

Probing the Dynamics of the Imine-Based Pentafoil Knot and Pentameric Circular Helicate Assembly

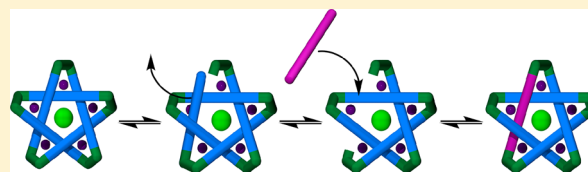
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Supporting Information

ABSTRACT: We investigate the self-assembly dynamics of an imine-based pentafoil knot and related pentameric circular helicates, each derived from a common bis(formylpyridine)-bipyridyl building block, iron(II) chloride, and either monoamines or a diamine. The mixing of circular helicates derived from different amines led to the complete exchange of the *N*-alkyl residues on the periphery of the metallo-supramolecular scaffolds over 4 days in DMSO at 60 °C. Under similar conditions, deuterium-labeled and nonlabeled building blocks showed full dialdehyde building block exchange over 13 days for open circular helicates but was much slower for the analogous closed-loop pentafoil knot (>60 days). Although both knots and open circular helicates self-assemble under thermodynamic control given sufficiently long reaction times, this is significantly longer than the time taken to afford the maximum product yield (2 days). Highly effective error correction occurs during the synthesis of imine-based pentafoil molecular knots and pentameric circular helicates despite, in practice, the systems not operating under full thermodynamic control.



INTRODUCTION

Self-assembled metallo-supramolecular architectures are often the most stable structures in a distribution of many possible products.^{1–5} The dynamic bonding in such systems provides a means of “error correction”, generally interpreted as the thermodynamically preferred species being selected from a landscape of possible alternatives that equilibrate during the course of the reaction.^{2–7} Some of the most celebrated examples are Lehn’s circular helicates,² typically derived from tris-bipyridine ligand strands and iron(II) or nickel(II) salts, used to exemplify such self-assembly processes in numerous textbooks and university courses. However, while it is recognized³ that “self-assembly under thermodynamic control” is likely an oversimplified description for a number of complex supramolecular assembly processes,^{3–5} the dynamics of such systems have rarely been investigated experimentally. Reports of the self-assembly of metallo-supramolecular structures under nonequilibrium conditions remain rare.^{8–10}

Here we investigate the process by which aldehyde **1** forms imine-based pentameric circular helicates¹¹ (such as **2**) and a molecular pentafoil knot (**3**)¹² (Scheme 1). The assembly of these structures occurs spontaneously from 21 individual components in the case of circular helicate **2** (16 for knot **3**) when dialdehyde **1**, amine **4** (or diamine **5**), and FeCl₂ are combined in an appropriate stoichiometry in dimethyl sulfoxide (DMSO).^{11,12} Initially formed linear oligomers and polymers (which give rise to the initial very broad ¹H NMR spectra of these reactions^{11,12}) rearrange to form essentially a single product over 48 h at 60 °C,¹³ a process accompanied by the appearance and growth over time of a single set of sharp ¹H NMR signals, reflecting the high conversion of the

oligomeric and polymeric intermediates to the low-molecular-weight, high-symmetry, circular helicate/knot.^{11,12}

To investigate the reversibility and dynamic nature of these remarkable self-assembling systems, we proposed a two-pronged approach. First, exchange¹⁴ of the imine *N*-alkyl moieties was probed by reacting dialdehyde **1** and FeCl₂ with different, but chemically similar, amines (Scheme 2). Second, exchange of the central aldehyde residues¹⁵ was investigated through the use of deuterium-labeled (**1-D₈**) and unlabeled (**1**) derivatives (Scheme 3).

RESULTS AND DISCUSSION

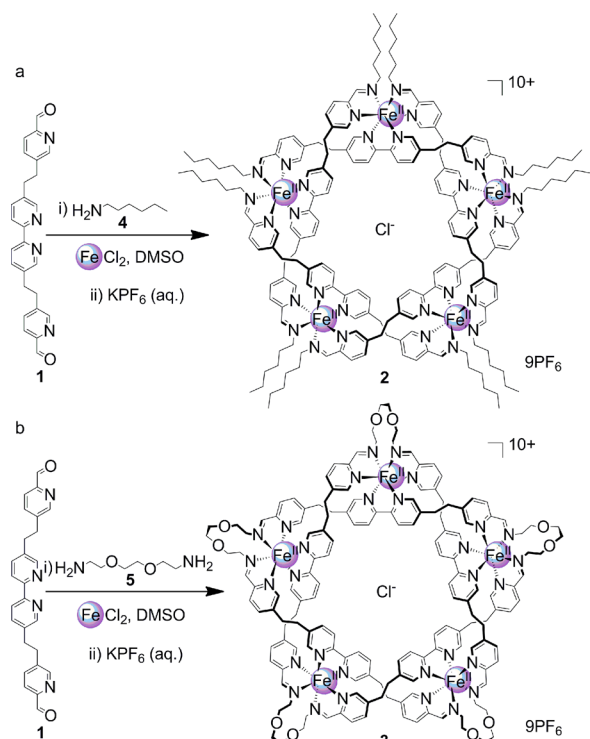
The addition of excess primary amine to pentameric cyclic helicate **2** led to the partial decomposition of the complex,¹¹ limiting the information that could be gathered about the building block exchange processes. However, by mixing two preformed pentameric helicates derived from different, but chemically similar, amines (e.g., circular helicates **2** and **6**, Scheme 2) the exchange process could be studied in the absence of significant amounts of free amine.

To follow the exchange processes, two reactions were monitored (Routes A and B, Scheme 2). A control reaction (Route A) used a 1:1 ratio of hexylamine **4** and methoxyethylamine **7** for the reaction with dialdehyde **1** and FeCl₂ to ensure that there was no thermodynamic bias between the two resulting structures (see the SI for experimental details). After anion exchange with aqueous potassium hexafluorophosphate and the take up of the product in acetonitrile, the sample was

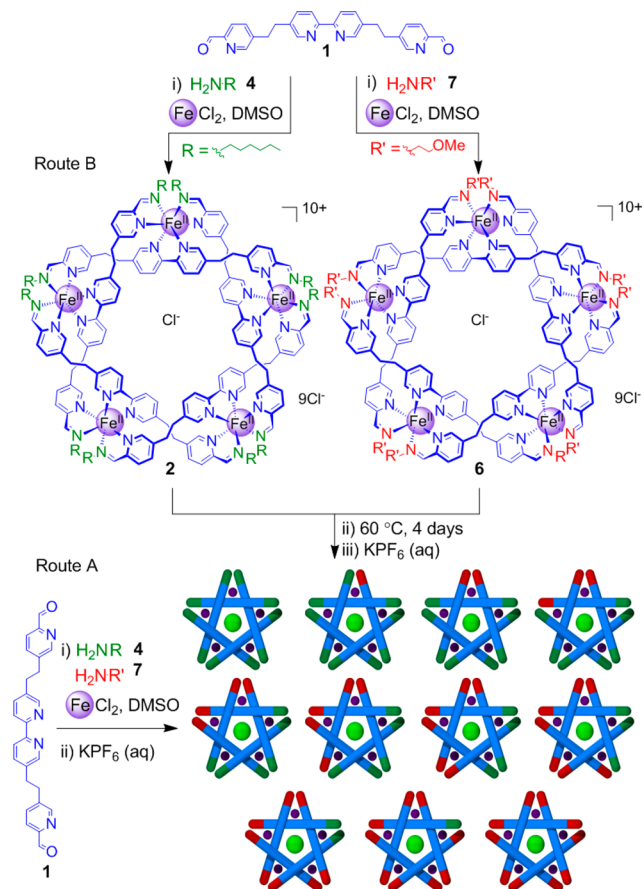
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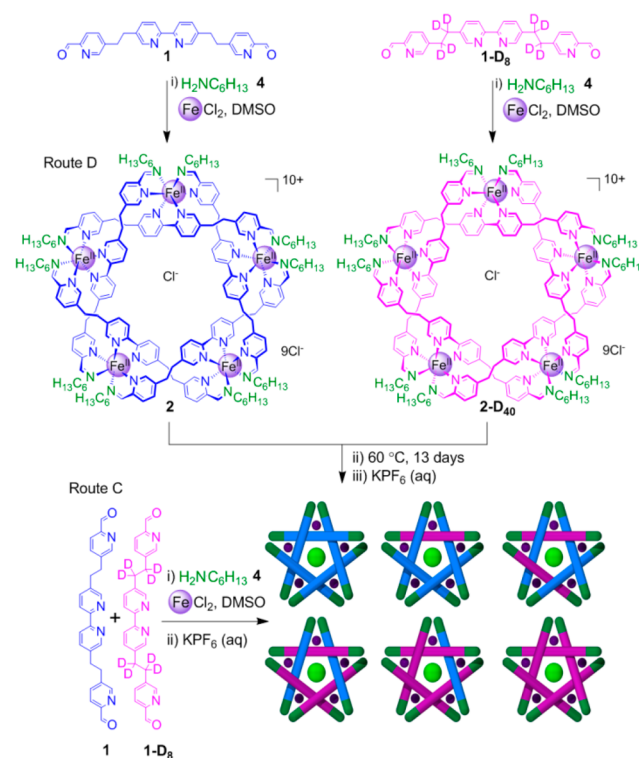
Scheme 1. Self-Assembly of (a) Open Pentameric Circular Helicate 2 and (b) Pentafoil Knot 3



Scheme 2. Exchange of Amine Residues on a Pentameric Circular Helicate



Scheme 3. Exchange of Labeled and Unlabeled Dialdehyde Residues That Form the Core of a Pentameric Circular Helicate



analyzed by ^1H NMR and electrospray ionization mass spectrometry (ESI-MS). The ^1H NMR spectrum showed broad peaks indicative of the formation of a large number of similar species (Figures S1 and S3a), and ESI-MS (Figure 1a) confirmed the expected statistical distribution of 11 (not including regional isomers) pentameric circular helicates bearing n hexylamine residues and $(10 - n)$ 2-methoxyethylamine residues (for $n = 0 - 10$). The results show that there is no statistical preference for incorporating hexyl or methoxyethyl chain amines into the circular helicates under the reaction conditions.

The second reaction (Route B, Scheme 2) monitors the exchange of amine residues between two preformed circular helicates, 2 and 6. After 24 h of heating reaction mixtures to form 2 and 6 separately, the reactions were combined and heated for another 4 days. Additional signals in the ^1H NMR spectra appeared over time (Figure S1), indicative of the formation of mixed-amine circular pentameric helicates. The exchange of amine groups, which may proceed by either direct attack by free amine or by hydrolysis, was confirmed by ESI-MS (Figures S2 and 1). After 4 days, ^1H NMR and ESI-MS showed no further changes in the amine-group distribution. The products were precipitated by the addition of aqueous KPF_6 , collected, washed, and taken up in CD_3CN . A comparison of the products from this route (B) with those of the control reaction (A) indicated that full scrambling of the amine residues had occurred: ^1H NMR (Figure S3) and ESI MS (Figure 1b) spectra for the two samples are indistinguishable, confirming that the exchange of amines via imines is dynamic under the experimental conditions, resulting in a statistical distribution of amines around and between the circular helicates. Samples of isolated (pure) helicates 2 and 6 were not found to undergo significant component exchange

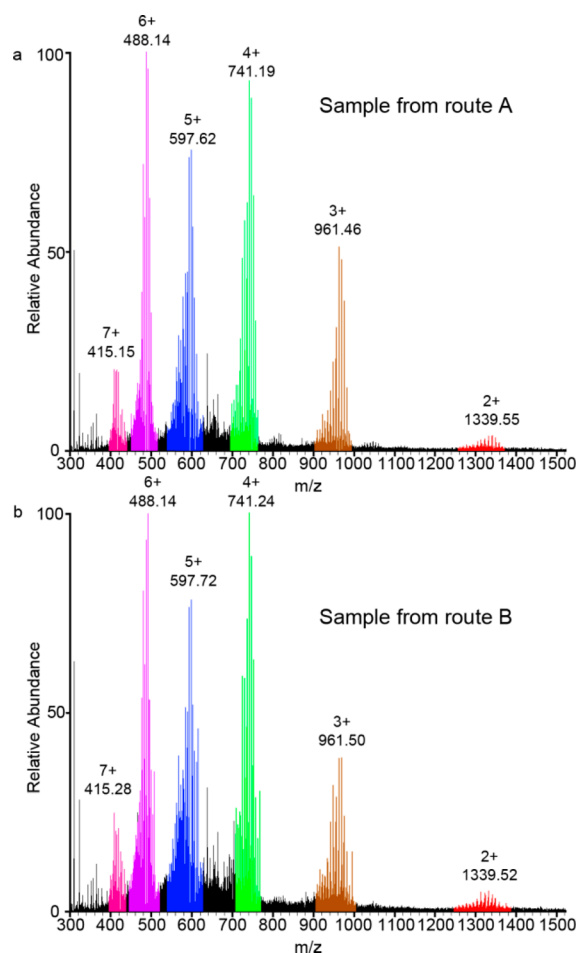


Figure 1. Electrospray ionization mass spectrometry (ESI–MS) analysis following the anion exchange of a control sample of circular pentameric helicates from route A, where amines **4** and **7** were mixed prior to addition to the reaction mixture and (b) circular pentahelicates from route B, where amines **4** and **7** were reacted separately with aldehyde **1** to generate helicates **2** and **6** which were subsequently mixed and heated for 4 days at 60 °C. Peaks corresponding to helicates bearing n hexylamine residues and $(10 - n)$ 2-methoxyethyl amine residues (for $n = 0-10$) with varying numbers of PF_6^- counterions.

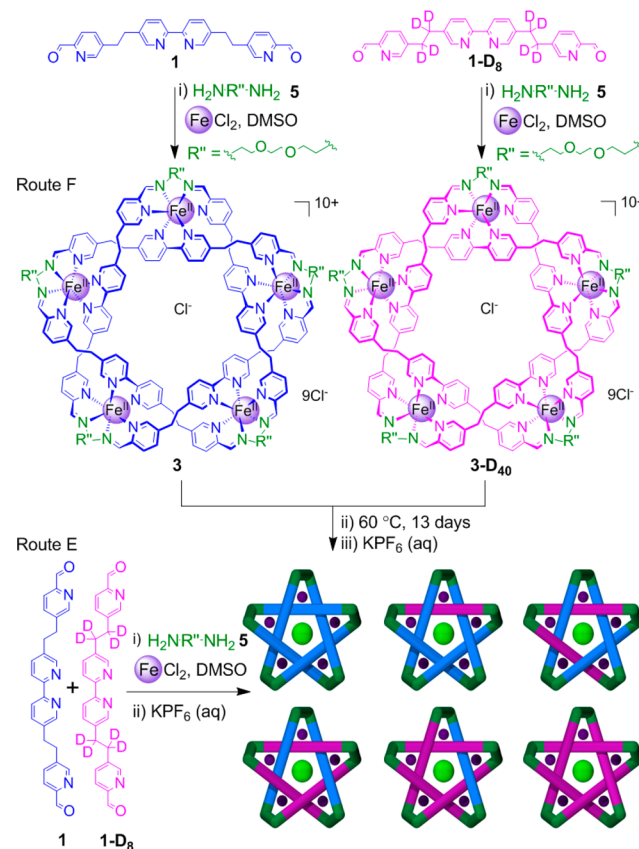
under similar reaction conditions, indicating that the presence of some reaction constituents (e.g., free amine, anions, and/or metal centers) is required for component exchange.

Having established the dynamic nature of the imine groups on the periphery of the structure, the exchange of the dialdehyde residues that form the central core of the helicate was examined. Unlike imine exchange, the exchange of a single dialdehyde building block requires major structural reorganization involving a significant number of other building blocks (amine groups, dialdehydes and metal ions). This contrasts with most complex metallocupramolecular assemblies in which the exchange of individual components can occur stepwise without requiring the disassembly of a large proportion of the structure.¹⁶ Such systems can remain largely intact throughout the ligand exchange process, resulting in a high degree of kinetic stability.

A deuterated analogue of aldehyde **1** (**1-D₈**) was prepared through a modification of the synthesis route to **1** (Scheme S2).¹⁵ Using deuterium-labeled and nonlabeled dialdehydes, it was possible to probe the dynamics of forming both the open

pentameric circular helicates and the closed-loop pentafoil knot (Schemes 3 and 4).

Scheme 4. Exchange of Labeled and Unlabeled Dialdehyde Residues That Form the Core of a Pentafoil Knot



The assembly of pentameric circular helicate **2** was investigated by a time-dependent mixing experiment (Scheme 3). A control reaction (Route C) of 0.5 equiv of aldehyde **1**, 0.5 equiv of aldehyde **1-D₈**, 2.2 equiv of hexylamine **4**, and 1.1 equiv of FeCl_2 in $\text{DMSO}-d_6$ was monitored over 14 days at 60 °C, with the analysis of the product confirming the statistical incorporation of **1** and **1-D₈** into the isotopomers of **2**. ESI-MS showed a 1:5:10:10:5:1 mixture of $2/2\text{-D}_8/2\text{-D}_{16}/2\text{-D}_{24}/2\text{-D}_{32}/2\text{-D}_{40}$ (Figure 2a, left) after 48 h. This distribution remained unchanged under the reaction conditions for another 12 days at 60 °C.

To monitor the exchange of dialdehyde components between labeled and nonlabeled circular helicates, dialdehyde **1** was reacted with FeCl_2 and hexylamine **4** under the standard conditions for 48 h. Dialdehyde **1-D₈** was reacted under similar conditions in a separate reaction. The two reaction mixtures were combined (Route D, Scheme 3) and monitored over the course of 13 days at 60 °C by ESI–MS. After 24 h, predominately two species, homoligand strand circular helicates **2** and **2-D₄₀**, were present. The number of mixed-ligand-strand circular helicates increased steadily over the next 12 days (Figure 2b–e, left) until an essentially fully scrambled statistical distribution was reached (Figure 2e, left). ^1H NMR analysis closely matched the spectrum of the control sample and showed no significant degradation of the circular helicates (Figure S5).

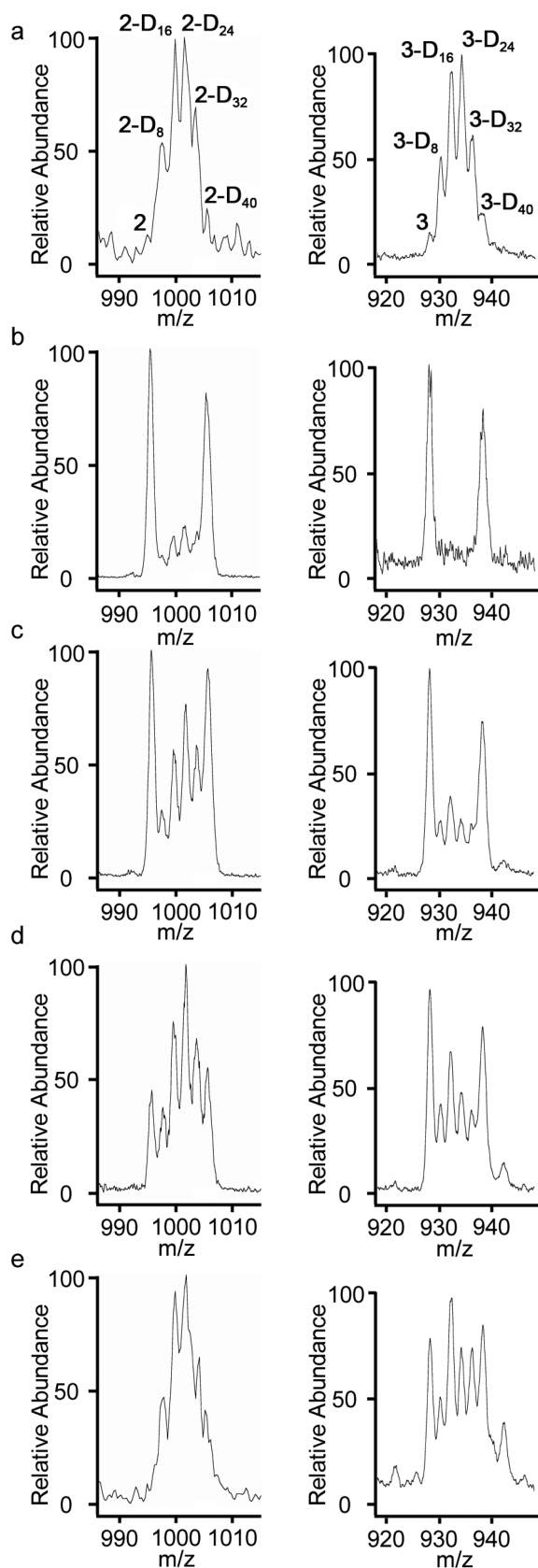


Figure 2. Electrospray ionization mass spectrometry (ESI-MS) analysis following anion exchange of (left, a) a control sample of pentameric circular helicate isotopomers from route C, where aldehydes **1** and **1-D₈** were mixed prior to the addition of amine **4**. (b–e) Pentameric circular helicate isotopomers from route D, where aldehydes **1** and **1-D₈** were reacted separately with amine **4** to

Figure 2. continued

generate helicates **2** and **2-D₄₀**, which were subsequently mixed and held at 60 °C. After (b) 1 day, (c) 3 days, (d) 6 days, and (e) 13 days. (Right, a) Control sample of pentafoil knot isotopomers from route E, where aldehydes **1** and **1-D₈** were mixed prior to the addition of diamine **5**. (b–e) Pentafoil knot isotopomers from route F, where aldehydes **1** and **1-D₈** were reacted separately with diamine **5** to generate pentafoil knots **3** and **3-D₄₀**, which were subsequently mixed and held at 60 °C. After (b) 1 day, (c) 3 days, (d) 6 days, and (e) 13 days.

A similar set of experiments was carried out to probe the dialdehyde residue exchange from the core of pentafoil knots (Scheme 4). A control reaction (Route E) of 0.5 equiv of aldehyde **1** and 0.5 equiv of aldehyde **1-D₈** with 1.1 equiv of diamine **5** and FeCl₂ in DMSO was held at 60 °C and monitored by ¹H NMR and ESI-MS. After 48 h, ESI-MS showed the expected 1:5:10:10:5:1 statistical distribution of mixed-ligand-strand pentafoil knots (**3/3-D₈/3-D₁₆/3-D₂₄/3-D₃₂/3-D₄₀**) (Figure 2a, right). The isotopomer distribution remained constant over longer reaction periods with no evidence of further changes in composition.

To monitor the exchange of dialdehyde components between labeled and nonlabeled pentafoil knots, dialdehyde **1** was reacted with FeCl₂ and diamine **5** under the standard conditions for 48 h. Dialdehyde **1-D₈** was reacted under similar conditions in a separate reaction. The two reaction mixtures were combined (Route F, Scheme 4), maintained at 60 °C, and monitored by ESI-MS. After 24 h, little exchange of the labeled and unlabeled dialdehyde building blocks between the **3** and **3-D₄₀** pentafoil knots was observed (Figure 2b, right). After 3 and 6 days, a small amount of exchange had occurred (Figure 2c,d, right), but after 13 days, the amount of dialdehyde exchange between the closed-loop pentafoil knots (Figure 2e, right) is comparable only to the amount exchanged between the open pentameric circular helicates after 6 days (Figure 2d, left). Even after 60 days under the reaction conditions at 60 °C, a fully scrambled statistical distribution was not reached. ¹H NMR indicated that by this time significant decomposition of the knots had occurred.

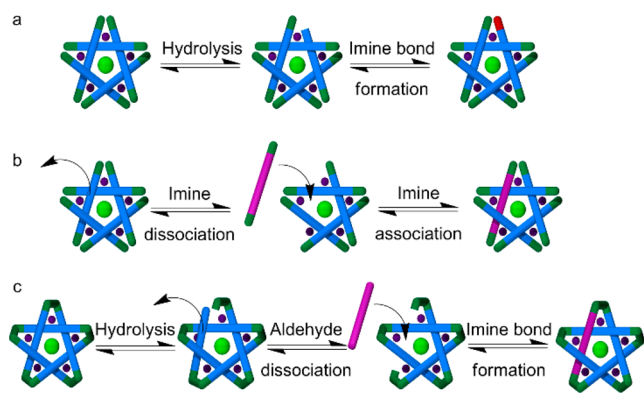
■ IMPLICATIONS FOR THE MECHANISM OF AN IMINE-BASED CIRCULAR HELICATE AND PENTAFOIL KNOT SELF-ASSEMBLY

The experimental observations regarding building block exchange shed light on the process of supramolecular assembly of imine-based circular helicates and pentafoil knots. Although both amine and dialdehyde components undergo intercomplex exchange under the conditions used for their synthesis from the parent building blocks, the time scale required for complete scrambling (13 days in the case of open pentameric circular helicates and >60 days for the pentafoil knot) is far longer than the reaction time that gives the maximum yield of the products (2 days), indicating that neither self-assembly reaction is under thermodynamic control under the most effective conditions for synthesis. Rather, the slow kinetics of component exchange (particularly of the core dialdehyde-derived units) in the circular helicate and knot act as kinetic traps as the initially formed linear oligomeric and polymeric intermediates undergo more rapid rearrangements and component exchange.

The difference in the exchange rates between the components on the periphery of the circular helicate (the

amines) and those that form the core (the dialdehydes) can be rationalized in terms of the number of bonds and stabilizing interactions that have to be broken during the exchange of each type of component. The hydrolysis of an imine bond (or direct displacement by a free amine) and the dissociation of the amine are the only requirements for the exchange of amine components (Scheme 5a). An intermediate aldehyde group is

Scheme 5. (a) Amine and (b and c) Dialdehyde Component Exchange Mechanisms for (a and b) Imine-Based Pentameric Cyclic Helicates and (c) Closed-Loop Pentafoil Knots



still able to coordinate to the iron(II) center (Scheme 5a, central structure), so amine exchange can occur without significantly destabilizing the supramolecular complex as a whole. However, the exchange of one of the core dialdehyde-derived components requires the breaking of two Fe–N(imine) and four Fe–N(pyridine) coordination bonds in addition to the hydrolysis (or direct amine exchange) of two imine covalent bonds (Scheme 5b).¹⁷ This is obviously a far more energetically demanding process and probably destabilizes the intermediate complex to the extent that further component exchange processes occur more rapidly on that intermediate than on the more kinetically stable circular helicate. In DMSO over the course of 13 days at 60 °C, both peripheral and core component exchange processes occur with sufficient frequency to generate a statistical distribution from isotopically labeled components in the products, and the assembly process is under complete thermodynamic control.

Component exchange processes with an imine-based pentafoil knot require even more disruption to the structure as a whole (Scheme 5c). The pentafoil knot is so kinetically stable that even though its self-assembly from the original building blocks, involving the rearrangement of initially formed linear oligomers and polymers, is complete after 48 h at 60 °C in DMSO, under the same conditions the components of the knot core have not been exchanged between knot molecules sufficiently to become statistically distributed after 60 days.

CONCLUSIONS

The high-yielding synthesis of imine-based pentameric circular helicates and pentafoil knots from amine and dialdehyde building blocks is a remarkable example of metallosupramolecular assembly. The products form as a result of numerous well-defined effects and interactions: octahedral metal-ion helicate formation entwines the ligand strands, short linkers between the chelating groups favor cyclic double helicates over linear triple helicates, chloride anions template

the size (pentamer) of circular helicate, and reversible imine bond formation enables error correction of initially formed linear oligomeric and polymeric species.^{11,12} Monitoring the exchange of chemically similar, but distinguishable, amines allows the dynamics of the *N*-alkyl groups that form the periphery of the self-assembled structures to be probed. Similarly, isotopic labeling enables the exchange of dialdehyde-derived components at the core of the circular helicates and knot to be monitored. The results show that these self-assembly reactions are not under thermodynamic control on the time scale and conditions generally used to synthesize these (supra)molecular structures. This finding illustrates the potential pitfalls in assuming that complex self-assembly processes proceed in a particular way without corroborating experimental evidence. In doing so, it also highlights the potential for supramolecular systems assembled using what are individually reversible and dynamic coordination bonds to be governed by a key kinetically slow, or irreversible, step (or steps), thereby delivering a particular type of nonequilibrium self-assembly process often exploited in nature.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b12800.

Experimental procedures and spectroscopic data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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