# **CHEMISTRY** A European Journal



## **Accepted Article**

Title: Equilibration of Imine-Linked Polymers to Hexagonal Macrocycles Driven by Self-Assembly

Authors: Anton D. Chavez, Austin M. Evans, Nathan C. Flanders, Ryan P. Bisbey, Edon Vitaku, Lin X. Chen, and William R. Dichtel

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: Chem. Eur. J. 10.1002/chem.201800459

Link to VoR: http://dx.doi.org/10.1002/chem.201800459

Supported by ACES



# Equilibration of Imine–Linked Polymers to Hexagonal Macrocycles Driven by Self-Assembly

Anton D. Chavez,<sup>[a,b]</sup> Austin M. Evans,<sup>[a]</sup> Nathan C. Flanders,<sup>[a]</sup> Ryan P. Bisbey,<sup>[a,b]</sup> Edon Vitaku,<sup>[a]</sup> Lin X. Chen,<sup>[a]</sup> and William R. Dichtel<sup>[a]</sup>\*

Abstract: Macrocycles based on directional bonding and dynamic covalent bond exchange can be designed with specific pore shapes, sizes, and functionality. These systems retain many of the design criteria and desirable aspects of two-dimensional (2D) covalent organic frameworks (COFs) but are more easily processed. Here we access discrete hexagonal imine-linked macrocycles by condensing truncated analogues of 1,3,5-tris(4-aminophenyl)benzene (TAPB) with terephthaldehyde (PDA). The monomers first condense into polymers but eventually convert into hexagonal macrocycles in high yield. The high selectivity for hexagonal macrocycles is enforced by their aggregation and crystallization into layered structures with more sluggish imine exchange. Their formation and exchange processes provide new insight into how imine-linked 2D COF simultaneously polymerize and crystallize Solutions of these assembled macrocycles were cast into oriented, crystalline films, expanding the potential routes to 2D materials.

The precise chemical structures and nanometer-scale internal cavities of shape-persistent macrocycles and cages have shown promise for applications in optoelectronics,<sup>[1–3]</sup> ion binding,<sup>[4,5]</sup> sensing,<sup>[6]</sup> ionic conductivity,<sup>[7]</sup> and templates for nanoparticle synthesis.<sup>[8,9]</sup> The rigidity and planarity of macrocycles lead to assemblies such as 2D networks,<sup>[10]</sup> liquid crystals,<sup>[11]</sup> or nanotubes with well-defined channels.<sup>[12]</sup> The solid-state ordering of shape-persistent macrocycles mimics that of 2D COFs, which

are extended, periodic structures with permanent porosity and high internal surface areas.<sup>[13–15]</sup> Macrocycle assemblies confer many of the same desirable features as COFs and offer superior processability and greater potential for stimuli-responsive functions.

Macrocycle formation and assembly can also provide insight into the analogous processes involved in 2D COF formation, which are poorly understood and uncontrolled. For example, both boronate ester-linked macrocycles<sup>[16]</sup> and 2D COFs assemble into layered, hexagonally packed structures through similar nucleation-elongation growth mechanisms.<sup>[17]</sup> Imine-linked structures have since emerged as the most application-relevant 2D COFs,<sup>[13]</sup> and reversible imine bond formation has also been used to form macrocycles, [18,19] cages, [20] and molecular ladders.<sup>[21]</sup> A mechanistic study of the 2D COF derived from TAPB and PDA demonstrated that the monomers rapidly condense into an amorphous network that later crystalizes into a TAPB-PDA COF.<sup>[22]</sup> Here we evaluate the formation of hexagonal iminelinked macrocycles and demonstrate that their assembly into layered structures slows imine exchange. Truncated analogues of TAPB react with PDA similarly to first form linear polymers and oligomers (Scheme 1). These soluble species are in equilibrium with hexagonal macrocycles, which aggregate into layered assemblies whose imines are far less dynamic, driving



Scheme 1. The rapid formation of polymers from the condensation of 1 and PDA that remain in equilibrium until aggregation of macrocycles stabilizes against dynamic imine exchange.

[a] A. D. Chavez, A. M. Evans, N. C. Flanders, R. P. Bisbey, Dr. E. Vitaku, Prof Lin X. Chen, Prof. W. R. Dichtel Department of Chemistry Northwestern University	[b]	A. D. Chavez, R. P. Bisbey Department of Chemistry and Chemical Biology Cornell University Ithaca, New York 14853
Evanston, Illinois 60208 E-mail: wdichtel@northwestern.edu		Supporting information for this article is given via a link at the end of the document.

#### COMMUNICATION



Figure 1. (A) MALDI-MS of 1-PDA macrocycle suggests that it is formed preferentially in 1,4-dioxane at extended reaction times. (B) Gel permeation chromatography traces of aliquots sampled at different reaction times from which condensation products of 1 and PDA (in the presence of 0.05 equiv  $CF_3CO_2H$ ) were precipitated.

macrocycle formation in high yield. In contrast, conditions that disfavor aggregation (good solvents, elevated temperatures) cause them to re-equilibrate with polymers and oligomers. The macrocycles may be solution cast into ordered, crystalline films with similar structural precision as COFs. These findings provide insight into the crystallization of imine-linked 2D COFs and portend future efforts to obtain 2D polymers by cross-linking assembled macrocycles in the solid-state,  $^{\left[23\right]}$  at the air-water interface,  $^{\left[24\right]}$  or on surfaces.  $^{\left[25\right]}$ 

A truncated analogue (1) of TAPB was prepared by replacing one of the three amines with a decyloxy group while maintaining the relative orientation of the two remaining aryl amines. A solution of 1 (10 mM) and PDA (10 mM) in 1,4-dioxane immediately yellows upon the addition of CF<sub>3</sub>CO<sub>2</sub>H (5 mM), and a precipitate forms within minutes. After isolation by centrifugation and washing with Et<sub>2</sub>O, the precipitate was identified as 1-PDA macrocycles, which formed in 75% isolated yield. Gel permeation chromatography (GPC) of the macrocycles showed a single narrow peak (Figure S1) and matrix-assisted laser desorption ionization mass spectrometry (MALDI-MS) analysis provided the expected [M+H]<sup>+</sup> peak of the hexagonal 1-PDA macrocycle at m/z = 3544.9 (Figure 1A). Masses corresponding to other ring sizes or linear oligomers were not observed. The modularity of this design strategy was evaluated using the extended dialdehyde, biphenyl-4,4-dicarboxaldehyde, in place of PDA. The product of this reaction, performed under identical reaction conditions, exhibited a similar GPC chromatogram (Figure S4) and selectivity for the hexagonal structural by MALDI-MS (Figure S5).

We probed the mechanism of macrocycle formation by decreasing the CF<sub>3</sub>CO<sub>2</sub>H concentration ten-fold (0.5 mM). These conditions delay the onset of macrocycle precipitation to approximately 35 min, providing more time to monitor the solution composition. Imine-containing products were isolated from aliquots by precipitation into Et<sub>2</sub>O, and GPC analysis of the recovered solids at 10 min revealed the initial formation of linear polymers as the major products, with peaks corresponding to macrocycles and oligomers appearing minor shoulders. (Figure 1B). At longer reaction times, the intensity of the high molecular weight peak decreased, and the peak corresponding to the hexagonal macrocycle became more prominent. Aliquots of the reaction mixture taken at 240 min show the macrocycle as the dominant species. Several examples of polymer-to-macrocycle transitions have been reported, [26-34] although mixtures of different macrocycle sizes are often observed.<sup>[26-30]</sup> The self-sorting process that provides the 1-PDA macrocycles requires no removal of byproducts, as it is driven by macrocycle aggregation. These observations parallel imine-linked COF formation, which initially form amorphous polymer networks that crystallize over time.<sup>[22]</sup> As such, these macrocycles are informative model systems for understanding imine-linked COF formation, in addition to being intriguing assemblies themselves.



Figure 2. (A) Photograph of reaction solutions of 1 and PDA with various 1,4-dioxane/THF solvent mixtures (10 mM 1, vol% dioxane shown in white) taken after 9 days. (B) Gel permeation chromatography traces of a precipitated (60% dioxane) and a soluble (50% dioxane) solution.

#### WILEY-VCH

### COMMUNICATION

The solubility of the macrocycles in the THF mobile phase of the GPC experiments, juxtaposed with their low solubility in 1,4-dioxane, led us to study the polymer/macrocycle equilibrationin mixtures of the two solvents. 1 (10 mM) was condensed with PDA (10 mM) in the presence of CF<sub>3</sub>CO<sub>2</sub>H (5 mM) in varied ratios of THF and 1,4-dioxane (Figure 2). Including THF as a co-solvent dramatically slowed the rate of precipitation from minutes to several days across the 50-100 vol% dioxane experiments. No precipitate formed from reactions that contained less than 50% 1,4-dioxane, even after 3 weeks. GPC analysis of aliquots taken from each reaction mixture (after precipitation of imine-linked products into Et2O) revealed that 1-PDA macrocycles were the major product from all reaction mixtures that formed precipitates. Reaction mixtures that did not form precipitates showed prominent peaks for the polymer by GPC (Figure S6). Furthermore, as each reaction mixture contains CF<sub>3</sub>CO<sub>2</sub>H, the imine bonds remain capable of exchange, and the polymer and macrocycle populations respond to changes in solvent composition. For example, adding 1,4-dioxane to the 20 vol% 1,4-dioxane reaction mixture (which contains mostly polymer) to obtain a diluted 70 vol% 1,4-dioxane solution results in macrocycle precipitation, as confirmed by GPC (Figure S7).

Likewise, adding THF to the 80 vol% 1,4-dioxane reaction mixture (which is a suspension of precipitated macrocycles) to obtain a diluted 30 vol% 1,4-dioxane solution resulted in complete dissolution of the precipitate over 2 weeks, after which polymeric products were observed by GPC (Figure S8). Finally, heating a 100 vol% 1,4-dioxane reaction mixture to 60 °C also dissolves the precipitated macrocycles, which re-equilibrate to polymeric species (Figure S9). Once cooled to room temperature, the solution precipitates again with only macrocycles observed by GPC. Collectively, these experiments demonstrate that macrocycle formation is driven by aggregation that depends strongly on solvation. Although solvation effects on macrocycle formation were noted by Moore and coworkers, [35,36] the reversible equilibration between polymers and discrete macrocycles has not been studied extensively. Even slight perturbations of the solvent composition or temperature influence the macrocycle solubility to the equilibrium to either product.

Crossover experiments discriminate whether the depolymerization process occurs through intermolecular or



Figure 3. Matrix-assisted laser desorption ionization mass spectra of macrocycles formed directly from 1-PDA (left) or 2-PDA (right) polymers or from mixtures of either 1-PDA or 2-PDA polymers (top middle) or macrocycles (bottom middle). Mixtures were reacted for 18 h.

## COMMUNICATION

intramolecular processes, such as imine hydrolysis. We prepared a diamine analogue, 2, which differs from 1 by one additional methylene unit in its alkoxy group. We prepared and isolated separate samples of the 1-PDA and 2-PDA polymers. Each polymer sample transforms into the corresponding macrocycle when redispersed in 1,4-dioxane in the presence of CF<sub>3</sub>CO<sub>2</sub>H (Figures 3 & S10-11). When equal equivalents of the two polymers were mixed and redispersed in 1,4-dioxane in the presence of CF3CO2H, a nearly statistical distribution of macrocycles containing mixtures of 1 and 2 was obtained (Figure 3). Therefore, 1 and 2 from different polymer chains are incorporated into each macrocycle with equal probability, suggesting that macrocycle formation occurs via small molecules liberated from each polymer. In contrast, when equal volumes of reaction mixtures containing 1-PDA and 2-PDA macrocycles were mixed in a 1:1 ratio, very little crossover of 1 and 2 among the macrocycles is observed. This result differs from reports of other macrocycles with dynamic linkages (including imines), which do exchange their building blocks in similar crossover experiments.<sup>[19,31,34]</sup> Our experiments suggest that macrocycle aggregation slows imine exchange, presumably by forming a layered structure that prevents nucleophiles from adding to iminium ion intermediates. Therefore, this crystallization is the driving force for the exclusive formation of the six-membered macrocycles, which presumably have minimal ring strain and a stronger tendency to aggregate relative to other potential products. The interlayer stacking provides a stabilizing force against imine hydrolysis. Conditions that interrupt this aggregation (dissolution by THF or heating) cause the macrocycles to re-equilibrate to mixtures containing linear oligomers and polymers. Similar aggregation-driven effects are likely during the formation of TAPB-PDA COF, and presumably other imine-linked 2D COFs, in which imines incorporated into 2D layered structures undergo hydrolysis and exchange much more slowly than those in solution or incorporated into amorphous regions. This understanding will inform future efforts to improve 2D COF materials quality as interlayer stacking is a key process that drives COF formation.[37-39]

The long-range order of the aggregated macrocycles was characterized by in situ wide-angle X-ray scattering. A 1-PDA macrocycle suspension in 1,4-dioxane provided diffraction peaks consistent with a hexagonal packed arrangement of macrocycles with P6 symmetry (Figure 4A). Transmission electron microscopy images of a drop-cast solution of precipitated 1-PDA macrocycles revealed the presence of micron-sized, rod-like crystallites. Higher magnification images of these crystallites showed the presence of distinctive line features with uniform spacings on the order of 3 nm, which is consistent with the expected size of a 1-PDA macrocycle. These images suggest that the macrocycles aggregate to form tubular structures that bundle hexagonally, (Figure 3B). The macrocycles are also amenable to forming thin films via drop-casting dilute solutions (100 µM in THF) onto a silicon wafer. After evaporation at 40 °C, grazing-incidence wideangle X-ray scattering analysis revealed the presence of a crystalline, oriented film (Figure S12). Although accurately modeling the X-ray pattern was not possible because the first



**Figure 4.** (A) Wide-angle X-ray scattering analysis of a **1-PDA** reaction solution in 100% dioxane. (B) Transmission electron microscopy (TEM) image of dropcast reaction solution **1-PDA**. (C) A magnified TEM image of B.

peak was partially blocked by the beam stop, the spacing and intensity of the peaks suggested a hexagonally packed network of macrocycles with a preferred orientation perpendicular to the surface. These results suggest that discrete macrocycles analogous to 2D COFs may serve as alternative building blocks of designed 2D materials.<sup>[40]</sup>

In conclusion, imine-linked macrocycles form in high isolated yields under conditions that favor macrocycle aggregation. The monomers first condense into a dynamic mixture of monomers, linear oligomers, and polymers that convert to aggregated macrocycles whose imines undergo exchange much more slowly. Experiments that varied solvent composition or temperature, as well as those that probe crossover, are consistent with aggregation serving as a kinetic trap that shifts the population of imine-linked structures to six-membered macrocycles in high yield. The assembled macrocycles represent dispersible building blocks for the formation of oriented films, potentially providing new routes to designed organic 2D materials. Given their structural similarity and the findings of previous mechanistic studies of imine-linked 2D COFs, it is very likely that this class of COFs forms through a similar pathway where the imine bonds become less dynamic as they form layered structures. This insight will shape the future development of 2D polymer syntheses with improved control and materials quality.

#### Acknowledgements

## COMMUNICATION

This work was funded by the Army Research Office through the Multidisciplinary University Research Initiative (MURI, W911NF-15-1-0447, to W.R.D.). A.D.C. was supported through a National Defense Science and Engineering Graduate Fellowship (NDSEG). This work made use of the Integrated Molecular Structure Education and Research Center (IMSERC) at Northwestern University, which has received support from the National Science Foundation (NSF; (CHE-1048773), the Soft and Hybrid Nanotechnology Experimental (SHvNE) Resource (NSF NNCI-1542205), the State of Illinois, and the International Institute for Nanotechnology (IIN). This research used resources of the Advanced Photon Source, a U.S. Department of Energy (DOE) Office of Science User Facility operated for the DOE Office of Science by Argonne National Laboratory under Contract No. DE-AC02-06CH11357. N.C.F is partially supported by Basic Energy Science, CBG Division, US Department of Energy and resources at the Advanced Photon Source were funded by the National Science Foundation under Award Number 0960140. A.M.E. is supported by the National Science Foundation Graduate Research Fellowship (DGE-1324585), and Northwestern University and the International Institute for Nanotechnology via a Ryan Fellowship.

Keywords: dynamic covalent chemistry • self-assembly • covalent organic frameworks • imines • supramolecular chemistry

- M. Iyoda, J. Yamakawa, M. J. Rahman, Angew. Chem. Int. Ed. 2011, [1] 50, 10522-10553
- S.-Q. Zhang, Z.-Y. Liu, W.-F. Fu, F. Liu, C.-M. Wang, C.-Q. Sheng, Y.-F. [2] Wang, K. Deng, Q.-D. Zeng, L.-J. Shu, et al., ACS Nano 2017, 11, 11701–11713.
- M. Ball, Y. Zhong, B. Fowler, B. Zhang, P. Li, G. Etkin, D. W. Paley, J. [3] Decatur, A. K. Dalsania, H. Li, et al., J. Am. Chem. Soc. 2016, 138, 12861-12867
- S. Lee, C.-H. Chen, A. H. Flood, *Nat. Chem.* **2013**, *5*, 704–710. C. N. Carroll, J. J. Naleway, M. M. Haley, D. W. Johnson, *Chem. Soc.* [4] [5]
- Rev. 2010. 39. 3875. [6] D. E. Gross, L. Zang, J. S. Moore, Pure Appl. Chem. 2012, 84, 869-
- 878
- B. Gong, Z. Shao, Acc. Chem. Res. 2013, 46, 2856-2866.
- [8] R. McCaffrey, H. Long, Y. Jin, A. Sanders, W. Park, W. Zhang, J. Am. *Chem. Soc.* **2014**, *136*, 1782–1785. L. Qiu, R. McCaffrey, Y. Jin, Y. Gong, Y. Hu, H. Sun, W. Park, W.
- [9] Zhang, Chem. Sci. 2018, DOI 10.1039/C7SC03148C.

- [10] K. Iritani, M. Ikeda, A. Yang, K. Tahara, K. Hirose, J. S. Moore, Y. Tobe, Langmuir 2017 33 12453-12462
- [11] T. Wöhrle, I. Wurzbach, J. Kirres, A. Kostidou, N. Kapernaum, J. Litterscheidt, J. C. Haenle, P. Staffeld, A. Baro, F. Giesselmann, et al., Chem. Rev. 2016, 116, 1139-1241.
- Y. Zhong, Y. Yang, Y. Shen, W. Xu, Q. Wang, A. L. Connor, X. Zhou, L. [12] He, X. C. Zeng, Z. Shao, et al., J. Am. Chem. Soc. 2017, 139, 15950-15957
- [13] C. R. DeBlase, W. R. Dichtel, Macromolecules 2016, 49, 5297-5305.
- [14] C. S. Diercks, O. M. Yaghi, Science 2017, 355, eaal1585.
- R. P. Bisbey, W. R. Dichtel, ACS Cent. Sci. 2017, 3, 533–543. [15]
- A. D. Chavez, B. J. Smith, M. K. Smith, P. A. Beaucage, B. H. Northrop, [16] W. R. Dichtel, Chem. Mater. 2016, 28, 4884-4888.
- H. Li, A. D. Chavez, H. Li, H. Li, W. R. Dichtel, J.-L. Bredas, J. Am. [17] Chem. Soc. 2017, 139, 16310-16318.
- J. Jiang, R. Y. Dong, M. J. MacLachlan, Chem Commun 2015, 51, [18] 16205-16208
- C. S. Hartley, J. S. Moore, J. Am. Chem. Soc. 2007, 129, 11682-11683. [19] A. G. Slater, M. A. Little, A. Pulido, S. Y. Chong, D. Holden, L. Chen, C. [20] Morgan, X. Wu, G. Cheng, R. Clowes, et al., Nat. Chem. 2017, 9, 17-
- [21] T. Wei, J. H. Jung, T. F. Scott, J. Am. Chem. Soc. 2015, 137, 16196-16202.
- B. J. Smith, A. C. Overholts, N. Hwang, W. R. Dichtel, Chem Commun [22] 2016. 52. 3690-3693.
- M. J. Kory, M. Wörle, T. Weber, P. Payamyar, S. W. van de Poll, J. [23] Dshemuchadse, N. Trapp, A. D. Schlüter, Nat. Chem. 2014, 6, 779-784.
- W. Dai, F. Shao, J. Szczerbiński, R. McCaffrey, R. Zenobi, Y. Jin, A. D. [24] Schlüter, W. Zhang, Angew. Chem. Int. Ed. 2016, 55, 213-217.
- [25] M. Bieri, M.-T. Nguyen, O. Gröning, J. Cai, M. Treier, K. Aït-Mansour, P. Ruffieux, C. A. Pignedoli, D. Passerone, M. Kastler, et al., J. Am. Chem.
- Soc. 2010, *132*, 16669–16676. G. Ercolani, L. Mandolini, P. Mencarelli, S. Roelens, *J. Am. Chem. Soc.* [26] 1993, 115, 3901-3908.
- X. Chi, A. J. Guerin, R. A. Haycock, C. A. Hunter, L. D. Sarson, J. [27] Chem. Soc. Chem. Commun. 1995, 2563.
- [28] G. Ercolani, J. Phys. Chem. B 1998, 102, 5699-5703.
- P. Hodge, React. Funct. Polym. 2014, 80, 21-32. [29]
- S. W. Sisco, B. M. Larson, J. S. Moore, *Macromolecules* **2014**, 47, 3829–3836. [30]
- W. Zhang, J. S. Moore, J. Am. Chem. Soc. 2005, 127, 11863–11870.
  Y. Jin, A. Zhang, Y. Huang, W. Zhang, Chem. Commun. 2010, 46, 8258.
  D. E. Gross, J. S. Moore, Macromolecules 2011, 44, 3685–3687. [31]
- [32]
- [33] [34]
- D. E. Gross, E. Discekici, J. S. Moore, Chem. Commun. 2012, 48, 4426. [35] D. Zhao, J. S. Moore, J. Org. Chem. 2002, 67, 3548-3554
- [36] D. Zhao, J. S. Moore, Macromolecules 2003, 36, 2712–2720.
- A. Halder, S. Kandambeth, B. P. Biswal, G. Kaur, N. C. Roy, M. [37]
- Addicoat, J. K. Salunke, S. Banerjee, K. Vanka, T. Heine, et al., Angew. Chem. Int. Ed. 2016, 55, 7806-7810.
- [38] F. Auras, L. Ascherl, A. H. Hakimioun, J. T. Margraf, F. C. Hanusch, S. Reuter, D. Bessinger, M. Döblinger, C. Hettstedt, K. Karaghiosoff, et al., J. Am. Chem. Soc. 2016, 138, 16703–16710.
- [39] S. B. Alahakoon, G. T. McCandless, A. A. K. Karunathilake, C. M.
- Thompson, R. A. Smaldone, Chem. Eur. J. 2017, 23, 4255–4259. [40] H. Yang, Y. Du, S. Wan, G. D. Trahan, Y. Jin, W. Zhang, *Chem. Sci.* **2015**, 6, 4049–4053.

#### WILEY-VCH

## COMMUNICATION

### COMMUNICATION



**Stuck in the Stacks:** Trigonal diamines condensed with linear dialdehydes provide discrete macrocycles that are structurally similar to two-dimensional covalent organic frameworks (COFs). Like their COF counterparts, the monomers first form linear polymers, which overtime convert exclusively into hexagonal macrocycles that aggregate into layered structures, slowing the kinetics of imine exchange.

Anton D. Chavez, Austin M. Evans, Nathan C. Flanders, Ryan P. Bisbey Edon Vitaku, Lin X. Chen and William R. Dichtel\*



Equilibration of Imine–Linked Polymers to Hexagonal Macrocycles Driven by Self-Assembly