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BOP-mediated one-pot synthesis of C_5-symmetric macrocyclic pyridone pentamers†

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We report here, for the first time, the BOP-mediated one-pot macrocyclization that is facilitated and guided by internally placed intramolecular H-bonds to allow for the highly selective formation of five-residue cation-binding macrocycles.

H-bonded macrocycles have received considerable recent interest,[1–3] largely due to their proven ability to (i) bind either neutral[2c,3g] or cationic species,[3b,f] (ii) stabilize DNA G-quadruplex structures,[3c] (iii) serve as an ion transporter across cell membranes,[3i] (iv) selectively recognize alkaline metal ions,[3k] and (v) induce well-defined fiber formation[4] as well as other possibly realizable functions such as targeting biological pentamers.[2m,3h] The ease of synthetic access to these H-bonded macrocycles is therefore important, yet still remains a significant challenge. Occasionally, efficient construction of H-bonded macrocycles of limited types can be achieved by one-pot, H-bonding-assisted multi-molecular macrocyclization reactions.[2]

Very recently, we described an entirely new class of pentameric macrocycles made up of five alkylated 4(1*H*)-pyridone motifs meta-linked by secondary amide groups (Fig. 1a).[4] Similar to other foldamer systems reported by us that are based on the use of building blocks of methoxybenzene,[5a,b] pyridine[5c,d] and fluorobenzene,[5e] the foldable pentamers **1–6** are also rigidified by internally placed high-strength intramolecular H-bonds formed among the interior carbonyl O-atoms and the amide protons, restricting the conformational freedom of the amide bonds and biasing the aromatic backbone into a crescent shape.[4] Geometrically, the circularly folded pyridone pentamers contain a rarely observed C_5-symmetry intrinsic to the molecules[2l,6] and perfect planarity in the pentameric backbone (Fig. 1b). Functionally, the convergently aligned, properly spaced O-atoms enclose a cooperative cation-binding cavity

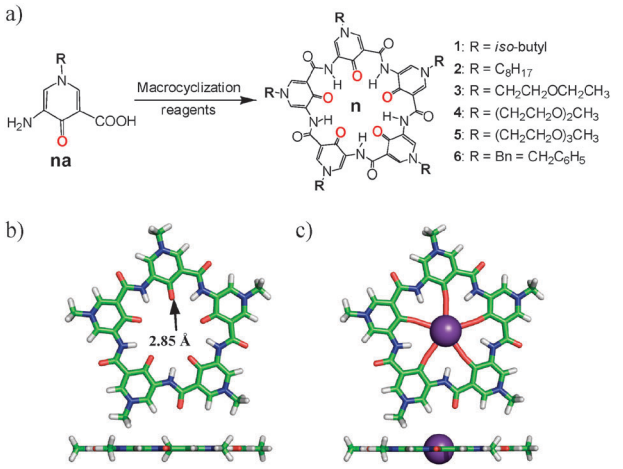

Fig. 1 (a) Schematic illustration of one-pot synthesis of macrocyclic pyridone pentamers **1–6** from their respective monomer precursors **na**. Computationally optimized structure of pyridone pentamer (b) without or (c) with a potassium cation in its interior at the level of B3LYP/6-31G*. An interior cavity of 2.85 Å in radius and macrocyclic planarity in both free and complexed forms clearly exist in these pyridone pentamers.

of 2.85 Å, near-identical to the average coordination bond distance between K^+ ions and covalently bound O-atoms (Fig. 1c). Accordingly, pentameric molecules such as **2** display high binding affinities of $\sim 10^8$ M^{-1} toward alkali metal cations. Aided further by their planar geometry, these pentamer molecules self-assemble into 1D columnar aggregates that associate to form unusual cation-containing or scarcely reported ion pair-induced fibers of varying morphologies controllable by alkali metal ions or halide salts.[4]

However, these pentameric macrocycles are typically obtained after 15–16 steps with an overall yield of 1–2%,[4] greatly limiting their potential uses in targeting biological pentamers,[3h] or as effective sequestrators of heavy metals, imaging reagents, *etc.*[7a] To overcome this low-yielding synthetic bottleneck and prompted by the successful precedents and our own recent works[2m–o] on the use of one-pot, H-bonding-assisted macrocyclization to efficiently generate varying macrocycles, we have investigated whether or not the H-bonded pyridone pentamers can be selectively produced also *via* one-pot macrocyclization starting from their

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respective monomer (Fig. 1a). And we report here our findings on the use of BOP to mediate the one-pot H-bonding-assisted construction of circular aromatic pentamers **1–6**.

Due to its poor solubility in almost all kinds of different organic solvents, pentamer **1** easily precipitates out of the solution and can be purified to high purity with ease by simply washing the precipitated **1** with excess solvents (CH_2Cl_2, MeOH, etc), **1** was therefore chosen as an ideal substrate for the initial screening of various reagents that can selectively promote one-pot synthesis of circular pentamers (Table 1).

As a recently discovered powerful macrocyclization reagent for promoting one-pot synthesis of closely related pentamers consisting of five methoxybenzene repeating units from their monomer units,[2m–o] phosphoryl trichloride ($POCl_3$, entry 1 of Table 1) was first attempted. Surprisingly, even with a complete consumption of starting monomer **1a**, no trace amount of **1** can be detected from the reaction product composed of unknown compounds of various types. The subsequent screening of other phosphorus-based reagents (entries 2 and 3, Table 1) was not encouraging either. Although we have shown previously that peptide coupling reagents including BOP that have advantages of simplicity in procedure and mild conditions are totally ineffective in promoting one-pot macrocyclization of methoxybenzene units,[2m] we still decided to carry out a further investigation on these reagents. Among a number of peptide coupling reagents tested, BOP was the only coupling reagent that allows for the preparation of **1** at a high concentration of >60 mM *via* one-pot macrocyclization in dichloromethane

Table 1 Suitable conditions[a] for one-pot preparation of circular pentamer **1** from monomer **1a**

Entry	Coupling reagent	Base	Solvent	Yield[b] (%)
1	$POCl_3$	DIEA	CH_2Cl_2 or CH_3CN	—[d]
2	$P(OPh)_3$	DIEA	CH_2Cl_2 or THF	—[d]
3	Ph_3PCl_2	DIEA	$CHCl_3$ or THF	—[d]
4	CDI	DIEA	CH_2Cl_2	—[d]
5	EDC	—[c]	CH_2Cl_2	—[d]
6	DCC	—[c]	DMF/CH_2Cl_2 (1 : 1)	—[d]
7	TSTU	DIEA	DMF/CH_2Cl_2 (1 : 1)	—[d]
8	HATU	DIEA	DMF/CH_2Cl_2 (1 : 1)	—[d]
9	HATU + HOBt	DIEA	DMF/CH_2Cl_2 (1 : 1)	—[d]
10	HBTU + HOBt	DIEA	DMF/CH_2Cl_2 (1 : 1)	—[d]
11	PyBOP	DIEA	CH_2Cl_2	—[d]
12	**BOP**	**DIEA**	**CH_2Cl_2**	**25**
13	BOP	TEA	CH_2Cl_2	2
14	BOP	Pyridine	CH_2Cl_2	—[d]
15	BOP	NMM	CH_2Cl_2	—[d]
16	BOP	DMAP	CH_2Cl_2	—[d]
17	BOP	DIEA	$CHCl_3$	19
18	BOP	DIEA	CH_3CN	17
19	BOP	DIEA	THF	17
20	BOP	DIEA	DMSO	6
21	BOP	DIEA	DMF	8
22	BOP	DIEA	DMF/CH_2Cl_2 (1 : 1)	11
23	BOP[e]	DIEA	CH_2Cl_2	18
24	BOP[f]	DIEA	CH_2Cl_2	26

[a] Reaction conditions: **1a** (0.2 mmol), coupling reagent (0.4 mmol), base (0.8 mmol), solvent (3.0 ml), room temperature, 30 hours. [b] Isolated yield by washing with CH_2Cl_2 and MeOH. [c] No base is used. [d] No product can be detected. BOP = benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate; DIEA = diisopropylethylamine; TEA = triethylamine; NMM = *N*-methyl-morpholine; DMAP = 4-dimethylaminopyridine. [e] 1.1 equivalents of BOP is used. [f] 3 equivalents of BOP is used.

(CH_2Cl_2) with a very decent chemical yield of 25% in about a day (entry 12, Table 1) that compares very favorably with an overall yield of 1–2% by the stepwise construction of **1** after months of dedicated efforts.[4] It would be interesting to note that PyBOP, structurally very similar to BOP, does not give rise to circular product **1**.

A further screening of other bases in CH_2Cl_2 does not improve the macrocyclization efficiencies (entries 13–16, Table 1) and neither does the screening of various solvents (entries 17–22). Possibly as a result of their strong H-bonding abilities that disrupt the crescent conformation in the intermediate oligomers, which is a prerequisite for the efficient backbone cyclization, the use of dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) seems to significantly impede the macrocyclization reaction, resulting in low yields of 6–11% (entries 20–22). By additionally varying the amounts of BOP used, it was found that two equivalents of BOP gives a satisfactory result (entry 12) better than or comparable to the use of less (entry 23) or more of it (entry 24).

The general utility of one-pot macrocyclization conditions was demonstrated by the satisfactory preparation of **2–5**, differing by exterior side chains (Table 2). Because the solubility of monomers **3a–5a** is not as good as **1a–2a** containing alkyl side chains, more CH_2Cl_2 (6 ml in Table 2 *vs.* 3 ml in Table 1) is needed to dissolve **3a–5a**. With the use of more solvent, yield for **1** decreases from 25% (entry 12, Table 1) to 23% (entry 1, Table 2) and **2–5** all can be produced satisfactorily.

However, one-pot synthesis of pentamer **6** turned out to be quite troublesome (Table 3). Under identical conditions using CH_2Cl_2 as the solvent where monomer **6a** can hardly dissolve, no product can be obtained (entry 1, Table 3). In DMF, a low but encouraging yield of 2% was obtained. As discussed above, the BOP-mediated one-pot reaction proceeds well in CH_2Cl_2 but not in DMF. We reasoned that a solvent pair involving both CH_2Cl_2 and DMF may better dissolve **6a** and thus may allow the reaction to proceed to a better extent. Hence, the subsequent screening was carried out by fine-tuning the solvent compositions (entries 3–6) with $\sim$10% yield obtained from CH_2Cl_2 : DMF (6 : 1, v : v). But the use of other solvents such as CH_3CN decreases yields to 3–5%.

Previously, $POCl_3$-mediated one-pot macrocyclization has been shown to occur by a chain-growth mechanism.[2n,o] By this mechanism, a hybrid pentamer consisting of two types of monomer units that differ by exterior side chains can be produced as a major product *via* co-macrocyclization of monomers of one type with other higher oligomers composed

Table 2 One-pot preparation[a] of circular pentamers **1–5** from their respective monomers **1a–5a**

Pyridone pentamer	R	Yield[b] (%)
1	*iso*-butyl	23
2	*n*-C_8H_{17}	18
3	$CH_2CH_2OCH_2CH_3$	12
4	$(CH_2CH_2O)_2CH_3$	10
5	$(CH_2CH_2O)_3CH_3$	16

[a] Reaction conditions: **na** (0.2 mmol), BOP (0.4 mmol), DIEA (0.8 mmol), CH_2Cl_2 (6.0 ml), room temperature, 30 hours. [b] Isolated yield by washing with CH_2Cl_2 and MeOH (**1** and **3**) or recrystallization from MeOH (**2**, **4** and **5**).

Table 3 One-pot preparation[a] of pentamer **6** from monomer **6a**

Entry	Solvent	Volume/ml	Yield[b] (%)
1	CH_2Cl_2	3	0
2	DMF	3	2
3	CH_2Cl_2 + DMF	3 + 1	3
4	CH_2Cl_2 + DMF	6 + 1	10
5	CH_3CN + DMF	3 + 1	3
6	CH_2Cl_2 + CH_3CN	3 + 3	5

[a] Reaction conditions: **6a** (0.2 mmol), BOP (0.4 mmol), DIEA (0.8 mmol), solvent, room temperature, 30 hours. [b] Isolated yield by washing with CH_2Cl_2 and MeOH.

of monomers of another type.[2n,o] To assess the applicability of a chain-growth mechanism to the BOP-mediated macrocyclization, dimer **2f** composed of two units of **2a** was reacted with three equivalents of **5a** in CH_2Cl_2 (Schemes S4 and S5, ESI†). Statistically, pentamer **5** could be a possible product along with other two hybrid pentamers **7** and **8** consisting of mixed units of **2a** and **5a** with a ratio of 1 : 3 and 2 : 1, respectively, and a predominant production of **7** (**2a** : **5a** = 1 : 3) would be consistent with a chain-growth mechanism. Analyses by HRMS, ^{1}H NMR and TLC of the reaction mixture confirm **7** as the major product with pentamers **5**, **7** and **8** produced in a molar ratio of 2 : 8 : 5 (Scheme S5 and Fig. S1 and S2, ESI†), suggesting that BOP-mediated one-pot macrocyclization proceeds largely by a chain-growth mechanism.

BOP, a commonly used peptide coupling reagent, has often been employed in making cyclic peptides *via* intramolecular cyclizations.[7b] Its present use in inducing one-pot H-bonding-assisted macrocyclizations, selectively leading to five-residue macrocycles **1–6** from their monomeric building blocks **1a–6a**, bears no literature precedents. At the present time, we are still totally puzzled by the fact that $POCl_3$ and BOP only allow the circular pentamers to be prepared from their monomeric methoxybenzene[2m–o] and pyridone building blocks, respectively, and that all the amide coupling conditions outlined in Table 1 including $POCl_3$ and BOP do not yield any circular pyridine tetramer or fluoropentamer, respectively, built from monomeric pyridine[5c,d] or fluorobenzene[5e] motifs. The inference is such that every type of monomer building block destined to form the most stable circular pentamer or tetramer requires its own unique "cognate" macrocyclization reagents that seem to be "orthogonal" to each other and function well only against their own specific set of "cognate" monomer units. The BOP-mediated one-pot macrocyclization protocol established here decently produces its "cognate" pyridone pentamers **1–6** at yields of 10–25% in about a day, a greener process that is far more cost-effective and time-saving than the step-by-step lengthy synthesis, producing **2** and **6** in 1–2% yields after months of efforts.[4] This one-pot macrocyclization protocol now enables facile access to cation-binding pentamers with tunable exterior side chains that may promise some interesting applications.

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