employed a pyridine/pyridinium buffer to suppress the intramolecular rearrangement of the *O*-acylisourea intermediate into the persistent *N*-acylurea side-product. Pyridine is known to facilitate the rapid conversion of *O*-acylisourea intermediates into acylpyridinium inter-

mediates, thereby minimizing *N*-acylurea formation.^[36,37] Additionally, tetrahydrofuran (THF) was introduced into the reaction mixture to prevent the precipitation of oligomers and enable accurate monitoring of solute concentrations using ¹H NMR spectroscopy. For kinetic studies, we employed a pyridine/pyridinium D₂O buffer (pD 5.5, 0.5 M pyridine-*d*₅, 0.1 M NaCl, 80 mM *N,N*-dimethylacetamide (DMA)) mixed with deuterated THF at a 1:1 ratio (v/v) (Supporting Information Section 1.1).

Upon adding 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) as a chemical fuel, two distinct sets of new peaks corresponding to the diester **A**₂ and triester **A**₃ emerged in the ¹H NMR spectra (Figure 2a). Using 24.2 mM of **A** and 23.3 mM of EDC, the maximum concentrations of **A**₂ and **A**₃ were observed to be 6.3 mM and 1.8 mM, respectively, with no additional transient species detected (Figure S2). Longer oligoesters, such as **A**₄ and **A**₅, were obtained when a larger amount of EDC (> 1.5 equiv. to **A**) was used but were excluded from the kinetic investigation (Figure S4). The presence of long oligomers in the CRN makes it challenging to interpret the reaction kinetics, as it leads to the formation of unobservable intermediate species and associated reactions (see Section 1.3 of the Supporting Information). Notably, the degradation of **A**₃ was significantly faster than that of **A**₂; **A**₃ fully decomposed within approximately 12 hours, whereas only 19 % of **A**₂ degraded after 19 days of incubation.

We attribute the significant difference in decay rates between **A**₂ and **A**₃ to the substituent effect.^[38] The ester group near the *O*-terminus (OH-terminus) of **A**₃ is influenced by a strong electron-donating *para*-hydroxy substituent, whereas the one near the *C*-terminus (CO₂H-terminus) has a *para*-acyloxy substituent with weaker electron-donating power (Figure S5).^[39] This difference presumably reduces the electrophilicity of the ester bond near the *O*-terminus.^[38,40,41] Additionally, deprotonation of the acidic hydroxy group could further decrease the electrophilicity (Figure S6). To investigate this phenomenon, we prepared three diesters with different *para*-substituents (OCH₃, CH₃, and H) and compare their hydrolysis rates with that of **A**₂. As expected, diesters with stronger electron-donating substituents generally exhibited slower hydrolysis rates (Figures S8–11), although experimental limitations prevented an accurate kinetic analysis (Figure S13).

Most importantly, we observed a simultaneous decrease in [**A**] and [**A**₃] after the exhaustion of EDC (regime 2 in Figure 2b), which was contrary to our initial assumption that [**A**] should increase when both **A**₂ and **A**₃ were undergoing hydrolysis (Figure S15). This unexpected outcome clearly suggests the occurrence of scrambling transesterification reaction, i.e., **A** + **A**₃ → 2**A**₂. This series of results suggests that the dissipative oligoesterification of **A** is indeed operating within a complex reaction network, prompting us to investigate the kinetics and prevailing reaction pathways.

According to studies on carbodiimide-driven transient anhydride formation, the acylpyridinium intermediate serves as a key intermediate, highly susceptible to nucleophilic addition.^[29,42,43] This intermediate can undergo several reactions, including esterification, anhydride formation, and

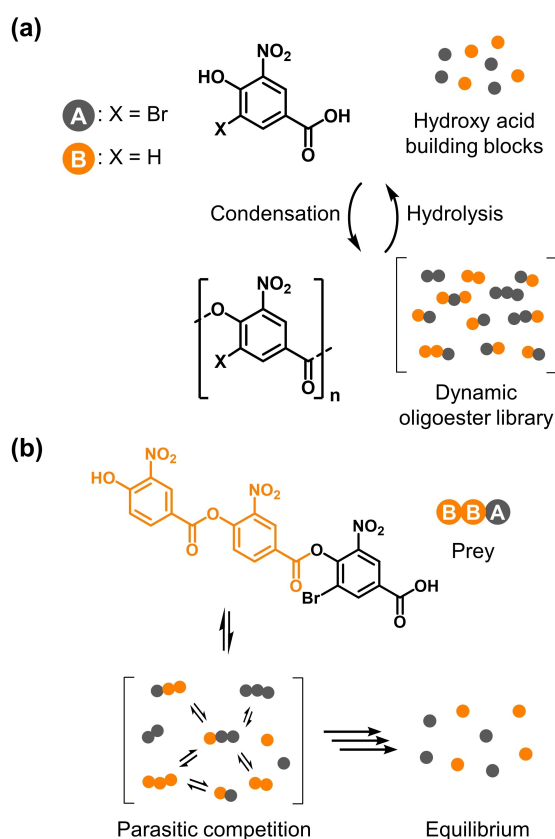


Figure 1. (a) Construction of a dynamic oligoester library via dissipative oligoesterification, involving reversible condensation and hydrolysis of hydroxy acid building blocks **A** (X = Br) and **B** (X = H); (b) Degradation pathways of oligoester **B**₂**A**, highlighting its role as "prey" in parasitic competition, where transient oligoesters dynamically exchange before reaching equilibrium.

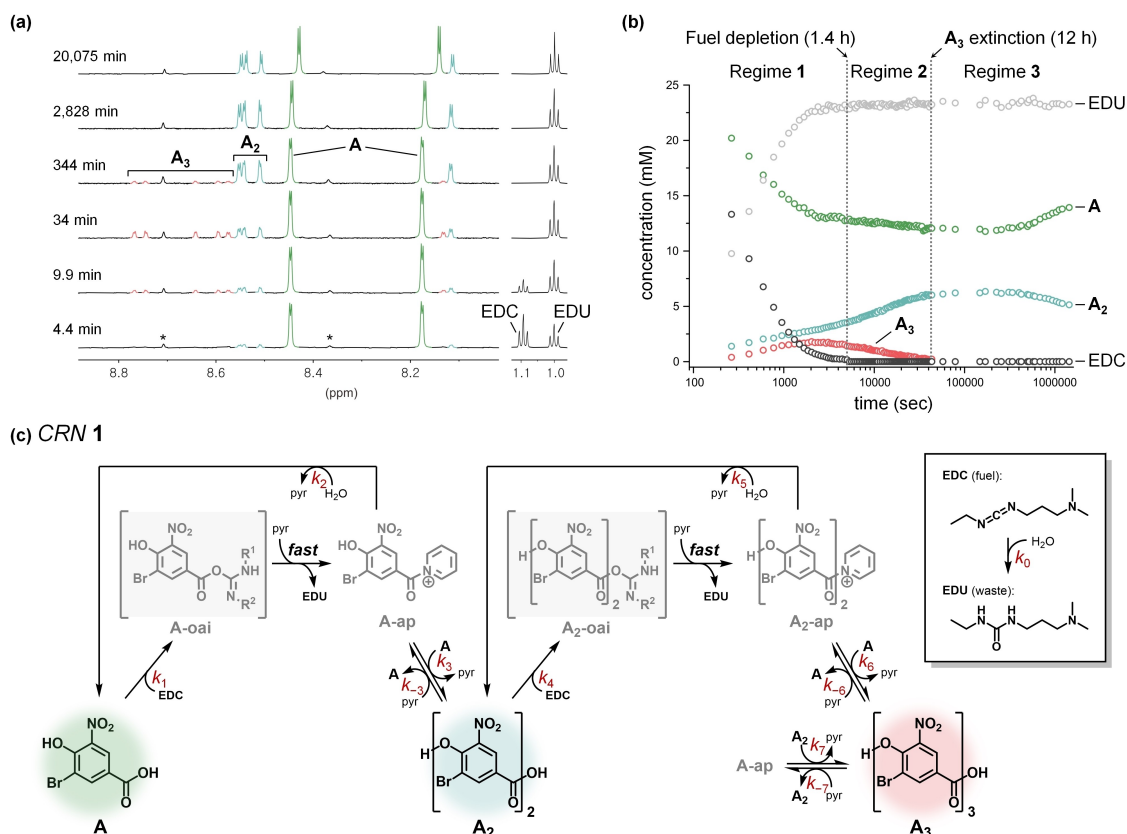


Figure 2. (a, b) ¹H NMR monitoring of carbodiimide-driven dissipative oligoesterification of **A**. Chemical shifts were calibrated using the acetyl signal of DMA as an arbitrary reference at 2.0 ppm; (c) Proposed chemical reaction network (CRN 1). Transient species unobservable by ¹H NMR spectroscopy are depicted in gray.

hydrolysis, resulting in a highly complex CRN involving many transient molecular species, all of which are ultimately expected to degrade hydrolytically and revert to monomer **A** (Figure S16). Even after the fuel is consumed, the length of oligoesters can change through processes such as deoligomerization (hydrolysis at the termini), fragmentation (e.g., hydrolysis of **A**₄ into two **A**₂), and transesterification. To focus on the kinetics of the prevailing reactions, we excluded transient species that were not present in measurable quantities (e.g., *O*-acylisoureas, anhydrides, and oligoesters longer than **A**₃), as well as uncatalyzed hydrolysis and transacylation reactions (CRN 1, Figure 2c, Supporting Information Section 1.3.1). We performed four ¹H NMR experiments with varying starting concentrations of **A** and EDC. A kinetic model encompassing ten elementary reactions was globally fitted to the entire dataset, yielding rate constants for each reaction, except for the background hydration of EDC (*k*₀, Figure S18).^[29–31,36]

Our initial attempts to achieve a convincing fit were unsuccessful, as the fits failed to accurately capture the decrease in [**A**] during regime 2 (Figure S19). For CRN 1, the only viable pathway for the scrambling transesterification (**A** + **A**₃ → 2**A**₂) is a two-step process. First, pyridine undergoes nucleophilic addition to the *O*-terminal carbonyl group of **A**₃, leading to the formation of an **A**₂ and an **A**-ap intermediate (*k*₋₇, Figure 2c). This intermediate then reacts

with **A** to produce a second **A**₂ molecule (*k*₃). However, the rate of this consecutive process may be insufficiently fast, likely due to the low susceptibility of the *O*-terminal carbonyl group to nucleophilic addition.

To gain deeper insight into the kinetics of the scrambling transesterification, we designed a new experiment (Supporting Information Section 1.3.2). In this revised experiment, **A** and EDC were dissolved in a pyridine/pyridinium buffer (pH 5.5, 0.5 M pyridine) mixed with THF at a 1:1 ratio (v/v). After confirming the emergence of **A**₂ and **A**₃, as well as the complete consumption of EDC, we introduced a new building block, 4-hydroxy-3-nitrobenzoic acid (**B**), into the reaction mixture. Transient oligomeric species were analyzed using reverse-phase high-performance liquid chromatography (RP-HPLC), mass spectrometry, and the benzylamine quenching method developed by Boekhoven and co-workers (Figure S21).^[44] We hypothesized that the hydroxy group of **B** would actively participate in transesterification, displacing the *C*-terminal unit of **A**₂ and **A**₃ to generate **AB** and **A**₂**B**, respectively (oligoester sequences represented in the *O*-to-*C* direction, left to right). Consistent with this hypothesis, we observed an accelerated decay of **A**₃ in the presence of **B** due to the formation of **A**₂**B**, as well as a slower growth of **A**₂, which was competing with **AB** formation (Figure 3a). Interestingly, a small amount of an

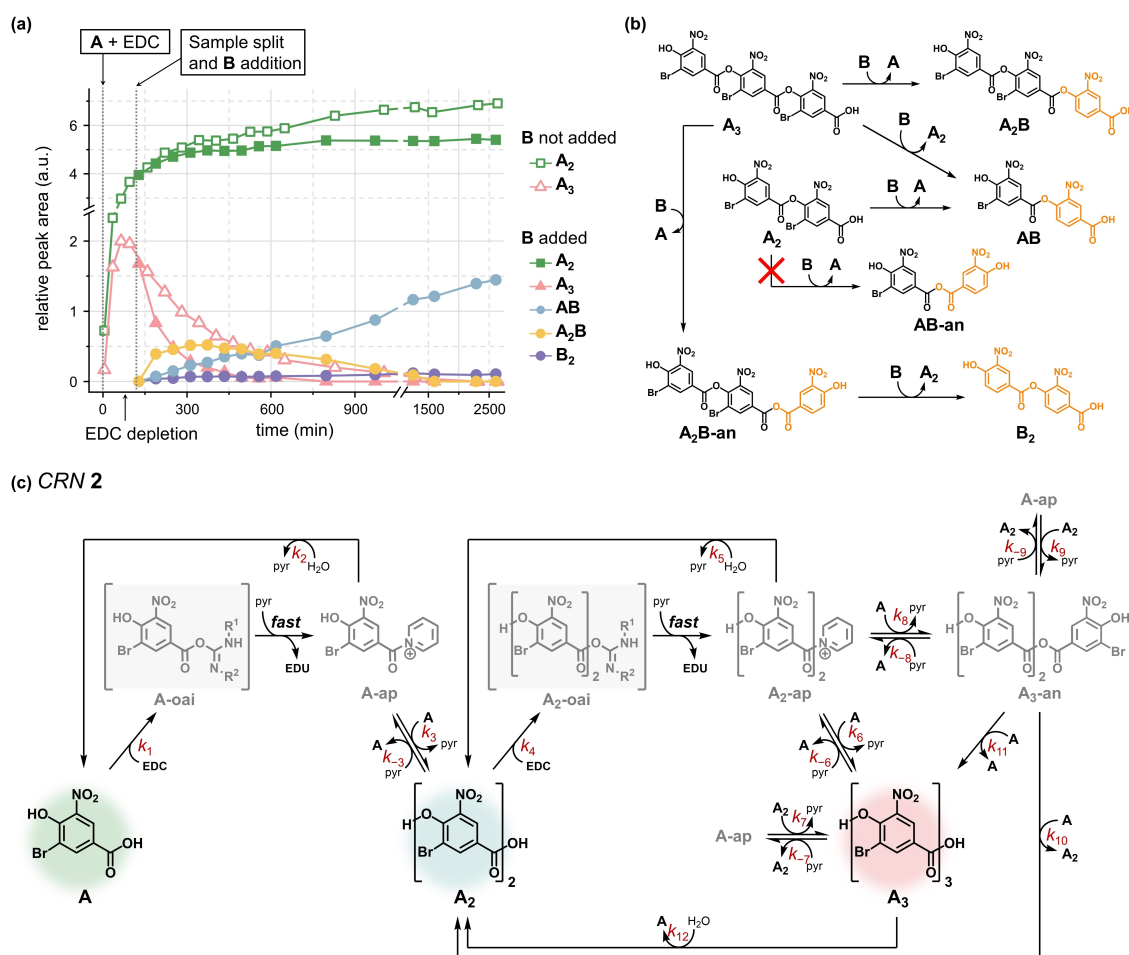


Figure 3. (a) RP-HPLC monitoring of the transacylation experiment; (b) Proposed reaction pathways for the formation of transacylation products AB, A₂B, and B₂; (c) Revised chemical reaction network (CRN 2). Transient species unobservable by ¹H NMR spectroscopy are depicted in gray.

unexpected species, B₂, was detected. The concentration of B₂ plateaued once trimeric species were no longer present.

The placement of B at the O-terminus of oligoesters indicates the activation of B's carboxylic acid. A plausible explanation for this dynamic exchange is that the energy stored in the ester bond near the C-terminus of triesters (A₃ and A₂B) drives the formation of an undetectable trimer with a mixed ester-anhydride backbone, A₂B-an (Figure 3b). Subsequently, A₂B-an undergoes rapid transacylation with B, resulting in the formation of B₂. In contrast, the ester bonds in A₂ and AB lack the ability to activate the carboxylic acid of B to produce an anhydride species (AB-an), as evidenced by the plateau in [B₂] levels once the trimeric species were depleted.

Consequently, we systematically expanded the CRN to include A₃-an, whose presence in the network was implied by A₂B-an in the aforementioned experiment, along with seven additional elementary reactions (CRN 2, Figure 3c, Supporting Information Section 1.3.3). Numerical fitting of the new kinetic model afforded simulations that closely aligned with experimental data, providing fitted parameters that revealed key reaction mechanisms (Figure 4a, Table S5, Supporting Information Section 1.3.5). First, the addition of

the A monomer to acylpyridinium intermediates (A-ap and A₂-ap) was found to be the dominant pathway for the formation of A₂ and A₃ during the first regime (k₃ and k₆) (Figures S41,44). This indicates that chain elongation primarily occurs via monomer addition to the C-terminus, analogous to protein translation. Second, during the second regime, the uncatalyzed nucleophilic addition of A to A₃-an, producing two A₂ molecules (k₁₀), was identified as the major pathway responsible for the simultaneous consumption of A and A₃ (Figures 4b,S41). Alternative pathways involving the A-ap intermediate were less significant, with its primary outflux being hydrolysis back to A (k₂) (Figure S48). Finally, during the third regime where A, A₂, and EDU are the only observable species, the hydrolytic degradation of A₂ through A-ap (k₋₃ and k₂) was virtually the sole active pathway (Figures S42,48). Elongation from A₂ to longer oligomers, such as the scrambling of two A₂ molecules to yield A and A₃, was found to be kinetically infeasible (k₇ and k₉) (Figure S48).

Encouraged by our understanding of reaction kinetics, we sought to construct a transient dynamic oligoester library using two hydroxybenzoic acid building blocks, A and B (Figure 5a). Upon fueling the system, new chromatographic

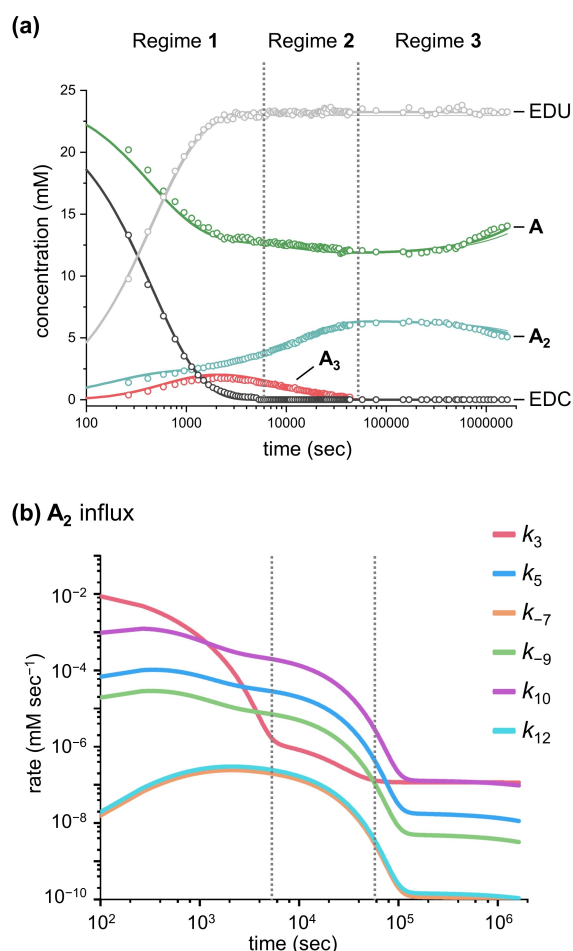


Figure 4. (a) ^1H NMR monitoring of the dissipative oligoesterification of **A** (circles) and fits to the kinetic model for CRN 2 (solid lines); (b) Rates of the individual reactions for **A**₂ influx.

peaks corresponding to dimeric and trimeric species appeared (Figure 5b, Supporting Information Section 1.4). We were able to unambiguously identify all four (2^2) diesters (**A**₂, **AB**, **BA**, and **B**₂) and five of the eight (2^3) possible triesters (**A**₃, **AB**₂, **BA**₂, **ABA**, and **B**₃) using independently synthesized oligoesters and the benzylamine quenching method (Figures S73–86). The transient oligoesters exhibited varied lifetimes with distinct patterns of growth and decay (Figure 5c). While most diesters, except for **BA**, increased steadily, all triesters decreased or were completely depleted over time. This highlights the inherent instability of ester bonds near the C-termini in triesters, as observed in the kinetic runs for **A**₂ and **A**₃. Notably, the monomer sequence strongly influenced the lifetimes of the oligoesters. Among **BA**₂ and **ABA**, both containing two **A** units and one **B** unit, **BA**₂ decayed significantly faster. Triesters with a C-terminal **A** unit, such as **BA**₂, **ABA**, and **A**₃, degraded more rapidly than others. These observations are presumably due to the 3-bromo substituent on **A**, which enhances its leaving group ability as a mild electron-withdrawing group. A direct comparison of **A** and **B**'s leaving group abilities, using independently synthesized **B**₃ and **B**₂**A**, confirmed this: **B**₂**A**

decayed faster than **B**₃ (Figure S57). These observations demonstrate that hydrolytic stability of the oligoesters depends heavily on their sequences.

During the hydrolytic degradation of **B**₂**A**—a species absent from the dynamic oligoester library—we identified transient species beyond the expected hydrolytic fragments (e.g., **B** and **BA**, **B**₂ and **A**). RP-HPLC purification revealed the formation of **A**₂ and four triesters—**A**₃, **BA**₂, **AB**₂, and **B**₃—which exhibited varying lifetimes (Figures 5d,e,S58). These unexpected oligoesters could not arise from simple deoligomerization or transesterification but required the activation of other building blocks' carboxylic acids (Figure 3b). This indicates that **B**₂**A** is not just hydrolyzed but also consumed by other species that compete for it as “prey,” leading to the formation of entirely new oligoesters of the same length. These paired processes of degradation and oligomerization mirror the interplay between catabolic and anabolic pathways in metabolism. The parasitic exchange, as a short-lived, self-sustaining dynamic observable only in the absence of fuel, resembles metabolic adaptation under starvation conditions.^[45] It is important to note that this parasitic exchange should be distinguished from the conventional definition of transesterification, in which the number of ester bonds remains unchanged. Instead, it involves the consumption of an ester bond to activate the carboxylic acid of another building block via an anhydride intermediate, which is then converted into a new ester bond.

In conclusion, we have demonstrated a chemically driven dissipative oligoesterification and thoroughly characterized the kinetics of the CRN that governs the composition of this dynamic system. We emphasize that our numerical fitting required consideration of 18 elementary reactions, even though the system was deliberately limited to only five observable species (**A**, **A**₂, **A**₃, EDC, and EDU). Our estimation suggests that at least 36 elementary reactions should be considered to incorporate tetrameric species into the CRN, which significantly exceeds the complexity of similar systems previously reported. A chemically driven dynamic oligoester library revealed sequence-dependent stability and intriguing exchange dynamics, where ester bonds are consumed to produce not only hydrolyzed fragments but also new ester species, mimicking aspects of protein metabolism.

While the complexity of CRNs is a key feature enabling the metabolism-like interplay of oligoesters, simplifying these reaction networks could improve their controllability and design flexibility. One possible approach is to use hydroxy acid building blocks in which the nucleophilic hydroxy group and the electrophilic carboxylic acid group are electronically decoupled (i.e., not conjugated). This separation would result in more predictable reaction kinetics, making it easier to model and regulate the network's dynamics. Furthermore, this strategy could facilitate the incorporation of longer oligoesters—often limited by poor water solubility—into CRNs. Ultimately, it could expand the potential for designing dissipative supramolecular systems that operate under continuous energy input.^[46–48]

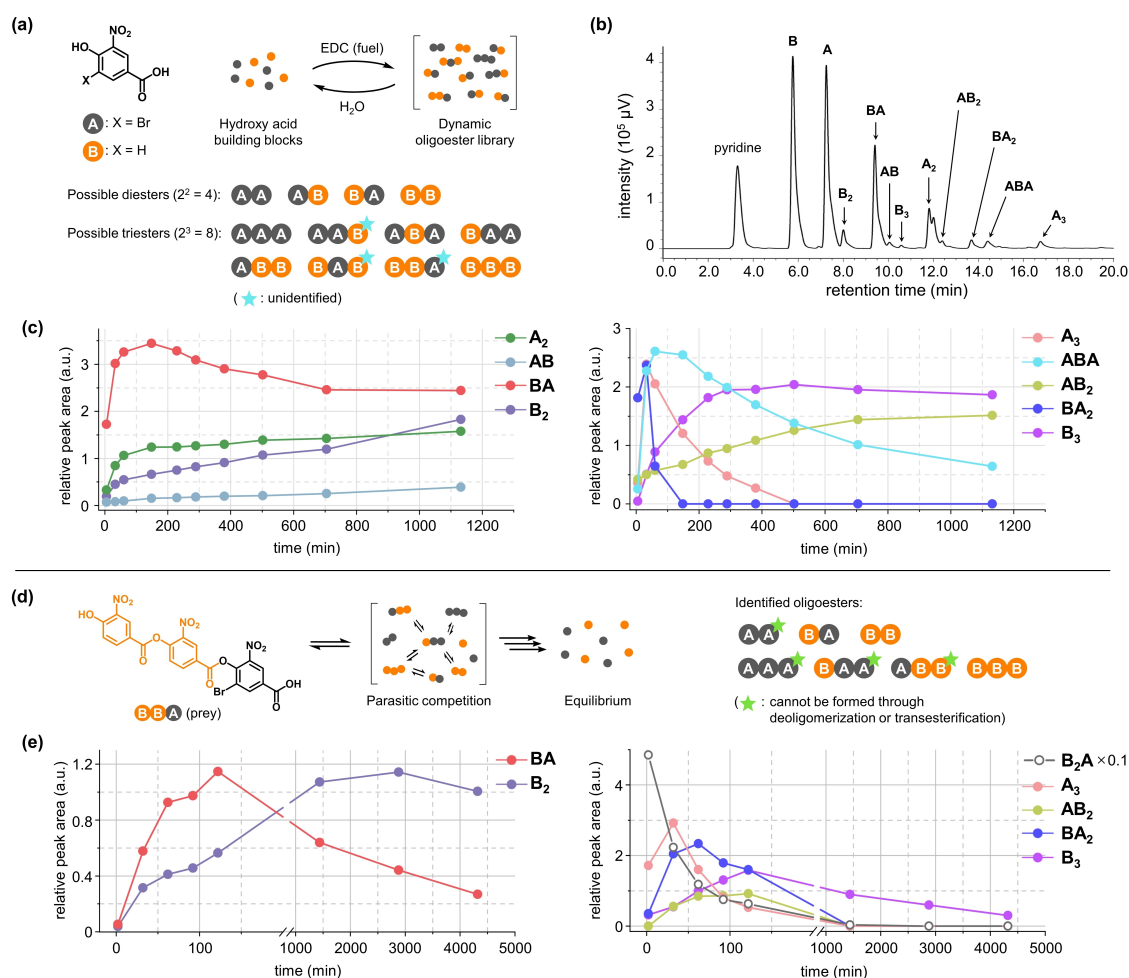


Figure 5. (a) Chemically driven generation of transient dynamic oligomer library; (b) RP-HPLC profile obtained 30 min after EDC fueling; (c) RP-HPLC monitoring of peak areas for diesters (left) and triesters (right); (d) Degradation dynamics of B₂A; and (e) RP-HPLC monitoring of peak areas for diesters (left) and triesters (right).

Despite extensive research, the complexity of synthetic dissipative systems remains limited compared to the intricate processes observed in living organisms. A comprehensive understanding of a new out-of-equilibrium system that generates transient oligomers with unique sequences is expected to provide essential design abilities for mimicking key biological processes, particularly those involving nucleic acids and proteins.^[49,50] For example, we envision potential biomimetic applications such as sequence-specific guest recognition (receptor-ligand interactions)^[51–53] and the integration of multiple CRNs for information transfer (e.g., transcription and translation).^[26,54] To this end, we are currently working on further complicating the dissipative oligoesterification process to design systems capable of information processing between orthogonal transient molecular species.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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- [1] J. H. van Esch, R. Klajn, S. Otto, *Chem. Soc. Rev.* **2017**, *46*, 5474–5475.
- [2] A. S. Y. Wong, W. T. S. Huck, *Beilstein J. Org. Chem.* **2017**, *13*, 1486–1497.
- [3] G. Ashkenasy, T. M. Hermans, S. Otto, A. F. Taylor, *Chem. Soc. Rev.* **2017**, *46*, 2543–2554.
- [4] O. Š. Miljanić, *Chem* **2017**, *2*, 502–524.
- [5] T. J. Erb, *Beilstein J. Org. Chem.* **2019**, *15*, 551–557.
- [6] P. Adamski, M. Eleveld, A. Sood, Á. Kun, A. Szilágyi, T. Czárán, E. Szathmáry, S. Otto, *Nat. Chem. Rev.* **2020**, *4*, 386–403.
- [7] S. Otto, *Acc. Chem. Res.* **2022**, *55*, 145–155.
- [8] S. Koppayithodi, P. Ranasingh, N. Singh, *ChemSystemsChem* **2024**, *6*, e202400028.
- [9] M. Méret, D. Kopetzki, T. Degenkolbe, S. Kleessen, Z. Nikoloski, V. Tellstroem, A. Barsch, J. Kopka, M. Antonietti, L. Willmitzer, *RSC Adv.* **2014**, *4*, 16777–16781.
- [10] B. J. Cafferty, A. S. Y. Wong, S. N. Semenov, L. Belding, S. Gmür, W. T. S. Huck, G. M. Whitesides, *J. Am. Chem. Soc.* **2019**, *141*, 8289–8295.
- [11] S. M. Morrow, I. Colomer, S. P. Fletcher, *Nat. Commun.* **2019**, *10*, 1011.
- [12] G. Monreal Santiago, K. Liu, W. R. Browne, S. Otto, *Nat. Chem.* **2020**, *12*, 603–607.
- [13] M. Kurisu, R. Katayama, Y. Sakuma, T. Kawakatsu, P. Walde, M. Imai, *Commun. Chem.* **2023**, *6*, 1–14.
- [14] K. Liu, A. W. P. Blokhuis, S. J. Dijt, J. Wu, S. Hamed, A. Kiani, B. M. Matysiak, S. Otto, *Nat. Chem.* **2024**, 1–8.
- [15] M. Bonora, S. Patergnani, A. Rimessi, E. De Marchi, J. M. Suski, A. Bononi, C. Giorgi, S. Marchi, S. Missiroli, F. Poletti, M. R. Wieckowski, P. Pinton, *Purinergic Signal.* **2012**, *8*, 343–357.
- [16] A. K. Sharma, R. Khandelwal, C. Wolfrum, *Cell Metab.* **2024**, *36*, 1184–1203.
- [17] J. Kaur, J. Debnath, *Nat. Rev. Mol. Cell Biol.* **2015**, *16*, 461–472.
- [18] S. Arsène, S. Ameta, N. Lehman, A. D. Griffiths, P. Nghe, *Nucleic Acids Res.* **2018**, *46*, 9660–9666.
- [19] M. C. M. Frenkel-Pinter, K. H. Smith, V. F. Rivera-Santana, A. B. Sargon, K. C. Jacobson, A. Guzman-Martinez, L. D. Williams, L. J. Leman, C. L. Liotta, M. A. Grover, N. V. Hud, *JACS Au* **2022**, *2*, 1395–1404.
- [20] M. M. Hossain, J. L. Atkinson, C. S. Hartley, *Angew. Chem. Int. Ed.* **2020**, *59*, 13807–13813.
- [21] D. Del Giudice, E. Spatola, M. Valentini, G. Ercolani, S. Di Stefano, *ChemSystemsChem* **2022**, *4*, e202200023.
- [22] K. Liu, S. Otto, in *Out-of-Equilibrium (Supra)Molecular Systems and Materials*, John Wiley & Sons, Ltd, **2021**, pp. 215–239.
- [23] C. M. E. Kriebisch, A. M. Bergmann, J. Boekhoven, *J. Am. Chem. Soc.* **2021**, *143*, 7719–7725.
- [24] S. Yang, G. Schaeffer, E. Mattia, O. Markovitch, K. Liu, A. S. Hussain, J. Ottelé, A. Sood, S. Otto, *Angew. Chem. Int. Ed.* **2021**, *60*, 11344–11349.
- [25] A. Sood, P. K. Mandal, J. Ottelé, J. Wu, M. Eleveld, J. Hatai, C. G. Pappas, I. Huc, S. Otto, *J. Am. Chem. Soc.* **2024**, *146*, 33386–33394.
- [26] C. M. E. Kriebisch, L. Burger, O. Zozulia, M. Stasi, A. Floroni, D. Braun, U. Gerland, J. Boekhoven, *Nat. Chem.* **2024**, *16*, 1240–1249.
- [27] M. J. Eleveld, Y. Geiger, J. Wu, A. Kiani, G. Schaeffer, S. Otto, *Nat. Chem.* **2025**, *17*, 132–140.
- [28] B. Liu, J. Wu, M. Geerts, O. Markovitch, C. G. Pappas, K. Liu, S. Otto, *Angew. Chem. Int. Ed.* **2022**, *61*, e202117605.
- [29] L. S. Kariyawasam, J. C. Kron, R. Jiang, A. J. Sommer, C. S. Hartley, *J. Org. Chem.* **2020**, *85*, 682–690.
- [30] I. M. Jayalath, H. Wang, G. Mantel, L. S. Kariyawasam, C. S. Hartley, *Org. Lett.* **2020**, *22*, 7567–7571.
- [31] I. M. Jayalath, M. M. Gerken, G. Mantel, C. S. Hartley, *J. Org. Chem.* **2021**, *86*, 12024–12033.
- [32] P. S. Schwarz, M. Tena-Solsona, K. Dai, J. Boekhoven, *Chem. Commun.* **2022**, *58*, 1284–1297.
- [33] S. Bal, K. Das, S. Ahmed, D. Das, *Angew. Chem. Int. Ed.* **2019**, *58*, 244–247.
- [34] S. Bal, C. Ghosh, T. Ghosh, R. K. Vijayaraghavan, D. Das, *Angew. Chem. Int. Ed.* **2020**, *59*, 13506–13510.
- [35] M. P. van der Helm, C.-L. Wang, B. Fan, M. Macchione, E. Mendes, R. Eelkema, *Angew. Chem. Int. Ed.* **2020**, *59*, 20604–20611.
- [36] L. S. Kariyawasam, C. S. Hartley, *J. Am. Chem. Soc.* **2017**, *139*, 11949–11955.
- [37] X. Chen, H. Soria-Carrera, O. Zozulia, J. Boekhoven, *Chem. Sci.* **2023**, *14*, 12653–12660.
- [38] S. L. Keenan, K. P. Peterson, K. Peterson, K. Jacobson, *J. Chem. Educ.* **2008**, *85*, 558.
- [39] A. Yokoyama, K. Iwashita, K. Hirabayashi, K. Aiyama, T. Yokozawa, *Macromolecules* **2003**, *36*, 4328–4336.
- [40] I.-H. Um, S.-J. Hwang, M.-H. Baek, E. J. Park, *J. Org. Chem.* **2006**, *71*, 9191–9197.
- [41] S.-I. Kim, M.-Y. Kim, I.-H. Um, *Bull. Kor. Chem. Soc.* **2014**, *35*, 225–230.
- [42] M. P. van der Helm, C.-L. Wang, B. Fan, M. Macchione, E. Mendes, R. Eelkema, *Angew. Chem. Int. Ed.* **2020**, *59*, 20604–20611.
- [43] W. S. Salvia, G. Mantel, N. K. Saha, C. W. H. Rajawasam, D. Konkolewicz, C. S. Hartley, *Chem. Commun.* **2024**, *60*, 12876–12879.
- [44] F. Schnitter, J. Boekhoven, *ChemSystemsChem* **2021**, *3*, e2000037.
- [45] R. Singh, A. M. Cuervo, *Cell Metab.* **2011**, *13*, 495–504.
- [46] M. Tena-Solsona, C. Wanzke, B. Riess, A. R. Bausch, J. Boekhoven, *Nat. Commun.* **2018**, *9*, 2044.
- [47] P. S. Schwarz, S. Laha, J. Janssen, T. Huss, J. Boekhoven, C. A. Weber, *Chem. Sci.* **2021**, *12*, 7554–7560.
- [48] N. Singh, A. Lopez-Acosta, G. J. M. Formon, T. M. Hermans, *J. Am. Chem. Soc.* **2022**, *144*, 410–415.
- [49] K. Dai, M. D. Pol, L. Saile, A. Sharma, B. Liu, R. Thomann, J. L. Trefz, D. Qiu, S. Moser, S. Wiesler, B. N. Balzer, T. Hugel, H. J. Jessen, C. G. Pappas, *J. Am. Chem. Soc.* **2023**, *145*, 26086–26094.
- [50] F. Späth, H. Soria-Carrera, M. Stasi, J. Sastre, B. A. K. Kriebisch, J. Boekhoven, *Angew. Chem. Int. Ed.* **2024**, *63*, e202407424.
- [51] S. Choi, R. D. Mukhopadhyay, Y. Kim, I.-C. Hwang, W. Hwang, S. K. Ghosh, K. Baek, K. Kim, *Angew. Chem. Int. Ed.* **2019**, *58*, 16850–16853.
- [52] M. M. Hossain, I. M. Jayalath, R. Baral, C. S. Hartley, *ChemSystemsChem* **2022**, *4*, e202200016.
- [53] M. P. Van Der Helm, G. Li, M. Hartono, R. Eelkema, *J. Am. Chem. Soc.* **2022**, *144*, 9465–9471.
- [54] M. G. Howlett, A. H. J. Engwerda, S. P. Fletcher, *Chem* **2024**, *10*, 2861–2871.

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