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# One-Pot Synthesis of Hybrid Macrocyclic Pentamers with Variable Functionalizations around the Periphery

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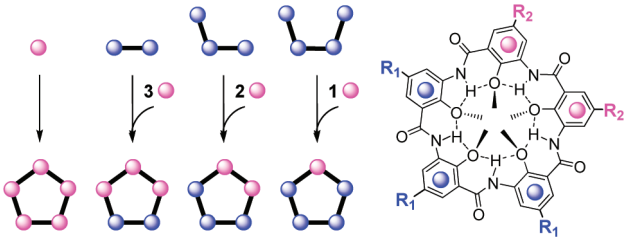
## ABSTRACT




**Rather than four- or six-residue macrocylces, one-pot macrocyclization allows for the highly selective formation of five-residue macrocycles rigidified by intramolecular hydrogen bonds. Variable functionalizations around the pentameric periphery were achieved by reacting monomers with higher oligomers bearing different exterior side chains. The formation of these hybrid pentamers suggests a chain-growth mechanism for the one-pot macrocyclization where the successive addition of monomers onto higher oligomers is faster than those between two monomers or two higher oligomers.**

The "macrocyclic effect" is physically conferred by the preorganized macrocyclic backbones, the formation of which, however, being entropically disfavored. This largely accounts for the low yield formation of the desired macrocycles along with an observation of many byproducts, including linear/cyclic oligomers of various lengths.[1a] To diminish this entropic cost and also to promote the effective macrocyclization, various strategies[1] have been developed that include one-step cyclization, templated cyclization, intramolecular ring closure, intermolecular coupling, and dynamic covalent bond formation.

Within the context of establishing alternative protocols for improved macrocyclization efficiency, conformation-assisted[2] and H-bonding-directed[3] macrocyclizations were conceived that utilize the conformationally biased

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(1) For selected reviews, see: (a) Zhang, W.; Moore, J. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 4416. (b) Faust, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 2825. (c) Höger, S. *Chem.—Eur. J.* **2004**, *10*, 1320. (d) Borisova, N. E.; Reshetova, M. D.; Ustynyuk, Y. A. *Chem. Rev.* **2007**, *107*, 46.

(2) (a) Eschenmoser, A. *Angew. Chem., Int. Ed.* **1988**, *27*, 5. (b) Blankenstein, J.; Zhu, J. P. *Eur. J. Org. Chem.* **2005**, 1949. (c) Imabeppu, F.; Katagiri, K.; Masu, H.; Kato, T.; Tominaga, M.; Therrien, B.; Takayanagi, H.; Kaji, E.; Yamaguchi, K.; Kagechika, H.; Azumaya, I. *Tetrahedron Lett.* **2006**, *47*, 413. (d) Campbell, F.; Plante, J.; Carruthers, C.; Hardie, M. J.; Prior, T. J.; Wilson, A. J. *Chem. Commun.* **2007**, 2240. (e) Yokoyama, A.; Maruyama, T.; Tagami, K.; Masu, H.; Katagiri, K.; Azumaya, I.; Yokozawa, T. *Org. Lett.* **2008**, *10*, 3207. (f) Katagiri, K.; Tohaya, T.; Masu, H.; Tominaga, M.; Azumaya, I. *J. Org. Chem.* **2009**, *74* (7), 2804. (g) Campbell, F.; Wilson, A. J. *Tetrahedron Lett.* **2009**, *50* (19), 2236. (h) He, L.; An, Y.; Yuan, L. H.; Feng, W.; Li, M. F.; Zhang, D. C.; Yamato, K.; Zheng, C.; Zeng, X. C.; Gong, B. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 10850. (i) Geng, M.; Zhang, D.; Wu, X.; He, L.; Gong, B. *Org. Lett.* **2009**, *11*, 923.

(3) (a) Carver, F. J.; Hunter, C. A.; Shannon, R. J. *Chem. Commun.* **1994**, 1277. (b) Bohme, F.; Kunert, C.; Komber, H.; Voigt, D.; Friedel, P.; Khodja, M.; Wilde, H. *Macromolecules* **2002**, *35*, 4233. (c) Srinivasan, A.; Ishizuka, T.; Osuka, A.; Furuta, H. *J. Am. Chem. Soc.* **2003**, *125*, 878. (d) Yuan, L.; Feng, W.; Yamato, K.; Sanford, A. R.; Xu, D.; Guo, H.; Gong, B. *J. Am. Chem. Soc.* **2004**, *126*, 11120. (e) Jiang, H.; Leger, J. M.; Guionneau, P.; Huc, I. *Org. Lett.* **2004**, *6*, 2985. (f) Xing, L. Y.; Ziener, U.; Sutherland, T. C.; Cuccia, L. A. *Chem. Commun.* **2005**, 5751. (g) Hui, J. K. H.; MacLachlan, M. J. *Chem. Commun.* **2006**, 2480. (h) Zhang, A. M.; Han, Y. H.; Yamato, K.; Zeng, X. C.; Gong, B. *Org. Lett.* **2006**, *8*, 803. (i) Ahn, H. C.; Yun, S. M.; Choi, K. *Chem. Lett.* **2008**, *37*, 10. (j) Feng, W.; Yamato, K.; Yang, L. Q.; Ferguson, J. S.; Zhong, L. J.; Zou, S. L.; Yuan, L. H.; Zeng, X. C.; Gong, B. *J. Am. Chem. Soc.* **2009**, *131*, 2629. (k) Li, F.; Gan, Q.; Xue, L.; Wang, Z.-M.; Jiang, H. *Tetrahedron Lett.* **2009**, *50*, 2367. (l) Ferguson, J. S.; Yamato, K.; Liu, R.; He, L.; Zeng, X. C.; Gong, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 3150. (m) Filarowski, A.; Koll, A.; Sobczyk, L. *Curr. Org. Chem.* **2009**, *13*, 172. (n) Qin, B.; Ong, W. Q.; Ye, R. J.; Du, Z. Y.; Chen, X. Y.; Yan, Y.; Zhang, K.; Su, H. B.; Zeng, H. Q. *Chem. Commun.* **2011**, DOI:10.1039/C0CC05791F.

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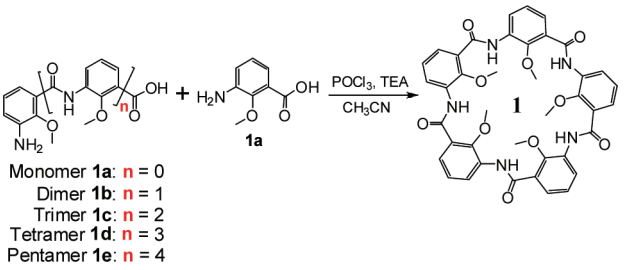
backbone to purposely predispose the two reactive termini into a predictable geometry and thus to induce a "template effect" to facilitate the intramolecular macrocyclization reaction. Despite these advancements, most of the cyclization reactions are still carried out under conditions of high dilution, and critical challenges remain in the efficient construction of macrocycles with precise control over the ring sizes and variable functionalizations around the periphery.

After extensive research, recently we successfully discovered phosphoryl trichloride, $POCl_3$, as a powerful macrocyclization reagent for selectively promoting the one-pot synthesis of aromatic pentamers such as **1** from its monomeric units **1a** (Table 1) whereby five identical unsymmetrical bifunctional monomers are assembled via intramolecular H-bonds to arrive at a unique pentagon shape,[3n] an intrinsic property shared by this class of crescent-shaped molecules,[4] and rarely found in others.[5]

As illustrated in the present work, our very recent continued exploration reveals further that $POCl_3$ also selectively produces five-residue macrocycles **2d**, **2f**, and **2d** (Figure 1 and Table 2) comprised of mixed building blocks that bear exterior side chains of different types, enabling variable functionalization around the pentameric periphery. To the best of our knowledge, we are not aware of other macrocyclic systems[1−3,5,6] that allow specific hybrid macrocycles containing variable repeating units to be prepared via one-pot comacrocyclization as the major product that is determined predominantly by a chain-growth mechanism rather than more or less by a statistical distribution pattern.[6d,e] Moreover, mechanistic investigations on one-pot macrocyclization[1−3,5a−5c,6d,6e] have been very rare with only one recent report by Gong.[3j]

**Table 1.** Chemical Yields[7a] for One-Pot Preparation[a] of Circular Pentamer **1** from the Corresponding Oligomers **1a**−**1e**




| entry | reacting partners | molar ratio | yield (%)[b] |
|---|---|---|---|
| **1** | **1a** | N.A.[c] | 46 (6)[d] |
| **2** | **1b:1a** | 1:3 | 49 |
| **3** | **1c:1a** | 1:2 | 38 |
| **4** | **1d:1a** | 1:1 | 40 |
| **5** | **1b:1c** | 1:1 | 39 |
| **6** | **1e** | N.A. | 76 |
| **7** | **1b** | N.A. | –[e] |
| **8** | **1c** | N.A. | 29[d] |
| **9** | **1d** | N.A. | –[e] |

[a] Reaction conditions: reactants **1a**−**1e** (total = 0.2 mmol), $POCl_3$ (0.4 mmol), TEA (0.6 mmol), $CH_3CN$ (2.0 mL), room temperature, 12 h. [b] Isolated yield by flash column chromatography. [c] N.A. = not applicable. [d] Yield of the hexamer. [e] No tetramer was formed.

It was demonstrated by Gong and his co-workers that, in the presence of a *symmetrical* bifunctional monomeric diacid chloride, longer oligomers such as a trimeric diamine and a trimeric diacid chloride still preferentially react with each other to undergo one-pot 3 + 3 bimolecular cyclization reactions, producing a H-bonded macrocyclic hexamer.[3j] This finding suggests that one-pot macrocyclization from the respective monomers to produce hexamers does not occur via a chain-growth mechanism.[3j] We were intrigued to find out whether this privileged cross-reactivity seen in higher oligomers is equally applicable to our *unsymmetrical* bifunctional building blocks or not. In other words, what is the mechanism that underlies the preferred formation of aromatic pentamers?

Among our initial attempts to identify the likely reaction mechanism, the macrocyclization yields of circular pentamer **1** were examined using various pairs of reacting partners (Table 1). Although it cannot be completely ruled out, the insignificant difference in yields among entries 1−5 does not favor the formation of **1** by a mechanism involving an $n + m$ (both $n$ and $m \geq 2$) bimolecular reaction between longer oligomers such as dimer **1b** and trimer **1c** (entry 5). The high yield production of **1** by acyclic pentamer **1e** (76%; entry 6) suggests the existence of low-yielding steps among entries 1−5. It is obvious that the bimolecular reaction of 2 + 3 type between dimer **1b** and trimer **1c** (entry 5) constitutes one of those low-yielding

(4) (a) Qin, B.; Chen, X. Y.; Fang, X.; Shu, Y. Y.; Yip, Y. K.; Yan, Y.; Pan, S. Y.; Ong, W. Q.; Ren, C. L.; Su, H. B.; Zeng, H. Q. *Org. Lett.* **2008**, *10*, 5127. (b) Qin, B.; Ren, C. L.; Ye, R. J.; Sun, C.; Chiad, K.; Chen, X. Y.; Li, Z.; Xue, F.; Su, H. B.; Chass, G. A.; Zeng, H. Q. *J. Am. Chem. Soc.* **2010**, *132*, 9564. (c) Yan, Y.; Qin, B.; Shu, Y. Y.; Chen, X. Y.; Yip, Y. K.; Zhang, D. W.; Su, H. B.; Zeng, H. Q. *Org. Lett.* **2009**, *11*, 1201. (d) Yan, Y.; Qin, B.; Ren, C. L.; Chen, X. Y.; Yip, Y. K.; Ye, R. J.; Zhang, D. W.; Su, H. B.; Zeng, H. Q. *J. Am. Chem. Soc.* **2010**, *132*, 5869.

(5) For reviews on H-bonded shape-persistent macrocycles, see: (a) Gong, B. *Acc. Chem. Res.* **2008**, *41*, 1376. (b) Li, Z. T.; Hou, J. L.; Li, C.; Yi, H. P. *Chem.—Asian J.* **2006**, *1*, 766. (c) Hecht, S. M.; Huc, I. *Foldamers: Structure, Properties and Applications*; Wiley-VCH: Weinheim, Germany, 2007; for reviews on foldamers, see: (d) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173. (e) Stigers, K. D.; Soth, M. J.; Nowick, J. S. *Curr. Opin. Chem. Biol.* **1999**, *3*, 714. (f) Gong, B. *Chem.—Eur. J.* **2001**, *7*, 4336. (g) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893. (h) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219. (i) Cubberley, M. S.; Iverson, B. L. *Curr. Opin. Chem. Biol.* **2001**, *5*, 650. (j) Sanford, A. R.; Yamato, K.; Yang, X.; Yuan, L.; Han, Y.; Gong, B. *Eur. J. Biochem.* **2004**, *271*, 1416. (k) Schmuck, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 2448. (l) Huc, I. *Eur. J. Org. Chem.* **2004**, 17. (m) Cheng, R. P. *Curr. Opin. Struc. Biol.* **2004**, *14*, 512. (t) Licini, G.; Prins, L. J.; Scrimin, P. *Eur. J. Org. Chem.* **2005**, 969. (n) Goodman, C. M.; Choi, S.; Shandler, S.; DeGrado, W. F. *Nat. Chem. Biol.* **2007**, *3*, 252. (o) Haldar, D. *Curr. Org. Synth.* **2008**, *5*, 61. (p) Horne, W. S.; Gellman, S. H. *Acc. Chem. Res.* **2008**, *41*, 1399. (q) Li, X.; Wu, Y.-D.; Yang, D. *Acc. Chem. Res.* **2008**, *41*, 1428. (r) Saraogi, I.; Hamilton, A. D. *Chem. Soc. Rev.* **2009**, *38*, 1726. (s) Zhao, X.; Li, Z. T. *Chem. Commun* **2010**, *46*, 1601.

(6) (a) Berni, E.; Dolain, C.; Kauffmann, B.; Lger, J.-M.; Zhan, C.; Huc, I. *J. Org. Chem.* **2008**, *73*, 2687. (b) Zhu, Y. Y.; Li, C.; Li, G. Y.; Jiang, X. K.; Li, Z. T. *J. Org. Chem.* **2008**, *73*, 1745. For one-pot synthesis of 3D-shaped pentameric macrocycle whose yields are more or less determined by a statistical distribution pattern, see: (c) Zhang, Z.; Xia, B.; Han, C.; Yu, Y.; Huang, F. *Org. Lett.* **2010**, *12*, 3285. (d) Zhang, Z.; Luo, Y.; Xia, B.; Han, C.; Yu, Y.; Chena, X.; Huang, F. *Chem. Commun.* **2011**, 2417. For an outstanding work on producing unsymmetrical macrocycles by programmed dynamic covalent assembly, see: (e) Hartley, C. S.; Moore, J. S. *J. Am. Chem. Soc.* **2007**, *129*, 11682.

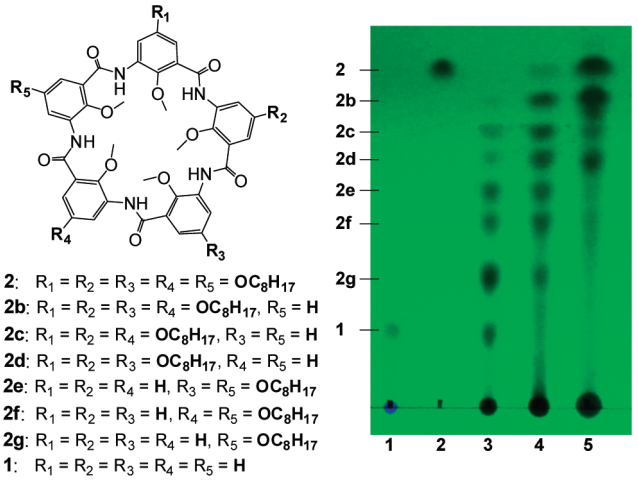
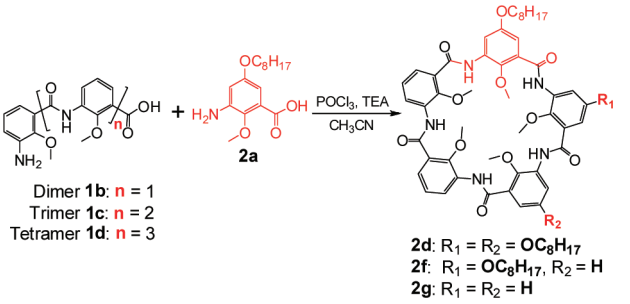



**Figure 1.** Structures of pentamers **1**, **2**, and **2b**–**2g** containing monomeric units of **1a** and **2a** in varying ratios. Using ethyl acetate/hexane/dichloromethane (5:18:5, v/v) as the eluent, all of the eight pentamers **1**, **2**, and **2b**–**2g** can be well separated in TLC plate. Lanes 3–5 = macrocylization reaction products generated by reacting **1a** and **2a** in molar ratios of 4:1, 1:1, and 1:4, respectively. From lanes 3–5, it can be seen that **1a** and **2a** indiscriminately cross-reacted with each other. Please note that the dark spots at the origin line actually derive from very tiny amounts of unknown compounds from the reaction.

steps with an estimated chemical yield of ~50% that leads to acyclic pentamer **1e**, which subsequently undergoes an intramolecular ring cyclization with a 76% yield to afford **1** in an overall yield of 39%. The 2 + 2 or 3 + 3 bimolecular reaction types involving dimer **1b** (entry 7) or trimer **1c** (entry 8), respectively, are not favored, either, as evidenced from no or low yield production of their respective cyclized tetramer or hexamer. In fact, the crescent-shaped acyclic tetramer cannot even undergo an intramolecular ring cyclization to produce the circularly folded tetramer (entry 9). The production of a hexamer from **1c** (entry 8) was also completely suppressed in the presence of competing monomer **1a** (entry 3), suggesting that the reaction between monomer **1a** and trimer **1c** or between dimer **1b** (generated *in situ* from **1a**) and trimer **1c** is faster than that between trimer **1c** itself. A low yield production of hexamer from entry 1 further suggests that the reaction rate involving an acyclic pentamer and a momomer to produce the hexamer is slower than that dictating the intramolecular cyclization of an acyclic pentamer into a circular one. Possibly, this may be due to the remote steric effect between the two end residues that disencourage the formation of oligomers longer than a pentamer.[3j] Therefore, in addition to a chain-extension

(7) (a) Our examination of possible identities of the remaining 50–60% reaction mixture produced from entry 1 of Table 1 by TLC, MS, and $^1$H NMR only allows us to confidently conclude that it does contain small amounts of intermediate amino acids (e.g., dimer amino acid, trimer amino acid, and tetra amino acid) and does not contain any unreacted starting monomer amino acid such as **1a**. Other than these, the identity of any other remaining is unknown to us. (b) Please note that pentamer **1** stains much less intensely when compared to pentamers **2** and **2b**–**2g**.

**Table 2.** Variable Functionalization of Pentamers **2d**, **2f**, and **2g** by One-Pot Co-macrocyclization[a] of Oligomers **1b**–**1d** with **2a**




| entry | reacting partners | molar ratio | product (yield, %)[b] |
|---|---|---|---|
| **1** | **1b:2a** | 1:3 | **2d** (38) |
| **2** | **1c:2a** | 1:2 | **2f** (42) |
| **3** | **1d:2a** | 1:1 | **2g** (39) |

[a] Reaction conditions: reactants **2a** and **1b**–**1d** (total = 0.2 mmol), $POCl_3$ (0.4 mmol), TEA (0.6 mmol), $CH_3CN$ (2.0 mL), room temperature, 12 h. [b] Isolated yield by flash column chromatography.

process that is highly likely, whether or not and to what extent a bimolecular reaction between *in situ* generated dimer **1b** and trimer **1c** does take place in entries 1–3, however, remain unclear.

To further clarify the reaction mechanism, a few competition experiments were designed and carried out. Although the macrocylization yields of **1** (46%, entry 1 of Table 1) and **2** (42%) from their respective monomers **1a** and **2a** are comparable,[3n] to ensure a fair comparison, the cross-reactivity between monomers **1a** and **2a** within the same experimental setting at a constant total concentration of 100 mM involving both reactants **1a** and **2a** was assessed first. Combinatorially, up to eight pentamers (Figure 1) containing monomers **1a** and **2a** in varying ratios in the backbone can be produced. After **1a** and **2a** were reacted in molar ratios of 4:1, 1:1, and 1:4 under the optimized one-pot cyclization conditions, the produced reaction mixtures containing circular aromatic pentamers of different types were analyzed using Thin Layer Chromatography (TLC) and the results are presented in Figure 1.

Mixing **1a** and **2a** in a 4:1 ratio produced two major spots, corresponding to pentamers **1**[7b] and **2g**, containing five and four **1a** units (Lane 3, Figure 1), respectively. Similarly, mixing **1a** and **2a** in 1:4 ratio produced two more major spots, corresponding to pentamers **2** and **2b**, containing five and four **2a** units (Lane 5, Figure 1), respectively. The isolated chemical yields for **2g** from Lane 3 and **2b** from Lane 5 were 20% and 21%, respectively, illustrating an excellent compatibility between **1a** and **2a** in the participating one-pot cyclization reaction. On the other hand, from the reaction involving **1a** and **2a** in equivalent amounts, the six pentamers **2b**–**2g** statistically should be produced in equal amounts that are five times as much as either **2** or **1** that also should be produced in equal amounts. This statistical distribution pattern matchs quite well with

the experimental distribution pattern seen by TLC (Lane 4 in Figure 1), further providing a convincing illustration of the excellent cross-reactivity between **1a** and **2a**, and among oligomers containing **1a** and **2a** in varying ratios.

On the basis of the above demonstrated excellent cross-reactivity between **1a** and **2a** as well as the *in situ* genearted oligomeric intermediates, competition experiments involving monomer **2a** and oligomers **1b**−**1d** in various ratios were performed (Table 2). The reaction involving a 1:3 molar ratio of **1b:2a** produced pentamer **2d** with an undetectable occurrence of pentamer **2** (entry 1), suggesting that the formation of pentamer **2d** proceeds largely by a chain-growth mechanism, rather than by 2 + 2 or 2 + 3 bimolecular condensation reactions between higher oligomers, e.g. between dimer **1b** and the *in situ* generated octyloxy-containing dimer or trimer. If the latter is the predominant mechanism to produce pentamer **2d**, the *in situ* generated octyloxy-containing dimer and trimer should be present in substantial amounts that should further couple to each other to form **2** directly by a 2 + 3 reaction, or indirectly by a 2 + 2 reaction, followed by a 4 + 1 reaction with a chemical yield comparable to that for **2d**. This, however, is contradictory with the negligible presence of pentamer **2** from the reaction. In addition, the 1 + 1 bimolecular reaction involving monomer **2a** should be comparably slower than $n + 1$ ($n \geq 2$) reaction involving oligomers **1b**−**1d** and monomer **2a**. Otherwise, the *in situ* generated octyloxy-containing dimer by the 1 + 1 reaction involving momomer **2a** may lead to an appreciable amount of pentamer **2** by 2 + 3 or 2 + 2 reactions.

The above conclusions are also consistent with and can be inferred from entries 2 and 3 from Table 2 whereby pentamers **2f** and **2g** were produced as major products with pentamer **2** remaining insignificant. Similar to **2d**, the formation of pentamers **2f** and **2g** as well as **1** (Table 1) should also proceed by a continuous chain-growth mechanism. Examination of similar chemical yields among entries 1−4 from Table 1 and entries 1−3 from Table 2 led to the inference that except for the 4 + 1 type reaction that could be a low yielding step, all the other chain growth steps of $n + 1$ type reactions likely give high yields of the corresponding oligomers. Reasonably assuming all $n + 1$ ($n = 1-3$) type reactions give a quantitative yield, then based on the respective 40% (entry 4, Table 1), 39% (entry 3, Table 2), and 76% (entry 6, Table 1) yields, the chemical yield of the 4 + 1 reaction to produce acyclic pentamers can be estimated to be ~50%. The predominant formation of hybrid pentamers **2d**, **2f**, and **2g** made up of different building blocks is a direct demonstration of variable functionalization around the periphery achievable by reacting monomers with higher oligomers that differ by exterior side chains.

In conclusion, we established here that the $POCl_3$-mediated one-pot macrocyclization proceeds predominantly by a chain-growth mechanism whereby the addition of a monomer into the growing backbones is faster than other competing bimolecular reactions between two monomers or between two higher oligomers. This one-pot macrocyclization protocol now allows an efficient preparation of aromatic pentamers carrying side chains of varying types in both its interior as previously reported by us[3n] and exterior as demonstrated in the present work. These H-bonded pentagon-shaped molecules with a modifiable interior and exterior may promise some good applications in chemistry, materials sciences, and biology.[3n,4a,4b]

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**Supporting Information Available.** Synthetic procedures and a full set of characterization data including $^1H$, $^{13}C$ NMR and MS. This material is available free of charge via the Internet at http://pubs.acs.org.