Supramolecular Chemistry Hot Paper

Zitierweise:
Internationale Ausgabe: doi.org/10.1002/anie.202001523
Deutsche Ausgabe: doi.org/10.1002/ange.202001523

Dissipative Assembly of Macrocycles Comprising Multiple Transient Bonds**

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Abstract: *Dissipative assembly has great potential for the creation of new adaptive chemical systems. However, while molecular assembly at equilibrium is routinely used to prepare complex architectures from polyfunctional monomers, species formed out of equilibrium have, to this point, been structurally very simple. In most examples the fuel simply effects the formation of a single short-lived covalent bond. Herein, we show that chemical fuels can assemble bifunctional components into macrocycles containing multiple transient bonds. Specifically, dicarboxylic acids give aqueous dianhydride macrocycles on treatment with a carbodiimide. The macrocycles are assembled efficiently as a consequence of both fuel-dependent and fuel-independent mechanisms; they undergo slower decomposition, building up as the fuel recycles the components, and are a favored product of the dynamic exchange of the anhydride bonds. These results create new possibilities for generating structurally sophisticated out-of-equilibrium species.*

Introduction

The use of chemical fuels to drive abiotic systems out of equilibrium is challenging but offers great potential for novel adaptive behaviors.[1–8] Using a variety of fuel reactions, nonequilibrium gels;[9–12] molecular switches,[13] shuttles,[14,15] and motors;[16] supramolecular assemblies;[17–20] molecular hosts;[21,22] and other species[23,24] have been reported. The behaviors of these dissipative systems can be complex, typically resulting from changes in noncovalent interactions following the generation of a new transient species by the fuel. The underlying (covalent) chemical transformations, however, have been very simple; the role of the fuel is generally the formation of a single unstable covalent bond. This simplicity contrasts sharply with the sophistication of dynamic systems under thermodynamic control, in which the simultaneous formation of many covalent bonds[25,26] can be used to self-assemble macrocycles,[27–29] cages,[30–34] ladders,[35,36] knots,[37–39] and other closed architectures.[40–42] This structural complexity leads to new function. For example, the products have interior spaces that can be used to bind guests,[30,43] and they can be incorporated into porous materials;[44,45] beyond synthesis, dynamic chemical libraries at equilibrium can themselves exhibit complex responsive behavior.[39,46–50]

Merging the structural sophistication of equilibrium assembly with the functional possibilities of dissipative assembly would enable new behavior. For example, transient hosts could be used for active transport, and dissipative dynamic libraries should exhibit new mechanisms of responding to their environments. However, it is not yet possible to assemble polyfunctional monomers into closed architectures using the energy of chemical fuels. The challenge is overcoming competing polymerization. For assembly at equilibrium, target structures can be produced in high yields because unstable kinetic products decompose, providing a form of error correction.[27] In general, closed architectures are favored entropically and thus can be produced efficiently so long as the precursors are suitably preorganized.[51] It is inherently more complex to achieve similar results away from equilibrium. By definition, transiently formed products are not thermodynamically favored and the time scales of the chemistry are limited. However, new mechanisms for error correction are also possible.

Herein, we demonstrate the efficient assembly of polyfunctional monomers into macrocycles using the energy of a chemical fuel. As shown in Scheme 1, we focus on diacid substrate **DA1** dissolved in water. On treatment with a carbodiimide, it assembles into macrocycle **M1** in competition with polymerization to oligomers $\mathbf{O1}_n$. Compound **M1**, comprising two unstable bonds (the anhydrides), is formed very efficiently. While it is a simple two-component macrocycle, analogous structures formed under thermodynamic control exhibit interesting host–guest and self-assembling behavior.[52–56] We find that the principles underlying the efficiency of assembly are distinctly different from those directing equilibrium assembly.

The chemical fuel for this system is the well-known carbodiimide reagent EDC (*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride). Carbodiimides are simply dehydrating agents that are kinetically stable in water; their hydration is catalyzed by carboxylic acids, yielding the unstable anhydrides as byproducts.[57,58] Recently, this chemistry has been used by Boekhoven[23,24,59] and us[11,22] to generate transient anhydrides with functional behavior. It is well-suited to polyfunctional assembly. Unlike other fuel reactions (e.g., methylation[10]), only the energy of the carbodiimide fuel is used; it does not transfer structural components to the transient state.

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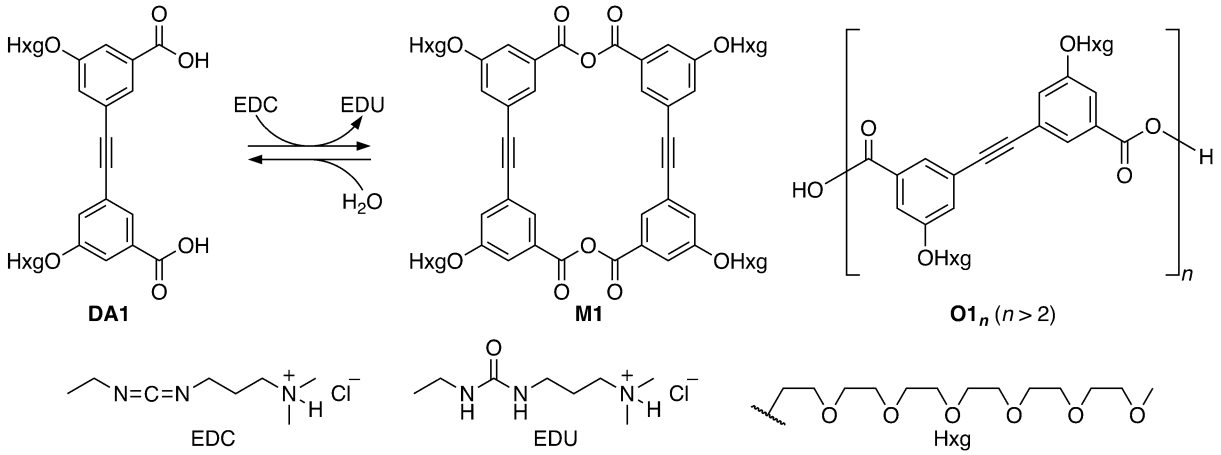
[**] A previous version of this manuscript has been deposited on a preprint server (https://doi.org/10.26434/chemrxiv.11426007).

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.202001523.



Scheme 1. Assembly of diacid **DA1** fueled by EDC.

Results and Discussion

Compound **DA1** was designed to have limited conformational mobility so that it would be well (but not too well) preorganized for assembly into **M1**. The hexaglyme groups were included to ensure good solubility in water. The synthesis of **DA1** is straightforward and is described in the Supporting Information. Ab initio geometry optimization of a simplified version of macrocycle **M1** shows that the core should be relatively free of strain, but distorted from planarity into a saddle conformation by twisting of the tolane moieties (Supporting Information, Figure S1).

The reaction of **DA1** (Scheme 1) with EDC was investigated in D_2O[60] at room temperature, maintaining the pD at 5.5 using a [D_5]pyridine buffer and the ionic strength (I) at 1.0 M using NaCl. These conditions closely parallel those we have used for other benzoic acids,[61] although the pD was increased from 4.5 to 5.5 here. The higher pD was chosen for experimental convenience; in preliminary experiments at pD 4.5, the **DA1** was consumed very quickly, making the reactions more difficult to monitor.

The system was first studied by ^{1}H NMR spectroscopy. Immediately after addition of the EDC, the reaction mixture was inserted into the spectrometer and monitored for 2 h. Spectra for a representative reaction, where 25 mM **DA1** was treated with 50 mM EDC, are shown in Figure 1. The aliphatic region of the spectrum shows clean conversion of the EDC to the corresponding urea EDU (Scheme 1). Inspection of the aromatic region shows that all of the **DA1** is consumed within approximately 10 min, with no concurrent appearance of sharp peaks that could be assigned to new species. Closer inspection reveals a very broad feature in the aromatic region, suggesting aggregation of the products of assembly.[62] The reaction mixture remains homogeneous throughout the experiment (as do all others reported here). The signals for **DA1** are absent over the course of hours but return once the reaction has sat overnight, indicating that it is regenerated once the fuel is consumed.

The reaction was also followed by in situ IR spectroscopy. Again 25 mM **DA1** was treated with 50 mM EDC in buffered D_2O. Immediately after addition of the EDC, a new band appears at 1794 cm^{-1}, as shown in Figure 2. This peak is characteristic of the symmetric stretching mode of the anhydride functional group, confirming that the underlying chemistry occurs effectively. The intensity of the band plateaus within 30 min then decays slowly. The overall time scale of this experiment is 15–20 h, consistent with the NMR monitoring results (and HPLC monitoring, described later).

The NMR and IR spectroscopy data indicate clean conversion of **DA1** to anhydrides and then its regeneration over the course of hours, but do not indicate whether the system

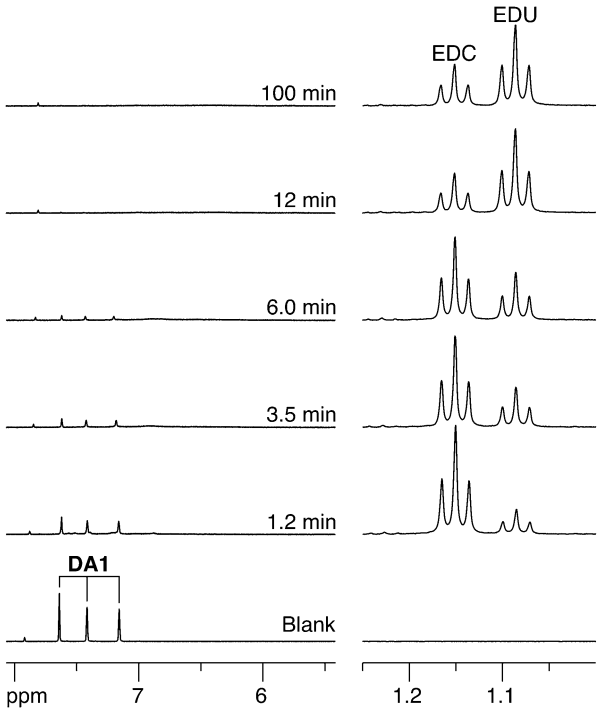


Figure 1. Reaction of **DA1** (25 mM) with EDC (50 mM) monitored by ^{1}H NMR spectroscopy at various reaction times (pD = 5.5, 250 mM [D_5]pyridine buffer, I = 1.0 M (NaCl), 298 K, 500 MHz). The blank solution (bottom) represents a control experiment with just the addition of D_2O instead of the EDC solution. The spectra are normalized to the intensity of an internal standard (*N*,*N*-dimethylacetamide).

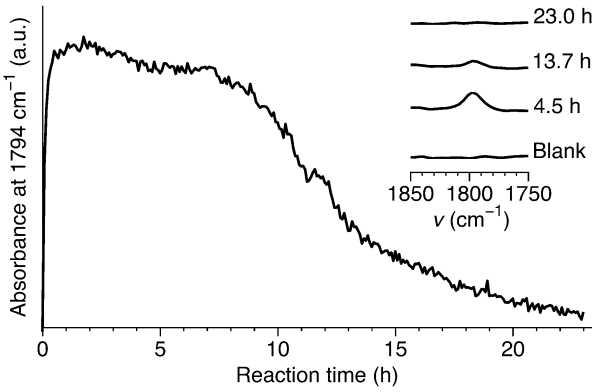


Figure 2. Treatment of **DA1** (25 mM) with EDC (50 mM) monitored by IR spectroscopy at 1794 cm^{-1} (pD = 5.5, 250 mM [D_5]pyridine buffer, I = 1.0 M (NaCl), rt). Inset: Absorption peak at 1794 cm^{-1} at various time points. The blank consists of all components of the reaction mixture except EDC.

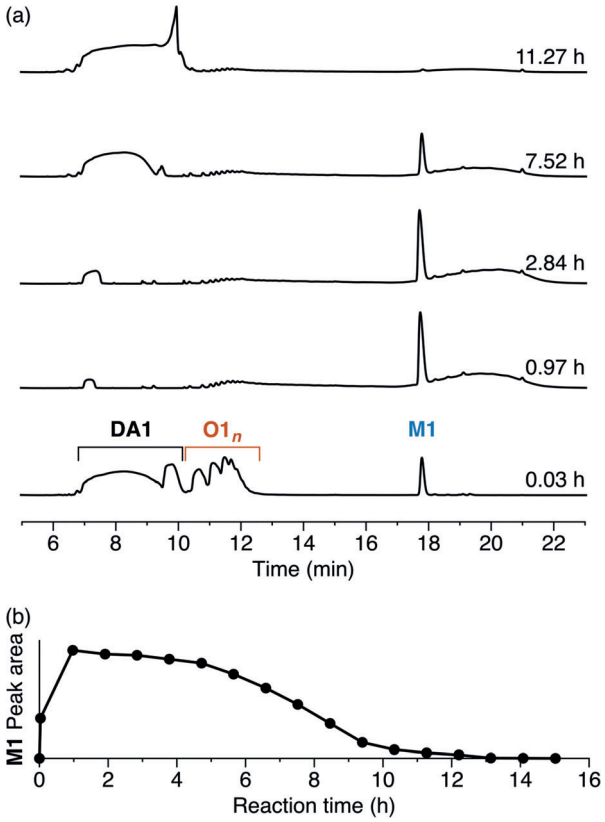


Figure 3. a) Assembly of **DA1** (25 mM) on treatment with EDC (50 mM) monitored by reversed-phase HPLC at various reaction times, detected by absorbance at 280 nm (pD = 5.5, 250 mM [D_5]pyridine buffer, I = 1.0 M (NaCl), rt). b) Dependence of the **M1** peak area on total reaction time.

favors macrocyclization to **M1**, polymerization to **O1$_n$**, or neither. We then monitored the system by HPLC. As a reference, it was possible to synthesize an authentic sample of **M1** by treating **DA1** with *N*,*N*′-dicyclohexylcarbodiimide following a previously reported method (see Supporting Information).[22] While somewhat unstable, the macrocycle could be unambiguously characterized by ESI mass spectrometry and NMR spectroscopy (Figures S22–S24, S53, and S54).

The reaction of **DA1** with EDC was carried out as before. Representative chromatograms are shown in Figure 3. The components of the mixtures elute in three distinct regions for **DA1**, **O1$_n$**, and **M1**, with each peak characterized by LC/MS (Figures S25–S32). The identities of **DA1** and **M1** were also confirmed by comparison with the authentic samples. As it is the least-polar possible component of the mixture, the peak for macrocycle **M1** is well-separated from the carboxylic-acid-containing species. The extinction coefficients of the various species at the detection wavelength (280 nm) should be similar (Figure S11), allowing qualitative comparisons of their relative populations (EDC and EDU are not observed because they do not absorb at this wavelength; detection at 220 nm shows that they elute at roughly 1 min).

Immediately after the addition of EDC, the HPLC analysis shows that assembly of **DA1** gives predominantly oligomers **O1$_n$**, with only a relatively small amount of macrocycle **M1**. Within less than an hour, however, the chromatogram is dominated by **M1**, indicating that macrocyclization is highly efficient given time. The consumption of EDC maintains the system for approximately 5 h at a nearly steady state. Compound **M1** then hydrolyzes slowly back to the starting **DA1** over the course of roughly 10 h. Notably, the macrocycle appears to hydrolyze directly back to **DA1** without any significant buildup of acyclic oligomers. That is, the relative populations of **M1** and **O1$_n$** are not solely a function of the net anhydride concentration.

As the concentration of **M1** builds up, a broad feature appears in the chromatograms immediately following its sharp peak. LC/MS analysis indicates that it also corresponds to **M1** (Figures S33 and S34). We assign this broad peak to stacked aggregates formed at higher concentrations, consistent with the signal broadening observed by ^{1}H NMR spectroscopy.[63] The broad HPLC peak grows in more slowly than the one for unaggregated **M1**, reaching its maximum area after 2.5–3 h, and persists longer as the macrocycle decomposes, suggesting that aggregation and disaggregation are relatively slow and that stacking impedes hydrolysis. The assignment of the broad peak to aggregates was further confirmed by HPLC analysis of the independently synthesized **M1**. A comparable feature was observed in its chromatogram, but only if the sample was prepared as a solution in the aqueous buffer used for the EDC-fueling experiments (Figures S14–S16). When the independently synthesized **M1** was injected directly from acetonitrile solution, in which aggregation is less significant,[64] only a sharp peak was observed. Aggregation was also observed by dynamic light scattering (Figures S17 and S18). A solution of 25 mM **DA1** in water yields an apparent average particle size of 2–3 nm, consistent with its structure.[65] On treatment with 50 mM EDC, the average particle size increases sharply, peaking at 12–13 nm, before returning slowly to the original value for the **DA1** over the course of roughly 20 h.

The assembly of shape-persistent macrocycles into stakked solution-phase aggregates is well-precedented,[66–68] par-

ticularly for amphiphiles, like **M1**, dissolved in solvents that are matched to the peripheral groups.[69,70] Our expectation of this system is that it is an isodesmic polymerization, at least initially, although we cannot exclude subsequent higher-order aggregation.[71] Comparable aggregation would not be expected for **DA1** as it has a smaller available surface area for arene–arene stacking and its core is much more hydrophilic (e.g., charged at the experimental pH). Further evidence for the promotion of macrocycle aggregation by water was obtained by extracting reaction mixtures containing **M1** with chloroform-*d*. In this solvent, the aromatic regions of the ^{1}H NMR spectra show clearly defined signals that could be assigned to **DA1** and **M1** alone (Figure S19). There is no peak broadening or significant concentration dependence for the signals assigned to **M1**.[72] While the HPLC analysis quite clearly showed that **M1** was the major component of the mixtures before extraction, substantial amounts of **DA1** were always observed in the NMR spectra of extracted mixtures. This suggests that significant hydrolysis occurs once the aggregates are broken up in (water-saturated) chloroform.

The lifetime of **M1** is, of course, dependent on the initial concentrations of diacid **DA1** and EDC. The effect of varying EDC concentration (12.5–50 mM) added to constant **DA1** (25 mM) is shown in Figure 4 (top) (results for other concentrations of **DA1** are given in Figures S2–S10). In all three experiments, the maximum concentration of assembled **M1** is achieved within an hour. The lifetimes of **M1** are roughly proportional to the amount of fuel added. Similarly, for a constant 50 mM EDC, shown in Figure 4 (bottom), the lifetime is increased with decreasing concentration of **DA1** over the range of 12.5–50 mM, consistent with expectations. With 50 mM **DA1**, the equimolar EDC should be consumed almost immediately, leaving macrocycle **M1** to simply undergo hydrolysis. For lower concentrations of **DA1** the remaining excess EDC will regenerate the anhydride as it decomposes, prolonging the lifetime of the transient state.

The results described above show that architectures linked by multiple transient bonds can be generated efficiently, and that a nonequilibrium system that gives misassembled products in the short term can self-correct within its limited experimental time scale. Several distinct processes could account for the high proportion of macrocycles in the products: 1) They could simply be the kinetic products of the reaction, formed preferentially on reaction of the diacid with the fuel. 2) They could be kinetically stable compared to polymeric byproducts; that is, the (aggregated) anhydrides of **M1** could undergo slower hydrolysis. Under these circumstances, even if the assembly is completely unselective, any $\mathbf{O1}_n$ produced would decompose and the regenerated **DA1** redistributed between **M1** and $\mathbf{O1}_n$ on reaction with additional EDC, gradually building up the concentration of **M1**. 3) All of the anhydride-containing species could exchange, allowing the system to favor local minima on its free energy surface, provided that exchange is fast compared to decomposition. Paralleling thermodynamically controlled assembly, this process would favor unstrained closed architectures because they are entropically favored relative to polymer and because of added stability from aggregation.[27,51,73]

These three processes are not mutually exclusive. However, it is clear that macrocycle **M1** is not the kinetic product of this system, since substantial quantities of oligomers $\mathbf{O1}_n$ are always observed in HPLC traces obtained at short reaction times. Thus, process 1 is not significant.

Assembly-induced slowing of hydrolysis has been observed by Boekhoven for transient anhydrides that undergo phase separation once formed.[23,24] To test whether this is occurring here, we examined the behavior of monoacid **Ac1**, as shown in Scheme 2, which mimics the structure of the anhydrides within acyclic $\mathbf{O1}_n$. We have previously used **Ac1** to study the kinetics of EDC-fueled anhydride formation.[61] While the missing alkynyl group would certainly exert a substituent effect, it would be expected to accelerate anhydride hydrolysis, and thus the measurements on **Ac1** provide a lower limit for the rate. Under conditions identical to those for **DA1** assembly, the reaction is complete within minutes, with almost no buildup of anhydride **An1** (Figure S20). Hydrolysis must therefore be faster than was observed for **M1** by orders of magnitude. This result strongly suggests that hydrolysis of acyclic oligomers $\mathbf{O1}_n$ is faster than that of (aggregated) macrocycle **M1**, and thus process 2 must be operative. The results from the extraction experiments (see above) also support this assertion.

It has long been known that anhydride exchange by transacylation is faster than hydrolysis, particularly in the presence of pyridine.[61,74,75] To probe its significance to assembly, we designed the system shown in Figure 5a. A pentaglyme-functionalized diacid, **DA2**, was prepared. Derivatives of **DA2** can be distinguished from those of **DA1** by HPLC and mass spectrometry (see below). ^{1}H NMR spec-

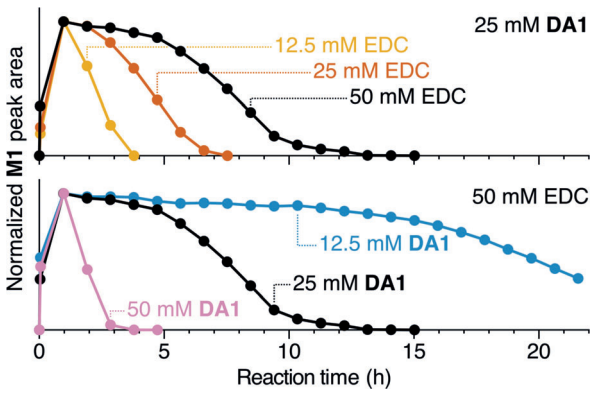
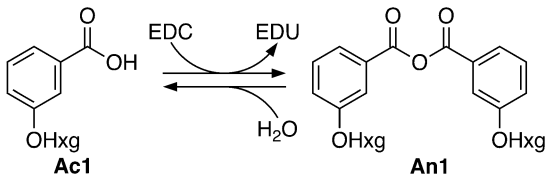


Figure 4. Effect of varying the concentration of **DA1** and EDC on the assembly of **M1**, monitored by HPLC (data are normalized to the maximum peak area for a given run, unnormalized data are in Figure S10). Top: Variable concentration of EDC added to 25 mM **DA1**. Bottom: Variable concentration of **DA1** treated with 50 mM of EDC.



Scheme 2. EDC-fueled assembly of monoacid **Ac1**.

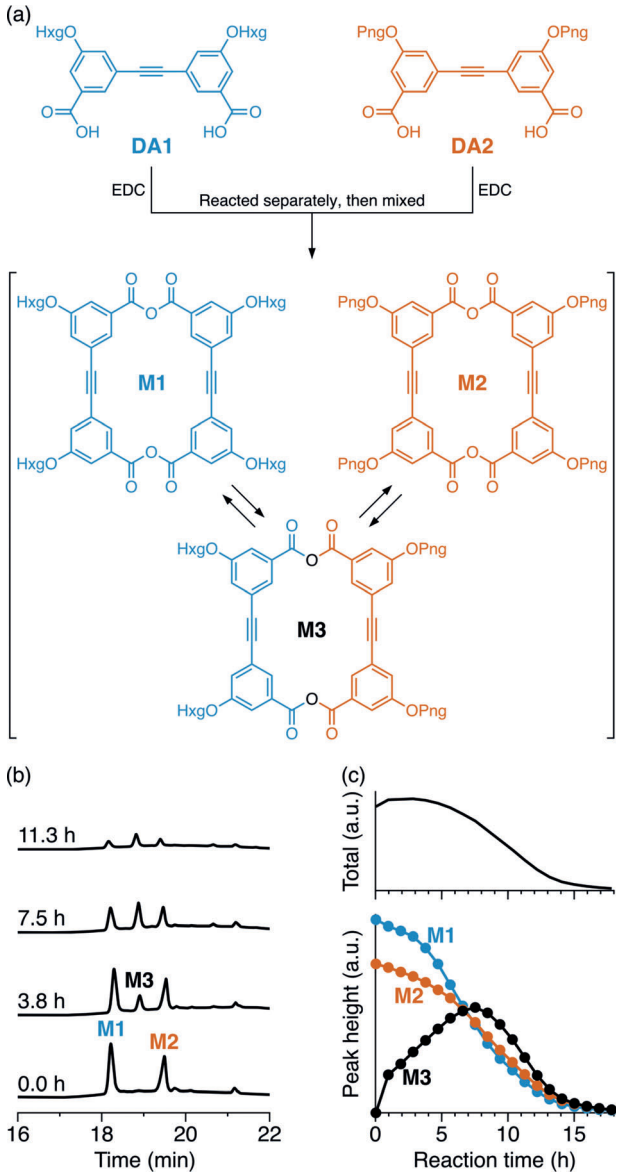


Figure 5. a) Dynamic exchange of anhydrides (Hxg = $(CH_2CH_2O)_6CH_3$, Png = $(CH_2CH_2O)_5CH_3$). The two macrocycles **M1** and **M2** (25 mM each) were generated separately by treatment with EDC (50 mM), then mixed once the acids were consumed (14 min) (pD = 5.5, 250 mM [D_5]pyridine buffer, I = 1.0 M (NaCl), rt). b) Monitoring of the mixture by HPLC. c) HPLC peak heights vs. reaction time for the experiment in (b); the total peak intensity is shown at the top. NMR monitoring experiments show that the EDC should be completely consumed within the first 5–6 h.

troscopy monitoring experiments confirmed that the reactivity of **DA2** is effectively identical to that of **DA1** and that the pentaglyme groups provide sufficient solubility for it and its associated macrocycle **M2** (Figure S21).

We carried out a simple mixing experiment to test for exchange. Separate solutions of **DA1** and **DA2** were prepared (25 mM each), treated with EDC (50 mM), and allowed to react for 14 min under conditions identical to those for macrocycle assembly alone. At this point, the NMR experiments had shown that the diacids should have reached maximum conversion. The two solutions were then mixed and the system was monitored by HPLC.

A chromatogram acquired immediately after mixing shows two separate peaks corresponding to macrocycles **M1** and **M2**, as shown in Figure 5b. A new peak appears between those for **M1** and **M2** within an hour. This peak was assigned to the mixed macrocycle **M3** (Figure 5a). The assignments were confirmed by LC/MS (Figures S35–S38). As shown in Figure 5c, the fraction of the total macrocycle population that is **M3** increases over the course of hours. It reaches a plateau of roughly 45% after 10–12 h, consistent with the 50% expected for the macrocycles at their equilibrium populations (1:1:2 ratio of **M1**/**M2**/**M3** on the basis of symmetry).

Under the conditions of the mixing experiment, NMR measurements show that the EDC should be completely consumed within 5–6 h (Figure S12), at which point no new anhydrides should be generated (i.e., process 2 should no longer occur). As shown in Figure 5c, the concentration of **M3** continues to rise for roughly 2 h after this point, even as the total concentration of macrocycles falls. Further, while the concentration of EDC should fall continuously over the first 6 h, the rate of buildup of **M3** remains approximately constant.

These results confirm that anhydride exchange is significant in these systems, indicating that process 3, self-correction akin to that observed in thermodynamically controlled self-assembly, should also play a role in directing the efficient formation of macrocycle. The time scale of exchange (10 h to reach a statistical distribution of macrocycles), is much longer than the time scale required for nearly complete assembly into the macrocycles (< 1 h). However, since the aggregates undergo slower hydrolysis, it is reasonable to assume that exchange would be as well; transacylation involving acyclic oligomers should be quite rapid. At this point, it is not possible for us to gauge the relative importance of the inherent stability of the free macrocycle compared to the added stability from aggregation in driving the system toward **M1**.

A proposed mechanism for out-of-equilibrium assembly in this system is shown in Figure 6. The generation of anhydrides is largely unselective, producing a mixture of macrocycles and acyclic oligomers. Self-correction is both fuel-mediated and fuel-independent; the fuel regenerates mixtures of macrocycles and oligomers, but since the oligomers preferentially decompose this should lead to a buildup of macrocycle over time. Simultaneously, transacylation allows the pool of anhydrides to rearrange to macrocycles, local minima on the free energy surface, in much the same way that equilibrium self-assembly eventually finds the global minimum. The experimental data suggests that both mechanisms play a significant role, but quantifying the relative contributions is challenging, particularly as they should both be time-dependent.

Conclusion

Bifunctional diacid **DA1** assembles effectively into macrocycle **M1**, with two transient anhydride bonds, on treatment with EDC, and is regenerated over the course of hours.

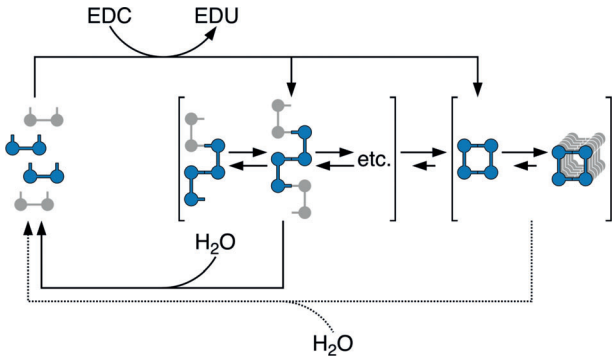


Figure 6. Proposed mechanism for the chemically fueled self-assembly of macrocycles in this system. Both the interconversion of the anhydrides and the difference in hydrolysis rates contribute to the efficiency.

Compound **M1** further undergoes aggregation in water similar to that known for many other shape-persistent macrocycles. The generation of anhydrides is unselective in these systems, but two other mechanisms contribute to the efficiency of self-assembly. First, the acyclic oligomers undergo rapid hydrolysis compared to the aggregated macrocycle; subsequent regeneration of anhydrides by the fuel eventually favors the more kinetically stable aggregated **M1**. Second, transacylation allows the anhydride-containing species to exchange; the macrocycle should be a local minimum on the system's free energy surface, allowing it to be populated preferentially. The latter mechanism is analogous to thermodynamically controlled self-assembly, but the former is unique to nonequilibrium systems.

This work demonstrates that well-defined closed architectures connected by multiple transient bonds can be assembled effectively using chemical fuels. In principle, it should allow the functional properties of macrocycles and cages, already well-established in thermodynamically controlled systems, to be applied in nonequilibrium systems, yielding new adaptive behavior.

Acknowledgements

This work was supported by the U.S. Department of Energy, Office of Science, Basic Energy Sciences, under Award # DE-SC0018645. We thank Lasith Kariyawasam for synthesizing **Ac1** and experimental assistance and Dr. Theresa Ramelot for help with the LC/MS experiments.

Conflict of interest

The authors declare no conflict of interest.

Stichwörter: aggregation · anhydrides · dissipative assembly · macrocycles · self-assembly

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[63] Quantitative comparisons of the amount of aggregated **M1** are of course impossible on the basis of HPLC because disaggregation will occur during the HPLC run.
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Manuskript erhalten: 29. Januar 2020
Veränderte Fassung erhalten: 18. April 2020
Akzeptierte Fassung online: 8. Mai 2020
Endgültige Fassung online: ■■. ■■ ■■■■

Forschungsartikel

Supramolecular Chemistry

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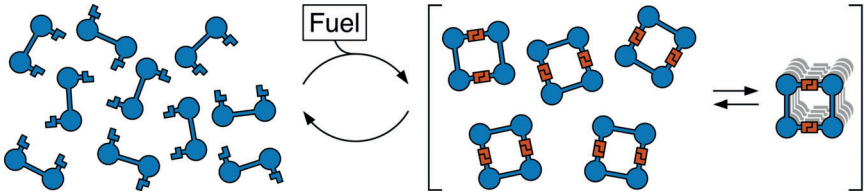
Dissipative Assembly of Macrocycles Comprising Multiple Transient Bonds



Out-of-equilibrium assembly: Diacid precursors assemble into unstable aqueous anhydride macrocycles on treatment with carbodiimide chemical fuels, even though initial anhydride generation is unselective for cyclization versus polymerization. The efficiency of assembly results from both fuel-independent (anhydride exchange) and fuel-dependent (selective hydrolysis) mechanisms.