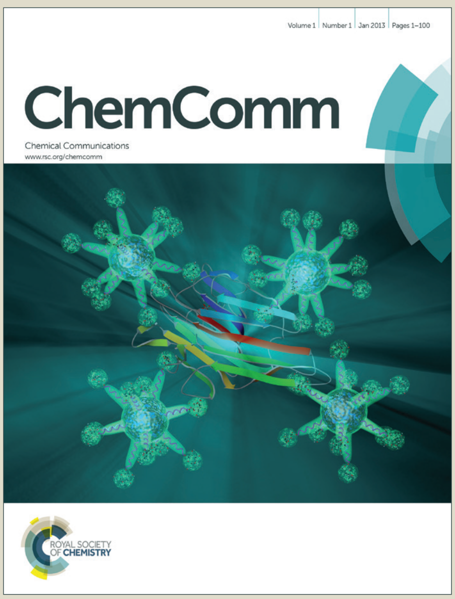
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ARTICLE TYPE

An Unusual Macrocyclization Reagent for Highly Selective One-Pot Synthesis of Strained Macrocyclic Aromatic Hexamers†

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One-pot, multi-molecular macrocyclization allows the highly selective preparation of strained macrocyclic aromatic hexamers structurally stabilized by an inward-pointing continuous hydrogen-bonding network.

Macrocyclic foldamers with their shape-persistent macrocyclic frameworks rigidified by strong intramolecuar H-bonds have attracted interest over the past decade.[1] A number of these H-bonded folding macrocycles have been shown to be capable of **i**) catalyzing highly efficient transition metal-free arylations of unactivated arenes,[2a] **ii**) selectively recognizing alkali metal ions,[2b,2c] organic cationic species,[2d,2e] or neutral guests,[2f,2g] **iii**) serving as an ion transporter across cell membranes,[2h] and **iv**) stabilizing DNA G-quadruplex structures.[2i] A rapid and efficient synthetic access to these H-bonded macrocycles should greatly facilitate their subsequent applications in the construction of increasingly sophisticated functional supramolecular architectures and materials. Accordingly, a one-pot H-bonding-assisted macrocyclization strategy has been recenly developed that, as one of the newest additions to the macrocyclization toolbox, has allowed the rapid construction of H-bonded macrocyclic foldamers of various structures, enclosing a cavity from as small as 1.4 Å to as large as 15 Å in radius.[1,3]

In line with these recent developments, we also reported "greener" one-pot syntheses of H-bonded pentameric macrocycles such as **2a**[4a-d] and **4a**[4e] respectively formed from monomeric methoxybenzene and pyridone motifs **1a** and **3a** with yields of as high as 46% in about a day (Figure 1a-b). These newly discovered greener protocols compare very favorably with our previously reported lengthy step-by-step processes[2b,2c,4f,4g] that produced circular pentamers in marginal yields of 1-5% after more than 15 steps with months' effort. One perplexing observation during our investigations is that $POCl_3$ and BOP only allow the circular pentamers **2a** and **4a** to be formed from building blocks **1a** and **3a**, respectively, and do not yield any circular fluoropentamer **6** or pyridine-based pentamer from their corresponding monomeric fluorobenzene **5**[5a,5b] or pyridine[5c-e] amino esters. This suggests that every type of monomer building block destined to form the most stable circular structure possibly may require its own unique "cognate" macrocyclization reagents that appear to be "orthogonal" to each other and function well only against its own specific set of "cognate" monomer units. It is therefore

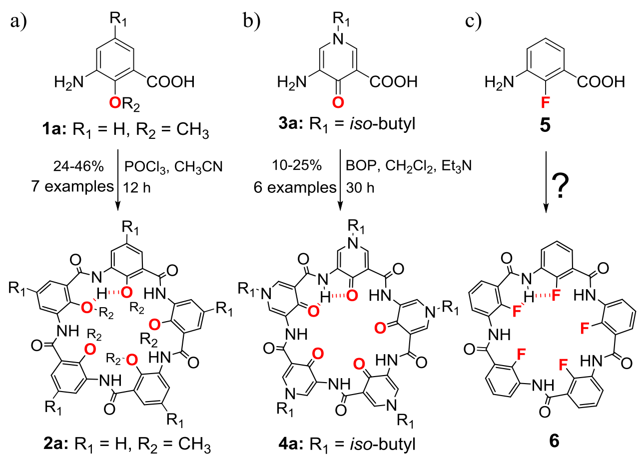


Fig. 1 (a) and (b) describe one-pot synthesis of macrocyclic pentamers **2a** and **4a** from **1a** and **3a** by using macrocyclization reagents $POCl_3$ and BOP respectively under mild conditions. (c) shows that no macrocyclization reagent thus far has been identified for the synthesis of fluoropentamer **6** from its monomeric amino ester **5**. Our computational results invariably suggest the pentameric backbones seen in **2a**, **4a** and **6** are more stable than their corresponding tetramers or hexamers.

of outstanding interest to us to continue searching for suitable one-pot macrocyclization reagents capable of selectively producing other types of pentamers such as **6** from its monomeric building block **5**.

Encouraged by the earlier and recent reports using strong alkali or other metal salts (NaH, BuLi, $AlMe_3$, etc) to directly convert unactivated esters into amides via ester aminolysis,[6] we decided to explore the possibility of using these metal salts to effect one-pot macrocyclization reactions for a possible production of circularly folded aromatic pentamers **2a**, **4a** and **6** (Figure 1). In a typical reaction setup, amino ester such as **7a** (0.5 mmol) was dissolved in anhydrous THF (5.0 mL), to which metal salt (1.5 mmol) was added in one pot under nitrogen. The reaction vessel was then tightly sealed and heated at 70 °C under constant stirring for 12 h. Under these reaction conditions and with the use of various metal salts (entries 1-6 of Table 1), hexamer **8a** (Figure 2a) was produced from **7a** in 24% yield along with trace amounts of pentamer **2a** by using aluminum salts (entries 5 and 6 of Table 1). Under the same conditions, no pyridone- or fluorobenzene-based circular pentamers **4a** and **6** or the hexameric versions

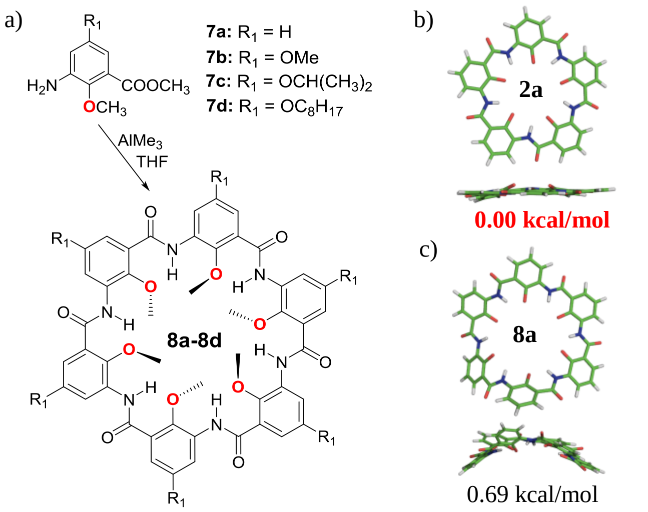


Fig. 2 (a) General structure of strained macrocyclic hexamers **8**. Top and side views of a*b initio*-optimized structures of methoxy-containing circularly folded pentamer **2a** (b) and hexamer **8a** (c) in tetrahydrofuran (THF) at the B3LYP/6-31G* level. Computationally, **8a** takes a highly distorted conformation that is less stable than nearly planar **2a** by 0.69 and 7.96 kcal/mol per repeating unit in THF and the gas phase, respectively. The computationally derived planar backbone and geometry in **2a** are nearly identical to those found in its crystal structure.[5f] For clarity of the view, all the interior methyl groups in (b) and (c) have been removed.

Table 1. Searching for suitable reagents[a] for one-pot preparation of hexamer **8a** from monomer **7a**.

Entry	Coupling reagent	Anhydrous solvent	Yield (%)[b] 2a	8a
1	MH (M = Li, Na, or K)	THF	-[c]	
2	CaH_2	THF	-[c]	
3	$ZnEt_2$	THF	-[c]	
4	LiHMDS	THF	-[c]	
5	$AlEt_3$	THF	1	11
6	**$AlMe_3$**	**THF**	**3**	**24**
7	$AlMe_3$	Toluene	6	17
8	$AlMe_3$	Dioxane	6	15
9	$AlMe_3$	CH_2Cl_2	4	15
10	$AlMe_3$	$CHCl_3$	-[c]	-[c]

[a] Reaction conditions: **7a** (0.5 mmol, 100 mM), coupling reagents (1.5 mmol), solvent (5.0 mL), 70 ºC, 12 h. [b] Isolated yield by flash column chromatography. [c] No circular products **2a** or **8a** were detected.

were generated from the corresponding monomeric amino esters.

Selective generation of hexamer **8a** vs pentamer **2a** is surprising in view of the computational results at the level of B3LYP/6-31G* (Figure 2b-c), pointing to a highly distorted structure for **8a** that is energetically less stable than the nearly planar **2a** by 0.69 and 7.96 kcal/mol per repeating unit in THF and the gas phase, respectively. This high level *ab initio* calculation has consistently allowed us to predict diverse structures of a series of H-bond-rigidified foldamer molecules including **2a** that subsequently were verified by their crystal structures.[2c,4f,5a,5f,7] The inherent instability and high structural distortion in **8a** may suggest more stable and more planar **2a** to be produced predominantly in the macrocyclization reactions. In

Table 2. Effects of solvent volume, reaction time and addition sequence involving $AlMe_3$ on one-pot preparation of hexamer **8a** from monomer **7a** in THF at 70 ºC.

Entry	Solvent volume (mL)	Reaction time (h)	Yield (%)[a,b] 2a	8a
1	**5.0**	**12**	**3**	**24**
2	2.5	12	2	22
3	10.0	12	2	18
4	15.0	12	2	15
5	10.0[c]	12	2	14
6	10.0	24	2	19
7	10.0[c]	36	2	19
8	10.0	48	2	20

[a] Reaction conditions: **7a** (0.5 mmol), $AlMe_3$ (1.5 mmol), THF, 70 ºC, 12 h. [b] Isolated yield by flash column chromatography. [c] $AlMe_3$ was added in three portions at intervals of 4 and 12 h for entries 4 and 7, respectively.

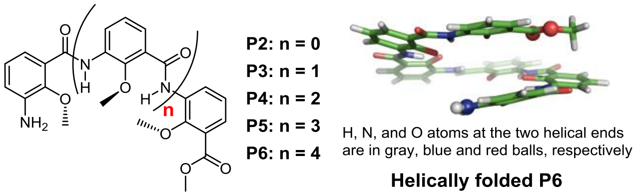
fact, our earlier investigations do show that macrocyclization regent $POCl_3$ invariably produces **2a** as the major product of up to 46% in yield and **8a** as the minor product of up to 33% in yield from monomer **1a** in acetonitrile.[4a-d] By using **7a** as the starting material and $AlMe_3$ as the macrocyclization regent, an opposite trend is found, i.e., less stable and more distorted **8a** was unexpectedly produced as the major product (entry 6, Table 1). This trend persists in solvents (eg, toluene, dioxane and dichloromethane) where macrocyclization can take place, albeit with lower yields of **8a** and higher yields of **2a** (entries 7-9). This $AlMe_3$–mediated cyclohexamerization reaction likely proceeds via an intermediate aluminium amide formed by reaction of $AlMe_3$ with RNH_2 with loss of methane, followed by coordination of the Al center to the carbonyl to activate the ester and deliver the amide nucleophile to form amide bonds. In light of this mechanism, such reactions are expected to be prone to inhibition by Lewis basic solvents and additives. The use of Lewis basic solvents such as DMF, DMSO, CH_3CN, acetone and ethyl acetate indeed completely halts the macrocyclization reaction, resulting in no generation of **2a** and **8a**. Similarly, in the presence of Lewis basic additives such as HMPA, TMEDA and PMDTA, circular products **2a** and **8a** remain undetectable either.

With respect to entry 1 in Table 2, either a deviation from the optimum reagent concentration of 100 mM as seen in entries 2-4 or addition of the same amount of $AlMe_3$ in three portions as seen in entry 5 decreases the yield of **8a** from 24% to 14 – 22 %. A prolonged reaction time of up to 48 hours marginally helps increase the yield of **8a** by up to 2% (entry 3 vs entries 6 and 8).

The substrate scope was then examined by applying the optimized macrocyclization conditions to monomeric **7b-7d** (Figure 2). Except for **7b** for which no macrocyclization product **8b** was observed, **8c** and **8d** both were produced satisfactorily from **7c** and **7d** with respective yields of 17% and 12%.

Previously, we showed that strained hexamer **8a** is generated predominantly from bimolecular reactions between dimer and tetramer molecules or between two trimer molecules for $POCl_3$-mediated one-pot cyclooligomerization of **1a**.[4d] This bimolecular reaction mechanism, rather than a chain-growth mechanism,[4c] seems to be in operation as well for $AlMe_3$-mediated one-pot cyclohexamerization of **7a** that affords **8a** (Table 3). Substantiated by the crystallographically proven helically folded

Table 3. Temperature-dependent distributions of intermediate and circular oligomers from one-pot cyclohexamerization of **7a** in THF.



Temp (°C)	Yield (%)[a,b]					
	Intermediate oligomers				Circular oligomers	
	P2	P3	P4	P5	2a	8a
25	20	15	12	7	1	4
40	14	7	11	6	1	11
60	6	4	7	4	2	19
70	3	2	3	3	3	24

[a] Reaction conditions: **7a** (0.5 mmol), $AlMe_3$ (1.5 mmol), THF (5 mL), 12 h. [b] Isolated yield by flash column chromatography.

structures adopted by hexamers of closely related structures,[4f,4g] hexamer **P6** is computationally determined to also take a helically folded structure that is rigidified by strong H-bonds (see structure in Table 3). As a result, the two reacting end groups in **P6** are rigidly placed far away from each other and the intramolecular ring closing reaction thus does not occur readily to produce **8a**. Consistent with this structural constraint and going from 25 ºC to 70 ºC, **8a** is produced increasingly more with increasing consumptions of **P2**-**P4** via bimolecular reactions. In regard with the yields of pentamer **2a**, the presence of equal or more amounts of **P5** at various temperatures suggests an energetically less favoured process for conversion of **P5** into **2a** during the $AlMe_3$-mediated cyclooligomerization reaction. Similar unfavorability is expected for conversions of **P5** into **P6** and of **P6** into **8a**.

To summarize, although we thus far have not been able to find any "cognate" macrocyclization reagent for monomeric fluorobenzene **5**[5a,5b] and pyridine[5c-e] motifs, our continued investigations do help identify trimethyl aluminum as a very surprising macrocyclization reagent, selectively producing an energetically less favored strained macrocyclic hexamer **8a** via one-pot cyclohexamerization of **7a**. We are currently investigating the possible structural origins accounting for this unusual selectivity.

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† Electronic Supplementary Information (ESI) available: A full set of characterization data including ^{1}H NMR, ^{13}C NMR, and (HR)MS. See DOI 10.1039/b000000x/

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