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Computation-guided improved one-pot synthesis of macrocyclic cation-binding aromatic pyridone pentamers†

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By using polar DMF to relax the H-bonded rigid backbone and to lower the energetic penalty associated with the sterically-crowded environment, the yields for BOP-mediated one-pot synthesis of pentameric macrocycles can be improved from 10–25% as obtained in CH_2Cl_2 to 13–47% when 15% DMF in CH_2Cl_2 was used as the reaction medium.

Since the first report by Gong in 2004,[1a] intramolecular H-bonds of various types have attracted good attention in their application to conformationally constrain macrocyclic backbones containing a non-collapsed cavity for both structural and functional evolution.[1b,c] Interesting functions arising from this unique class of H-bonded macrocycles that have been demonstrated include G-quadruplex stabilization,[2a] ion transport[2b] and recognition,[2c–i] guest encapsulation,[3a,b] reaction promotion[3c,d] and catalysis,[3e] molecular sensing,[3f] solvent gelling,[3g,h] and formation of defined nanostructures.[4]

Concurrent with the above advances in structure and function of H-bonded macrocycles, H-bonding-assisted one-pot synthesis has also been actively pursued, allowing for the rapid and efficient production of a number of these H-bonded macrocycles from their corresponding simple repeating units[1b,c] as reported by Gong,[1a,5] Huc,[3a] Li,[3b] Jiang[6] and Zeng.[2i,7] These one-pot macrocyclization protocols have greatly facilitated and, together with those emerging, undoubtedly will continue to further the functional investigation of H-bonded macrocycles.

In particular, Zeng and his co-workers recently described an interesting new class of H-bonded macrocyclic pentamers **1–6**, which comprise five alkylated pyridone motifs that enclose a cooperative cation-binding cavity of 2.85 Å in radius as measured from the center of oxygen nucleus to the cavity center (Fig. 1).[2e] These highly rigidified pentamers exhibit not only tight binding of ~10^8 M^{-1} toward alkali metal cations[2h] but also highly selective recognition of Cs^+ ions in the presence of 23 other metal ions.[2f] Even more interestingly, while pentamer **1** in the solid state is able to retain both high binding selectivity and capacity in recognizing ions such as Cs^+, Rb^+ and Ba^{2+}, closely resembling the characteristics of the binding profile exhibited by this type of pentamer in solution, ions of various types remain poorly extractable by both **2** and **3** in the solid state.[8]

A relatively efficient **BOP**-mediated one-pot synthesis protocol has been elaborated by the same group, producing pentamers carrying different side chains in yields of 10–25% in about a day (Fig. 1).[7c] Apparently, this protocol is much

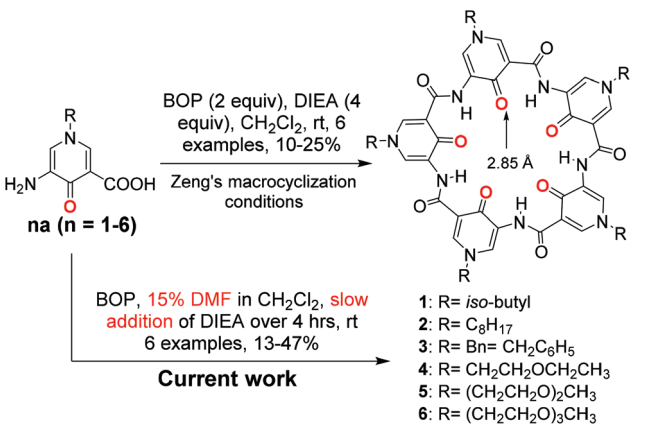

Fig. 1 Comparisons of reaction conditions and synthetic efficiency between Zeng's macrocyclization conditions[7c] and those of our current work. A more efficient synthesis of **1–6** was achieved in our work largely *via* the use of polar DMF to relax the H-bonded rigid backbone during the one-pot macrocyclization process. **BOP** = benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate; DIEA = diisopropyl ethylamine.

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greener than the stepwise lengthy synthesis process, producing **2** and **3** in 1–2% yields after months of efforts.[2e]

We became interested in this type of pentamer as we envisioned that suitable modifications of the side chains around the pentameric exterior might lead to a new class of pentagon-shaped molecules capable of interacting with pentameric proteins[9] or even G-quadruplex structures.[2a] Therefore, it would be more desirable if one-pot synthesis of these pentamers can be further improved. While looking into the ways of improving the synthesis, we were intrigued to find out how **BOP**, a sterically bulky coupling reagent, could interact with the key uncyclized intermediate, *i.e.*, the H-bonding-rigidified near-planar pentamer **7** (Fig. 2c), to produce pentamers **1–6.**

According to the mechanism of **BOP**-mediated coupling of an acid with an amine to produce an amide bond (Scheme 1) proposed by Castro,[10] the first reactive intermediate **I** seems to experience the largest steric hindrance and should incur the largest energetic penalty compared to other steps. We therefore decided to focus on evaluating the energetics of two type **I** intermediates, *e.g.*, **7A** and **7B** that differ from each other mainly by the relative orientation of the end carboxylate group (Fig. 3), using a computational approach.

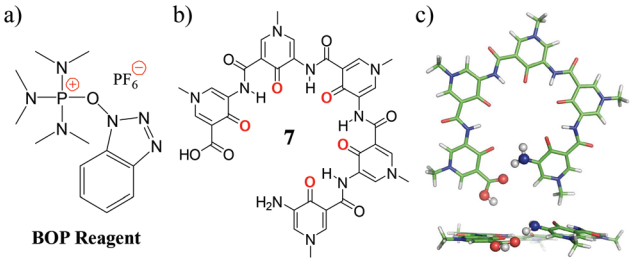
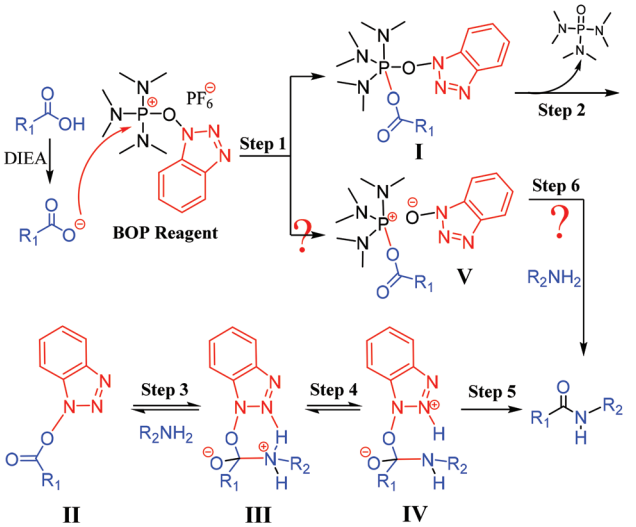


Fig. 2 (a) Structure of **BOP**. (b) and (c) describe the structure of a simplified pentameric intermediate **7** (R = methyl) and its computationally optimized structure at the level of B3LYP/6-31G(d,p) in the gas phase. A near-planar geometry leaving no space for **BOP** can be clearly seen in **7**.



Scheme 1 Mechanism of **BOP**-mediated coupling to produce an amide bond from acid and amine groups *via* intermediates **I–IV** as proposed by Castro.[10] Based on our current computational findings (Table 1), the reaction might also go through intermediate **V**, which was not proposed previously but more stable than **I** by 11.7 kcal mol^{-1}.

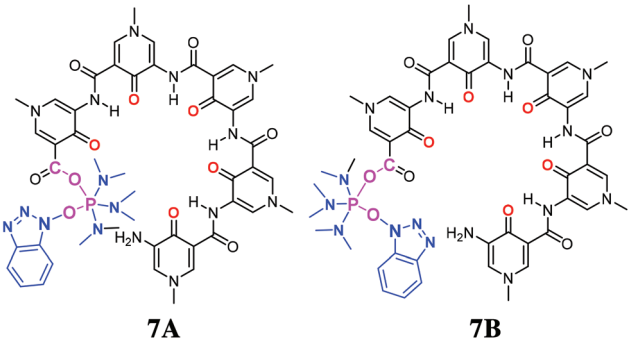


Fig. 3 Structures of two **7**–**BOP** conjugates type **I**, **7A** and **7B**, produced from the reaction between **7** and **BOP**. Four and eight alternative conformations can be generated for **7A** and **7B** for computational evaluation, respectively. The dihedral angle of C–OP–O and the corresponding atoms are shown in purple.

For both **7A** and **7B**, four dihedral angles of C–OP–O (*e.g.*, 45, 135, −45 and −135°, see purple atoms in Fig. 3) were used to define four starting conformations. For each of these four dihedral angles, the N=N bond in the triazole group of **BOP** can lie at either the left or the right side of the O–N single bond, leading to a total of eight possible conformations. In **7A**, the placement of the **BOP** motif toward the interior results in significant steric hindrance that limits the rotational freedom of the triazole moiety. As such, only four alternative conformations **7A$_1$**–**7A$_4$** could be generated. For **7B**, the triazole group is freely rotatable and a total of eight conformations **7B$_1$**–**7B$_8$** could be generated for analysis and comparison.

After subjecting these 12 initial structures to computational optimization and energy calculation at the levels of B3LYP/6-31G(d,p) and B3LYP/6-311+G(2d,p) in the gas phase, respectively, we surprisingly found that, except for **7A$_4$** that remains as a type **I** structure, the other 11 structures actually were changed into the structures of types **II** or **V**. Table 1 tabulates these changes and the corresponding relative energies normalized based on the most stable conformation **7A$_2$** with their corresponding structures compiled in Fig. S1 and S2.†

We have further compared the energy of the near-planar pentameric backbone in **7** (Fig. 2c) with its correspondingly distorted backbones in various **7**–**BOP** conjugates, *i.e.* type **I**, **II** and **V** intermediates after reaction with **BOP**. The relative energies normalized based on near-planar **7** were also included in Table 1 with their corresponding structures compiled in Fig. S3 and S4.†

Not surprisingly, type **II** intermediate **7A$_2$** with the loss of the bulky hexamethylphosphoramide group not only is the most stable among the 12 structures, but also contains the least distorted pentameric backbone that is less stable than planar **7** by only 5.2 kcal mol^{-1}. For comparison, the same

Table 1 Structural changes after computation and relative energies in **7–BOP** conjugates and in **7** [a]

Isomer	Dihedral angle (C–OP–O, °)	Structure after computation (**7–BOP**)	Relative energy (kcal mol^{-1})	
			7–BOP[b]	**7**[c]
7A$_1$	45	**V**	19.3	18.9
7A$_2$	135	**II**	0.0	5.2
7A$_3$	−45	**V**	13.8	26.1
7A$_4$	135	**I**	25.5	8.3
7B$_1$	45	**V**	41.3	9.3
7B$_2$	45		33.8	7.2
7B$_3$	135		24.1	14.0
7B$_4$	135		35.5	9.8
7B$_5$	−45		33.6	7.4
7B$_6$	−45		19.6	17.5
7B$_7$	−135		18.9	9.7
7B$_8$	−135		21.7	15.1

[a] Computational optimization and energy calculation were carried out at the levels of B3LYP/6-31G(d,p) and B3LYP/6-311+G(2d,p) in the gas phase, respectively. [b] Relative energy was normalized based on **7A$_2$**, the most stable **7–BOP** conjugate. [c] Relative energy was normalized based on near-planar **7** (Fig. 2c).

pentameric backbone in type **I** (*e.g.*, **7A$_4$**) and the most stable type **V** (*e.g.*, **7A$_3$**) intermediates are less stable than planar **7** by 8.3 and 26.1 kcal mol^{-1}, respectively.

These computational results suggest that the energetic penalty associated with induction of the H-bonding-rigidified planar pentameric backbone in **7** (Fig. 2c) into a distorted helical backbone as seen in various **7–BOP** conjugates (Table 1, Fig. 4 and S1–S4†) could amount to as high as 26.1 kcal mol^{-1} *via* the most stable type **V** intermediate (*e.g.*, **7A$_3$**) or at least 8.3 kcal mol^{-1} if the reaction occurs *via* the type **I** intermediate (*e.g.*, **7A$_4$**) as proposed by Castro.[10] Since **7A$_4$** is less stable than **7A$_3$** by 11.7 kcal mol^{-1}, both might be the possible intermediates of the **BOP**-mediated coupling reaction. The corresponding transition states, which are difficult to assess here, could be even higher in energy. One possible method to decrease this energetic penalty is to relax the rigidity of the H-bonded backbone by using polar molecules such as DMF or DMSO, which are able to strongly compete with H-bond donors and acceptors in the formation of H-bonds.

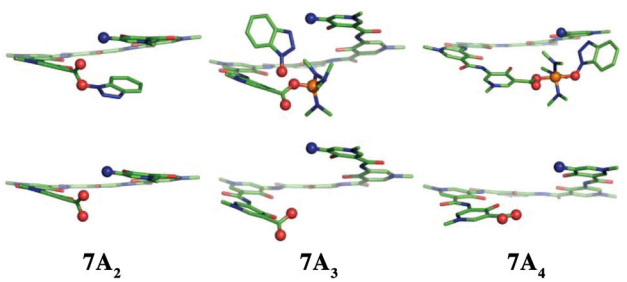


Fig. 4 Structures of **7A$_2$** and **7A$_3$** that correspond to the most stable conformation from type **II** and **V** intermediates and of **7A$_4$** that belongs to type **I** intermediate. The structures shown at the bottom illustrate the pentameric backbone of **7** in **7A$_2$**–**7A$_4$**, respectively. Note that after computational optimization, the O–N bond in **BOP** (Fig. 2a) breaks to produce the P=O bond, releasing the neutral hexamethylphosphoramide group to generate neutral **7A$_2$**.

Zeng's early investigations, however, demonstrated that the yields of the **BOP**-mediated one-pot synthesis of **1** decrease from 25% to 8, 11 and 6% when 100% DMF, 50% DMF in CH_2Cl_2 and 100% DMSO were used as the reaction medium, respectively.[7c] From these experimental observations, we reasoned that excessive amounts of DMF or DMSO may greatly weaken the intramolecular H-bonds in **7** and over-linearize its otherwise crescent-shaped backbone to such an undesired extent that the reactive amine and carboxylate groups at the helical ends were placed distant from each other, making the intramolecular ring closure reaction difficult to occur. In light of this reasoning and on the basis of our current computational findings, we postulated that the use of lower but right amounts of polar solvent might relax the H-bonding-rigidified backbone to some good extent to allow the **BOP** group to come in with ease and the ring closure reaction to take place more efficiently, rather than over-linearize the backbone to impede the macrocyclization reaction.

With the above hypothesis in mind, we evaluated the impact the way the organic base DIEA was added might have on the macrocyclization reaction. We found that slow addition of DIEA into a CH_2Cl_2 solution containing **BOP** and the corresponding monomer **1a** over a period of four hours increases the yield of **1** by 5% to 30% (entry 2, Table 2). We also found that lowering the reaction temperature to 0 °C is not helpful either, reducing the yield to 17% (entry 3, Table 2). Consequently, the subsequent screening using varying amounts of DMF, which increase in small increments of 1–2.5%, were mostly conducted *via* slow addition of DIEA over four hours at room

Table 2 Effects of DMF of varying percentages in CH_2Cl_2 on **BOP**-mediated one-pot preparation of pentamer **1** from monomer **1a** [a]

Entry	% DMF in CH_2Cl_2	Temperature	Yield[b] (%)
1	0%	25 °C	25[c]
2	0%		30
3	0%	0 °C	17
4	2.5%	25 °C	34
5	5.0%		36
6	7.5%		36
7	10%		35
8	12%		35
9	14%		39
10	15%		**47**
11	16%		38
12	18%		37
13	20%		29
14	15%	30 °C	40
15	15%	35 °C	39

[a] Typical reaction conditions: DIEA (0.8 mmol) was added over a course of four hours into a solution (3 mL) containing **1a** (0.2 mmol) and **BOP** (0.4 mmol) under constant stirring. After addition, the reaction mixture was stirred at a certain temperature for another 26 h. [b] Isolated yield by washing with CH_2Cl_2 and MeOH. [c] DIEA was added in one pot instead of over four hours; this is the condition reported by Zeng and his co-workers.[7c]

temperature. Interestingly, while the yields of **1** remain similar at 34–36% when the percentage of DMF in CH_2Cl_2 varies from 2.5 to 12%, such yields significantly increase to 39% in 14% DMF in CH_2Cl_2 and reach as high as 47% in 15% DMF in CH_2Cl_2. After this, the yields decrease to 38, 37 and 29% with the use of 16, 18 and 30% DMF in CH_2Cl_2 as the reaction medium, respectively. At higher temperatures, the yields also decrease to 40% or lower (entries 14 and 15, Table 2). This suggests the pentameric backbone in **7** to be more flexible at higher temperatures than at 25 °C, placing the reactive amine and carboxylate groups farther away from each other and decreasing the ring closure reaction extent.

Although additional screening of other polar solvents does not result in improved macrocyclization efficiencies (Table 3) when compared to DMF, the obtained yields of 19–28% are still significantly better than those previously reported.[7c] Among the polar solvents studied, THF, acetonitrile and DMSO produce more of **1** than acetone and NMP by 6–9%.

Using the above optimized one-pot macrocyclization conditions, pentamers **2** and **3** (Fig. 1) were produced in respective yields of 29% and 13%, which are better than 18% and 10% as reported previously.[7c] For one-pot synthesis of **4–6**, 6 ml, rather than 3 ml, of the reaction solvent was used due to the poor solubility of **4a–6a**. The yields of 22, 15, and 19% for **4–6** are also better than the previously reported values of 12, 10 and 16%, respectively.[7c] The satisfactory preparations of **1–6** establish the general utility of the one-pot synthesis protocol in the rapid and efficient production of other closely related pentamers.

In summary, we have demonstrated here, by an experimental–theoretical synergy, an improved **BOP**-mediated one-pot synthesis protocol that allows for significantly more efficient production of macrocyclic pyridone-based aromatic pentamers with yields as high as 47%. More specifically, the computationally elucidated energetic penalty accompanying the formation of **7–BOP** conjugates can be effectively minimized *via* the use of a carefully optimized appropriate amount of polar DMF, which helps to relax the otherwise highly rigidified pentameric backbone to just the right extent that in turn maximally increases the intramolecular ring closure efficiency.

Table 3 Effects of other types of polar co-solvents on **BOP**-mediated one-pot preparation of pentamer **1** from monomer **1a** [a]

Entry	15% co-solvent in CH_2Cl_2	Yield[b] (%)
1	THF	28
2	Acetonitrile	27
3	DMSO	26
4	Acetone	20
5	NMP	19

[a] Typical reaction conditions: DIEA (0.8 mmol) was added over a course of four hours into a solution (3 mL) containing **1a** (0.2 mmol) and **BOP** (0.4 mmol) under constant stirring. After addition, the reaction mixture was stirred at room temperature for another 26 h. [b] Isolated yield by washing with CH_2Cl_2 and MeOH. NMP = *N*-methyl-2-pyrrolidone.

We believe that this one-pot macrocyclization protocol should enable facile access to a unique class of pentagon-shaped pentavalent ligands that may promise some interesting applications in biology,[2a,9] in addition to those already demonstrated in chemistry.[2f,h,4b,8]

Acknowledgements

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