Improving the Efficiency of Forming 'Unfavorable' Products: Eight-Residue Macrocycles from Folded Aromatic Oligoamide Precursors

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Abstract: Oligoamide macrocycles consisting of eight *meta*-linked benzene residues were synthesized based on the cyclization of aromatic oligoamide precursors having folded backbones rigidified by three-center hydrogen bonds. An alternative route based on the condensation of pentadimeric diamine and trimeric diacid provided the cyclic octamer in 75% yield using EDCI/HOBt as the coupling reagent.

Key words: macrocycles, synthesis, hydrogen bonds, folding oligoamides, cyclizations

Macrocyclization facilitated by noncovalent interactions, such as hydrogen bonding, has attracted increasing attention for constructing well-defined structures.[1] Among known strategies such as templation[2] and high dilution,[2,3] for forming macrocycles, especially those with shape-persistency[4] that have great potentials as scaffolds for various applications,[5–7] macrocyclization assisted by hydrogen bonding stands out due to its high efficiency. Macrocyclization facilitated by intramolecular H-bonding has allowed the construction of macrocylces having various lumens. For instance, by locking diamide precursors into a *cis* conformation within a framework containing a 2,6-disubstitutedpyridyl unit, reacting acid chloride and amino groups were brought into close proximity for cyclization, which led to a macrocylce in 88% yield that was in sharp contrast to a much lower yield of 30% in the absence of intramolecular H-bonds.[8] Taking advantage of folded conformations of uncyclized precursors, which was enforced by intramolecular hydrogen bonding via stabilization of imine bonds, a 14-membered macrocycle was obtained by the condensation of ethylene diamine and dialdehyde.[9] The directionality of hydrogen bonds also led to the formation of macrocyclic trimer even in a highly polar solvent at high temperature (100 °C).[10] A discovery made by us provided an efficient means to the formation of a series of six-residue, cavity-containing oligoamide macrocycles in over 80% yield based on the condensation of simple monomeric diamines and diacid chlorides.[11] The high efficiency demonstrated by our system was believed to be due to the cyclization of reactive oligomeric precursors having rigidified, folded backbones enforced by three-center intramolecular hydrogen bonds.

As part of our ongoing interest in the construction of functional oligoamide macrocycles, we started to sythesize six-residue macrocycles such as **3a** that carries olefinic side chains based on procedures we reported.[11] During this investigation, we observed the presence of a trace amount of an eight-residue macrocycle in the reaction mixture, in addition to the expected six-residue macrocyle.

In this paper we probe conditions under which the formation of this otherwise unfavorable eight-residue macrocycle could be improved. We first investigated the one-step condensation of the corresponding monomeric diacid chloride and diamine at various temperatures. An alternative strategy that led to the preparation of the same macrocycle in significantly enhanced yields was also examined.

As shown in Scheme 1, the coupling of diamine **1** (1 equiv) with diacid chloride **2** (1 equiv) following the previously reported procedure in the presence of triethylamine at –20 °C led to **3a** as the major product in a yield of 65%. A trace amount of a cyclic species (<1%), which was indicated by a signal {m/z = 2577.1 [M + K^+]} in the MALDI-TOF spectrum, was also detected. This minor product was initially assumed to be the dimeric aggregate of a four-residue macrocycle resembling calix[4]arenes, but was soon found to be more consistent with the eight-residue macrocycle **4a**. Subsequent reaction of **1** and **2b** also led to the detection of macrocycle **4b** in the crude product {m/z = 1807.5 [M + Na^+]}, again in a very low yield (<5%). The presence of **4a** and **4b** as minor products in these one-step reactions prompted us to investigate the possibility of optimizing the formation of macrocycles larger than the six-residue ones.

Due to the folded (rigidified) conformation of the oligomeric precursors and intermediates, which belong to a class of folded oligomers whose folding has been well established by us[12] to be enforced by highly favorable intramolecular three-center hydrogen bonds, the cyclization of oligoamide precursors with lengths beyond six residues would be hampered because of the strain associated with macrocyclic products with twisted backbone and the

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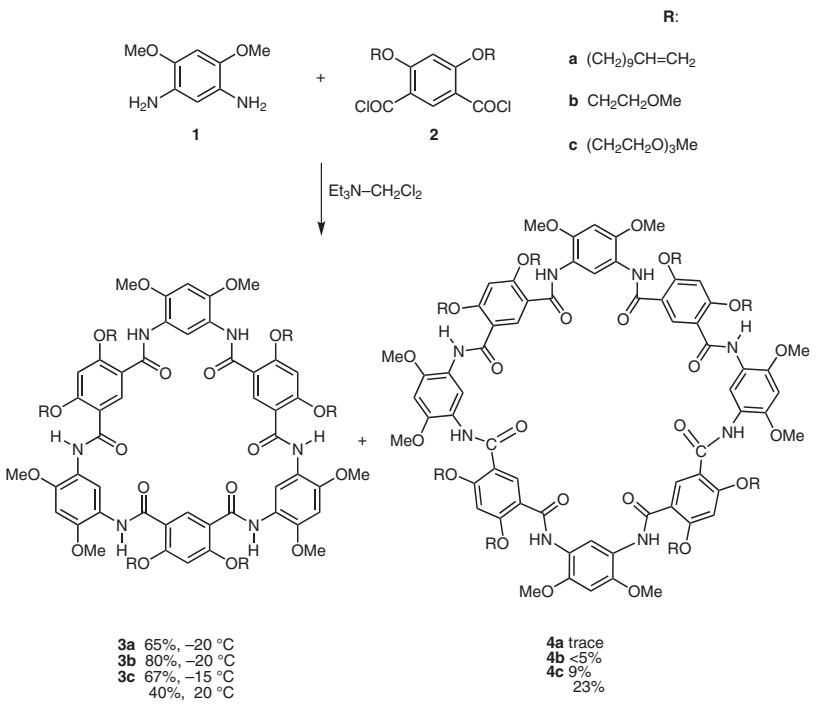


Scheme 1 Macrocyclization based on the condensation of monomeric diamine **1** and diacid chlorides **2**

increased entropic barriers associated with the formation of larger macrocycles. Furthermore, reaction steps leading to the direct precursors of macrocycles with more than six *meta*-linked residues are discouraged because of steric hindrance associated with the rigidified backbones of the reacting oligmeric intermediates lead to these long oligomers.

The above analysis agrees with the observed low yields of **4a** and **4b**. Thus it seems that rigidification of the oligomeric intermediates and precursors of expanded macrocycles such as **4a** and **4b** is the major reason for the low efficiencies observed for their formation. We then reasoned that by adopting conditions under which the conformational flexibility of the oligoamide backbones gets enhanced, the entropic and steric barriers associated with the formation of macrocycles larger than the six-residue ones should be alleviated. Based on this consideration, diacid chloride **2c** was treated with diamine **1** at various temperatures in $CHCl_3$. The results are listed in Table 1.

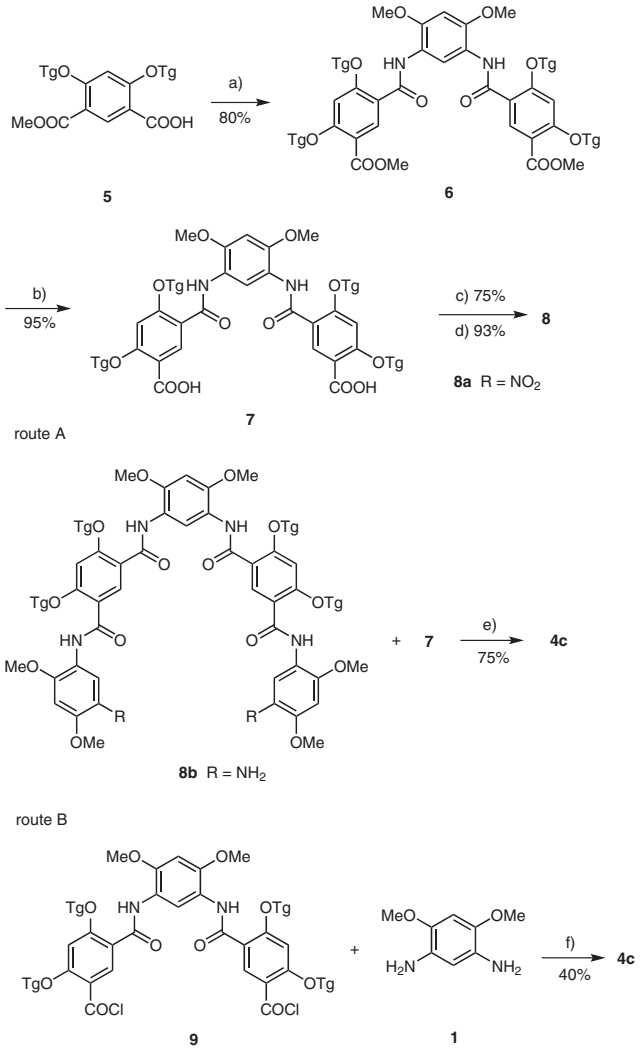
Analyzing the crude reaction mixture by ^1H NMR and subsequent isolation of the product revealed that the yields of the six-residue macrocycle **3c** kept decreasing with increasing temperature. In contrast, the yields of macrocycle **4c** increased from <5% to 23% as the temperature was raised from –30 to 20 °C. However, the yields of **4c** declined at higher temperature, with 7% at 40 °C and less than 5% at –30 °C. The fact that an optimum temperature exists for forming **4c** suggests that in this system different reactions are competing at different temperature range, which provides a potential strategy for maximizing the yield of an otherwise unfavorable product. Indeed, at 60 °C, besides **3c** (17%) and **4c** (<5%) isolated, the majority of the reaction mixture seemed to be linear oligomers and polymers of higher molecular weights. Although remained to be characterized, these linear oligomers and polymers are interesting since they should fold into helical conformations containing hydrophilic holes, channels running down their long axes. In addition, at 20 °C, higher concentration seems to facilitate the formation of the eight-residue **4c**. For example, the yield reached 30% at 50 mM.

That the yield of the eight-residue macrocycle **4c** could indeed be improved under different conditions led to a further investigation on the possibility of optimizing the corresponding macrocyclization using an alternative strategy. One straightforward approach involves adopting a synthetic route that excludes the formation of the six-

Table 1 Temperature Effect on Yields of **3c** and **4c**[a]

Temp (°C)	Yield of **3c** (%)	Yield of **4c** (%)
–30	70	<5
–15	67	9
0	56	12
	40	23
20	37[b]	30[b]
	32[c]	20[c]
40	22	7
60	17	<5

[a] Initial concentration: 10 mM, 20 °C.
[b] 50 mM.
[c] 100 mM.



Scheme 2 *Reagents and conditions*: a) (i) $(COCl)_2$, CH_2Cl_2; (ii) **1**, Et_3N, r.t.; b) NaOH, H_2O–MeOH, reflux; c) 2,4-dimethoxy-5-nitroaniline, Ph_3PCl_2, 45 °C; d) H_2, Pd/C; e) EDCI/HOBt, **7**, r.t. f) (i) $(COCl)_2$, CH_2Cl_2; (ii) **1**, Et_3N, r.t.

residue macrocycles. One such route is shown in Scheme 2, involving the coupling of pentameric diamine **8b** and trimeric diacid **7**.

The combination of **8b** and **7** cannot lead to six-residue macrocycle **3c**. Instead, only the eight-residue macrocycle **4c** or longer oligomers are possible products. Starting from monomethyl ester acid **5**, trimeric diacid **7** was obtained by coupling diamine **1** with **5** followed by hydrolyzing the formed trimeric dimethyl ester **6**. Pentameric diamine **8b** was prepared by the catalytic hydrogenation of the corresponding dinitro compound **8a**, which was obtained from the reaction between **7** and 4-dimethoxy-5-nitroaniline,[13] using triphenylphosphine dichloride (Ph_3PCl_2) as the coupling reagent. By coupling trimeric diacid **7** with pentameric diamine **8b** at 28 °C using EDCI/HOBt as the coupling reagent, macrocycle **4c** was isolated in a yield of 75%.[14] That macrocycle **4c** was formed as the dominant product from this reaction was demonstrated by MALDI-TOF (Figure 1), which revealed a very strong and distinct signal even for the reaction mixture.

The above strategy, which involves the coupling of oligomers, is quite flexible. Other synthetic routes can be similarly designed. For example, eight-residue macrocycles such as **4c** may also be obtained by coupling trimeric diacid such as **7** with monomeric diamine **1**. This possibility was tested by treating the diacid chloride **9** with diamine **1**, from which macrocycle **4c** was obtained in a yield of 40%. The MALDI-TOF and ^1H NMR spectra indicated that the crude mixture comprised **4c**, along with unreacted starting material, and other acylic species.

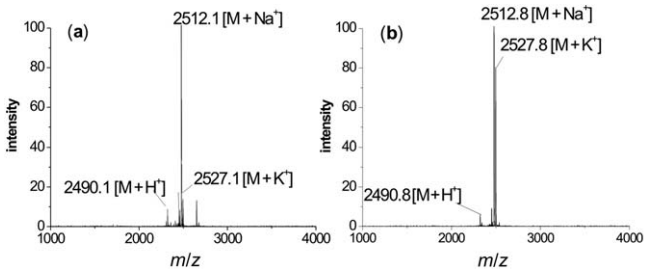


Figure 1 The MALDI-TOF spectra of (a) the reaction mixture, and (b) purified **4c**, based on route A.[15] Calculated value for the $C_{120}H_{168}N_8NaO_{48}$[M + Na^+] ion of **4c**: 2512.08.

In summary, we have investigated the formation of oligoamide macrocycles **4** consisting of eight *meta*-linked benzene residues. Although six-residue macrocyle predominated in the one-step coupling reaction of monomeric diamine and diacid chloride at low temperature, the yields of eight-residue macrocycles can be improved at higher temperatures. The enhanced yields of the otherwise unfavorable eight-residue macrocycles from the one-step condensation reaction can be attributed to the increased flexibility of the folded oligomeric intermediates and precursors at elevated temperatures. An alternative coupling route based on the coupling of pentameric diamine **8b** and trimeric diacid **7**, which precluded the six-residue macrocycle from forming, led to the eight-residue **4c** in a significantly improved yield. This work has presented strategies that allow the augmentation of an unfavorable product either by tuning reaction conditions or by adopting an alternative synthetic route. The approach described here should be of value to the preparation of macrocycles that would be difficult to obtain under regular conditions.

Acknowledgment

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(14) **Selected Spectroscopic Data of Compounds 4–8**
Compound **4c**: ^{1}H NMR (400 MHz, 95% $CDCl_3$–5% CD_3OD): δ = 10.00 (s, 4 H), 9.90 (s, 4 H), 9.40 (s, 2 H), 9.23 (s, 2 H), 9.00 (s, 2 H), 8.70 (s, 2 H), 6.80 (s, 2 H), 6.69 (s, 2 H), 6.50 (s, 4 H), 4.47 (s, 16 H), 3.99–3.43 (m), 3.28 (s, 24 H). MS (MALDI-TOF): *m/z* calcd for $C_{120}H_{168}N_8NaO_{48}$ [M + Na]: 2512.08; found: 2512.1. ESI-HRMS: *m/z* [M + Na] calcd for $C_{120}H_{168}N_8NaO_{48}$: 2513.0882; found: 2513.0955.
Compound **6**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.75 (s, 2 H), 9.37 (s, 1 H), 8.88 (s, 2 H), 6.63 (s, 2 H), 6.55 (s, 1 H), 4.40 (t, *J* = 4.8 Hz, 4 H), 4.25 (t, *J* = 4.8 Hz, 4 H), 4.00 (t, *J* = 4.8 Hz, 4 H), 3.94 (t, *J* = 4.8 Hz, 4 H), 3.92 (s, 6 H), 3.84 (s, 6 H), 3.80 (t, *J* = 4.8 Hz, 4 H), 3.68 (m, 12 H), 3.58 (m, 12 H), 3.47 (q, 4 H), 3.37 (s, 6 H), 3.32 (s, 6 H). ESI-HRMS: *m/z* [M + H] calcd for $C_{54}H_{81}N_2O_{24}$: 1141.5179; found: 1141.5125.
Compound **7**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.57 (s, 2 H), 9.21 (s, 1 H), 8.96 (s, 2 H), 6.65 (s, 2 H), 6.41 (s, 1 H), 4.48 (t, *J* = 4.8 Hz, 4 H), 4.33 (t, *J* = 4.8 Hz, 4 H), 4.01 (t, *J* = 4.8 Hz, 4 H), 3.87 (s, 6 H), 3.84 (t, *J* = 4.8 Hz, 4 H), 3.71 (m, 8 H), 3.63 (m, 8 H), 3.57 (m, 12 H), 3.47 (m, 4 H), 3.37 (s, 6 H), 3.32 (s, 6 H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.8, 161.2, 160.9, 160.7, 145.6, 138.1, 120.1, 116.1, 111.4, 98.2, 94.4, 71.9, 71.8, 70.6, 70.5, 70.5, 70.4, 70.3, 69.4, 69.2, 69.0, 68.5, 58.9, 58.8, 55.8. ESI-HRMS: *m/z* [M – H] calcd for $C_{52}H_{75}N_2O_{24}$: 1111.4710; found: 1111.4769.
Compound **8a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.88 (s, 2 H), 9.65 (s, 2 H), 9.20 (s, 3 H), 8.98 (s, 2 H), 6.63 (s, 2 H), 6.56 (s, 1 H), 6.47 (s, 2 H), 4.49 (t, *J* = 4.8 Hz, 4 H), 4.36 (t, *J* = 4.8 Hz, 4 H), 4.07 (s, 6 H), 3.96 (t, *J* = 4.8 Hz, 4 H), 3.92 (d, 12 H), 3.76 (t, *J* = 4.8 Hz, 4 H), 3.70 (t, *J* = 4.8 Hz, 4 H), 3.64 (t, *J* = 4.8 Hz, 4 H), 3.56 (m, 12 H), 3.46 (m, 12 H), 3.31 (s, 12 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.6, 160.1, 160.0, 153.8, 151.0, 146.3, 137.0, 121.4, 120.6, 117.4, 115.3, 114.6, 97.7, 95.6, 95.2, 71.8, 70.7, 70.6, 70.6, 70.5, 70.4, 70.3, 69.4, 69.1, 69.0, 58.9, 56.7, 56.5, 56.1. ESI-HRMS: *m/z* [M + H] calcd for $C_{68}H_{93}N_6O_{30}$: 1473.5936; found: 1473.5927.
Compound **8b**: prepared from hydrogenation of its dinitro compound **8a** in 90% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.07 (s, 2 H), 10.02 (s, 2 H), 9.32 (s, 1 H), 8.91 (s, 2 H), 7.90 (s, 2 H), 7.10 (s, 2 H), 6.96 (s, 1 H), 6.75 (s, 2 H), 4.63 (s, 8 H), 4.03 (s, 6 H), 4.01–3.98 (m, 8 H), 3.91 (s, 6 H), 3.84 (s, 6 H), 3.65 (m, 8 H), 3.60–3.40 (m, 8 H), 3.36 (m, 8 H), 3.23 (s, 6 H), 3.21 (s, 6 H), 3.16–3.10 (m, 8 H).(15)

Procedure For Macrocyclization

Route A

A mixture of **7** (23.7 mg, 0.021 mmol), EDCI (10.2 mg, 0.053 mmol), and HOBt (7.3 mg, 0.054 mmol) in CH_2Cl_2 (10 mL) was stirred at r.t. for 50 min and then **8b** (30.0 mg, 0.021 mmol) was added. The mixture was stirred at 28 °C overnight. After washing with H_2O, the residue was subjected to chromatography ($CHCl_3$–MeOH, 5:1) to afford the product **4c** as an off-white solid (37.5 mg, 75%).

Route B

The diacid chloride (0.020 mmol), prepared from diacid **7** and $(COCl)_2$ in CH_2Cl_2, was added to the diamine **1** (0.020 mmol) in the presence of Et_3N in 0.5 h. The mxiture was stirred 6 h. After washing with 10% HCl, the residue was recrystallized several times from acetone to provide **4c** in 40% yield.

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