Aromatic oligoamide macrocycles from the bimolecular coupling of folded oligomeric precursors†‡

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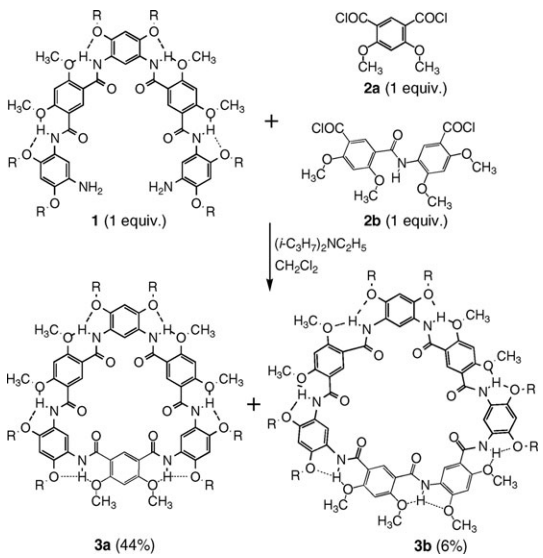
Aromatic oligoamide macrocycles consisting of six to ten *meta*-linked residues were prepared based on bimolecular coupling/cyclization of a pentameric diamine and oligomeric diacid chlorides, and adopt folded conformations enforced by intramolecular three-center H-bonds.

The efficient preparation of various macrocycles[1,2] has long been an intriguing subject for creating well-defined and functionally-adjustable structures. Of particular interest are methods for forming shape-persistent macrocycles[3] that may be used for designing novel materials[4] and catalysts.[5] Known approaches for preparing macrocycles include (a) templation,[6] (b) high dilution[7] and (c) dynamic covalent bond formation, such as Schiff base-type cyclization,[8,9] cross-coupling cyclooligomerization,[3,10] disulfide exchange[11] and metathesis.[12] Recently, we discovered the almost exclusive formation of a series of six-residue oligoamide macrocycles from a one-step condensation of monomeric diamines and diacid chlorides.[13] This one-step condensation provided a highly efficient method for preparing a novel series of shape-persistent macrocycles consisting of *meta*-linked benzene rings, as exemplified by the structure of **3a**, as shown in Scheme 1.[14] It was believed that the observed high efficiency was due to folding[15] of the uncyclized oligomer precursors of these macrocycles into rigid, crescent conformations. By bringing its two termini into close proximity upon folding, the direct precursor of the macrocycle is predisposed to undergo a highly favorable intramolecular cyclization.

In spite its high efficiency, this one-step macrocyclization is limited in that (1) only the six-residue macrocycle is formed,[14] (2) the AB-type backbone is not compatible with macrocycles having an odd number of residues and (3) the incorporation of a single functional side chain into the macrocycle is not possible. To address these limitations, we describe herein an approach based on bimolecular coupling/cyclization involving pentameric diamine **1** and a series of bifunctional oligomers bearing terminal acid chloride groups.

Results from our previous studies on analogous oligoamide foldamers consisting of *meta*-linked benzene rings show that it takes about 6.5 benzene residues to complete a turn,[15] which suggests that aromatic oligoamide macrocycles with seven *meta*-linked residues may also be formed efficiently. While seven-residue macrocycles cannot be formed from the condensation of monomeric diacid chlorides and diamines, coupling diamine **1** with dimeric **2b** may get around this limitation. Thus, based on a competition reaction, the formation of six- and seven-residue macrocycles was compared. A mixture containing one equivalent (0.5 mM) each of diamine **1**, and diacid chlorides **2a** and **2b** in CH_2Cl_2 (Scheme 1), was stirred at 0 °C for 2 h, followed by warming up to room temperature, stirring overnight and then heating under reflux for 2 h. Based on the ^{1}H NMR spectrum of the crude reaction mixture, using *p*-xylene as the internal standard, a yield of 43.8% was determined for **3a**, while the seven-residue **3b** formed in a surprisingly low yield of 5.9%.‡ This result



Scheme 1 Competition reactions of pentameric diamine **1** with diacid chlorides **2a** and **2b**.

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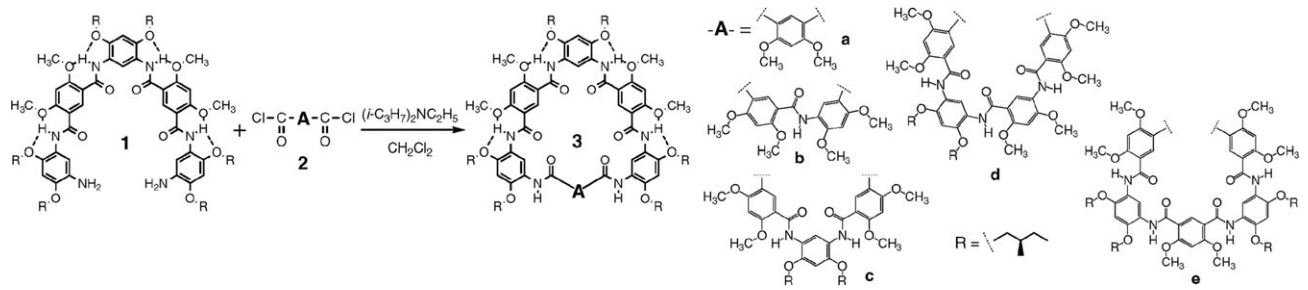

Scheme 2 Bimolecular coupling/cyclization involving **1** and diacid chlorides of various sizes.

demonstrated that the formation of six-residue macrocycles, such as **3a**, was overwhelmingly favored over macrocycles of other sizes, even if the product, such as **3b**, has a size that is well accommodated by the geometry of the *meta*-linked backbone.

One likely strategy to promote the formation of macrocycles of other sizes involves ruling out the possibility of forming the highly favorable six-residue macrocycle. This possibility was first probed by carrying out coupling reactions involving **1** and each of diacid chlorides **2a–2e** under identical conditions (Scheme 2). In addition to **3a** and **3b**, macrocycles **3c–3e**, which consist of eight to ten *meta*-linked residues, may also be formed if ring closure happens in these condensation reactions. One potential complication may arise from the folding and rigidification of uncyclized precursors, which could direct the reactive ends of uncyclized precursors of **3c–3e** away from one another and thus retard the cyclization reactions.

Each of the coupling reactions was conducted under identical conditions, involving stirring a 1 : 1 mixture of diamine **1** (0.5 mM) and the corresponding diacid chloride **2** (0.5 mM) in CH_2Cl_2 at 0 °C for 3 h, followed by warming up to room temperature. After stirring for another 8 h, the reaction mixture was heated under reflux for 1 h, after which methanol and HCl was added.

It was found that six-residue **3a** was obtained in a high (84%) yield after purification. Coupling between **1** and dimeric **2b** afforded macrocycle **3b** in a reasonable (50%) yield. In contrast, the eight-residue macrocycle, **3c**, formed in a significantly lower (14%) yield from the coupling of **1** and **2c**.

The low yield of **3c** indicates that as the ring size extends beyond that of six-residue **2a**, the formation of the corresponding macrocycle becomes increasingly inefficient. It was not clear, based on the same coupling and cyclization reactions, whether macrocycles with sizes beyond that of **3c** could still form. Surprisingly, treating **1** and the corresponding diacid chlorides **2d** and **2e** afforded the nine-residue **3d** and ten-residue **3e**, respectively, which were revealed by MALDI-TOF spectra‡ and subsequently isolated in yields of 10 and 6.2%, respectively.

The structures of macrocycles **3** were confirmed by ^{1}H and ^{13}C NMR, ESI-HRMS and MALDI-TOF analysis. Compared to the simplicity of the NH and aromatic ^{1}H NMR signals of symmetrical **2a**, **2c** and **2e**, the presence of multiple NH signals from 9.6 to 10.4 ppm in the ^{1}H NMR spectra of **3b** and **3d** is consistent with the unsymmetrical nature of their structures.

The bimolecular coupling/cyclization shown in Scheme 1 is particularly valuable for preparing macrocycles such as **3b** and **3d**, which have odd numbers of residues. These macrocycles, with their unsymmetrical backbones, cannot be obtained based on the direct coupling of monomeric diacid chlorides and diamines. Given the usually difficult preparation of macrocycles with expanded sizes, the successful synthesis of **3d** and **3e** shows great promise for preparing macrocycles of a variety of sizes based on this bimolecular coupling/cyclization method. In addition, this synthetic strategy should also allow the site-specific incorporation of a single functional group into a macrocycle, the product from which should serve as a valuable building block for further derivatization and modification.

It was later found that the yields of individual coupling reactions could be optimized by conducting the reaction at a higher temperature and by controlling the way (*e.g.*, rate and duration of addition) the acid chlorides were added. For example, the yield of macrocycle **3b** was optimized to ~70% and that of **3e** was raised to ~15% when the coupling reactions were carried out at around 20 °C in CH_2Cl_2, followed by heating the reaction mixtures under reflux.

The structures of macrocycles **3a**, **3b**, **3c** and **3e** were optimized by using an *ab initio* method at the B3LYP/6-31(g)d level of theory. As shown in Fig. 1, the energy-minimized conformations of six-residue **3a** and seven-residue **3b** are nearly flat, with that of **3a** resembling a very shallow bowl and that of **3b** being overall flat. The flat conformations of **3a** and **3b** demonstrate that these macrocycles are relatively strain-free, and that the backbone-rigidifying three-center H-bonds undergo insignificant twisting. In contrast, macrocycles **3c** and **3e**, with their numbers of *meta*-linked benzene residues being well beyond one full turn, are expected to have significant ring strain. Indeed, neither **3c** nor **3e** has an overall flat shape. In fact, both macrocycles adopt saddle-shaped conformations, with that of **3c** being reminiscent of a shallow saddle and the shape of **3e** being a deep saddle. To accommodate the ring strain, some of the intramolecular H-bonded rings of **3c** are noticeably twisted. Consistent with significant ring strain, parts of the backbone of **3e** are twisted to such an extent that some intramolecular H-bonds are completely interrupted.

In summary, we have investigated the formation of aromatic oligoamide macrocycles consisting of six to ten residues based on the bimolecular coupling and subsequent cyclization of pentameric diamine **1** and diacid chlorides. Pentamer **1** showed an overwhelming preference towards

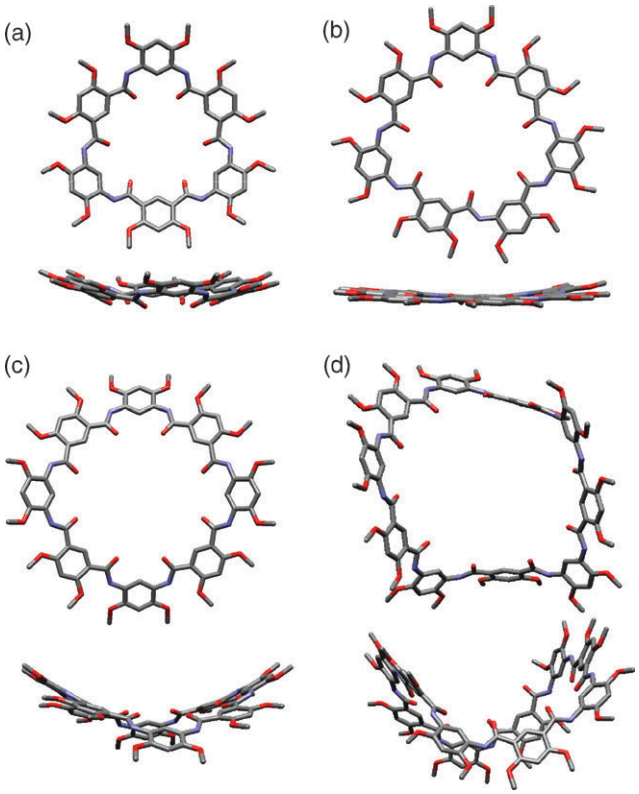

Fig. 1 The top and side views of the structures of macrocycles (a) **3a**, (b) **3b**, (c) **3c** and (d) **3e** optimized at the B3LYP/6-31(g)d level. The hydrogen atoms are removed for clarity.

monomeric diacid chloride **2a**, which resulted in the highly efficient formation of six-residue macrocycle **3a**. Coupling **1** with diacid chlorides of increasing sizes led to the corresponding macrocycles in yields that decreased as the ring size expanded. The fact that macrocycles with more than eight *meta*-linked residues were formed suggests that the corresponding uncyclized oligomer precursors, in spite of their H-bond-rigidified backbone, still possess a certain degree of conformational flexibility to cyclize. Given the obvious large ring strain, the formation of **3e** is quite surprising and bodes well for the construction of macrocycles of a variety of sizes based on this strategy. The fact that no special effort was made to optimize the reactions suggests that H-bond-enforced folding of the oligomeric precursors may be promoting, rather than hampering, the formation of macrocycles accompanied by a large ring strain, and thus contain severely twisted backbones.[16] These macrocycles, with different cavity sizes and unique conformations, provide a new series of structures, upon which novel hosts and materials could be developed.

Experimental

General synthetic procedure for macrocycles

A mixture of diacid (1 equiv.), dry CH_2Cl_2 (20 mL), oxalyl chloride (3 equiv.) and DMF (4 μL) was stirred for 5 h at room temperature. The solvent was then removed and the resulting diacid chloride **2(a, b, c, d or e)** dissolved in CH_2Cl_2. This solution was then added immediately to a pre-cooled solution at 0 °C of diamine salt **1** (1 equiv.) in CH_2Cl_2 containing DIEA (5 equiv.). The final concentration of **1** was 0.5 mM. The reaction mixture was stirred at 0 °C for 3 h and then at room temperature for 8 h, followed by refluxing for 1 h. After quenching with CH_3OH and removing the solvent, the residue was triturated with CH_3OH and EtOAc. Filtration provided the crude product. Further recrystallization with $CHCl_3/CH_3OH$ and/or purification by preparative TLC ($CHCl_3$/EtOAc/CH_3OH, 10 : 1 : 1.5) provided the pure product.

Six-residue macrocycle 3a. Prepared according to the general synthetic procedure for macrocycles. 4,6-Dimethoxyisophthalic acid (17.5 mg, 0.077 mmol) and oxalyl chloride (29.3 mg, 0.23 mmol) were used to prepare **2a**. Diamine salt **1** (100.0 mg, 0.077 mmol), DIEA (50.0 mg, 0.39 mmol) and CH_2Cl_2 (150 mL) were used for the macrocyclization. Yield 84.5%. ^{1}H NMR (400 MHz, 90% $CDCl_3$–10% CD_3OD): δ 9.52 (s, 6 H), 9.43 (s, 3 H), 9.12 (s, 3 H), 6.46 (s, 3 H), 6.23 (s, 3 H), 4.04 (s, 18 H), 3.93 (m, 6 H), 3.83 (m, 6 H), 1.93 (m, 6 H), 1.49 (m, 6 H), 1.37 (m, 6 H), 1.14 (d, J = 6.5 Hz, 18 H) and 1.08 (t, J = 7.3 Hz, 18 H). ^{13}C NMR (100 MHz, 90% $CDCl_3$–10% CD_3OD): δ 162.2, 160.5, 144.4, 138.8, 120.6, 116.0, 114.7, 96.1, 94.2, 74.1, 56.4, 35.1, 25.9, 16.6 and 11.2. MALDI-TOF MS (m/z) calc. for $C_{68}H_{92}N_6O_{18}Na$ ($M + Na^+$) 1433.7; found 1434.1 ($M + Na^+$). ESI-HRMS (m/z) calc. for $C_{68}H_{93}N_6O_{18}$ ($M + H^+$) 1411.7329; found 1411.7405 ($M + H^+$).

Seven-residue macrocycle 3b. Prepared according to the general synthetic procedure for macrocycles. Diacid **9** (31.3 mg, 0.077 mmol) and oxalyl chloride (29.3 mg, 0.23 mmol) were used to prepare **2b**. Diamine salt **1** (100.0 mg, 0.077 mmol), DIEA (50.0 mg, 0.39 mmol) and CH_2Cl_2 (150 mL) were used for the macrocyclization. Yield 49.7%. ^{1}H NMR (400 MHz, 90% $CDCl_3$–10% CD_3OD): δ 10.25 (s, 2H), 10.20 (s, 1H), 10.15 (s, 1H), 10.09 (s, 1 H), 9.94 (s, 2 H), 9.36 (s, 1 H), 9.16 (s, 1 H), 9.09 (s, 2 H), 8.97 (s, 3 H), 6.56–6.31 (m, 7 H), 4.17–3.86 (s, 36 H), 1.98 (m, 6 H), 1.64 (m, 6 H), 1.35 (m, 6 H), 1.10 (m, 18 H) and 1.01 (m, 18 H). ^{13}C NMR (100 MHz, 90% $CDCl_3$–10% CD_3OD): δ 162.4, 161.6, 161.4, 160.9, 154.2, 152.0, 144.1, 137.0, 122.1, 121.3, 121.0, 120.9, 120.5, 114.3, 114.1, 113.1, 112.6, 97.1, 96.4, 95.4, 95.1, 94.3, 74.7, 74.4, 57.1, 56.8, 56.7, 56.3, 35.2, 25.9, 16.5, 16.4 and 11.1. MALDI-TOF MS (m/z) calc. for $C_{87}H_{111}N_7O_{21}Na$ ($M + Na^+$) 1612.8; found 1613.3 ($M + Na^+$). ESI-HRMS (m/z) calc. for $C_{87}H_{112}N_7O_{21}$ ($M + H^+$) 1590.7911; found 1590.7941 ($M + H^+$). Anal. calc. for $C_{87}H_{111}N_7O_{21}$: C, 65.68; H, 7.03; N, 6.16; found: C, 65.58; H, 7.07; N, 6.36%.

Eight-residue macrocycle 3c. Prepared according to the general synthetic procedure for macrocycles. Diacid **7b** (26.9 mg, 0.039 mmol) and oxalyl chloride (14.7 mg, 0.12 mmol) were used to prepare **2c**. Diamine salt **1** (50.0 mg, 0.039 mmol), DIEA (25.0 mg, 0.19 mmol) and CH_2Cl_2 (75 mL) were used for the macrocyclization. Yield 13.8%. ^{1}H NMR (400 MHz, 90% $CDCl_3$–10% CD_3OD): δ 10.18 (s, 8 H), 9.33 (s, 4 H), 8.99 (s, 4 H), 6.78 (s, 4 H),

6.64 (s, 4 H), 4.20 (s, 24 H), 4.00 (m, 8 H), 3.88 (m, 8 H), 1.98 (m, 8 H), 1.64 (m, 8 H), 1.37 (m, 8 H), 1.34 (m, 8 H), 1.10 (d, 24 H) and 1.08 (t, 24 H). ^{13}C NMR (100 MHz, 90% $CDCl_3$–10% CD_3OD): δ 162.1, 161.5, 145.8, 136.7, 122.9, 120.7, 115.3, 99.1, 96.4, 74.8, 57.1, 35.1, 26.2, 16.7 and 11.3. MALDI-TOF MS (m/z) calc. for $C_{104}H_{136}N_8O_{24}Na$ ($M + Na^+$) 1905.0; found 1905.8 ($M + Na^+$). ESI-HRMS (m/z) calc. for $C_{104}H_{137}N_8O_{24}$ ($M + H^+$) 1882.9779; found 1882.9792 ($M + H^+$).

Nine-residue macrocycle 3d. Prepared according to the general synthetic procedure for macrocycles. **11** (20.4 mg, 0.023 mmol) and oxalyl chloride (8.82 mg, 0.070 mmol) were used to prepare **2d**. Diamine salt **1** (30.0 mg, 0.023 mmol), DIEA (15.0 mg, 0.12 mmol) and CH_2Cl_2 (45 mL) were used for the macrocyclization. Yield 10.0%. ^{1}H NMR (400 MHz, 90% $CDCl_3$–10% CD_3OD): δ 10.14–9.80 (m, 9 H), 9.25–8.92 (m, 9 H), 6.74–6.58 (m, 9 H), 4.23–4.10 (m, 30 H), 3.97–3.85 (m, 16 H), 1.97 (m, 8 H), 1.61 (m, 8 H), 1.37 (m, 8 H), 1.08 (m, 24 H) and 0.99 (m, 24 H). MALDI-TOF MS (m/z) calc. for $C_{113}H_{145}N_9O_{27}Na$ ($M + Na^+$) 2084.0; found 2083.3 ($M + Na^+$). ESI-HRMS (m/z) calc. for $C_{113}H_{146}N_9O_{27}$ ($M + H^+$) 2062.0362; found 2062.0374 ($M + H^+$). Anal. calc. for $C_{113}H_{145}N_9O_{27}$: C, 65.84; H, 7.09; N, 6.12; found: 65.85; H, 7.12; N, 6.32%.

Ten-residue macrocycle 3e. Prepared according to the general synthetic procedure for macrocycles. **13** (27.5 mg, 0.023 mmol) and oxalyl chloride (8.82 mg, 0.070 mmol) were used to prepare **2e**. Diamine salt **1** (30.0 mg, 0.023 mmol), DIEA (15.0 mg, 0.12 mmol) and CH_2Cl_2 (45 mL) were used for the macrocyclization. Yield 6.2%. ^{1}H NMR (400 MHz, 90% $CDCl_3$–10% CD_3OD): δ 10.27–9.80 (m, 10 H), 8.95 (m, 10 H), 6.72–6.04 (m, 10 H), 4.17–4.05 (m, 30 H), 3.95–3.85 (m, 20 H), 1.97 (m, 10 H), 1.61 (m, 10 H), 1.37 (m, 10 H), 1.09 (m, 30 H) and 0.97 (m, 30 H). MALDI-TOF MS (m/z) calc. for $C_{130}H_{170}N_{10}O_{30}Na$ ($M + Na^+$) 2375.2; found 2374.4 ($M + Na^+$). ESI-HRMS (m/z) calc. for $C_{130}H_{171}N_{10}O_{30}$ ($M + H^+$) 2353.2196; found 2353.2183 ($M + H^+$). Anal. calc. for $C_{130}H_{170}N_{10}O_{30}$: C, 66.36; H, 7.28; N, 5.95; found: C, 66.56; H, 7.21; N, 5.75%.

Experimental procedure of the competition reaction

A mixture of 4,6-dimethoxy-isophthalic acid (8.7 mg, 0.039 mmol), diacid **9** (15.6 mg, 0.039 mmol), dry CH_2Cl_2 (20 mL), oxalyl chloride (39.2 mg, 0.309 mmol) and DMF (4 μL) was stirred for 5 h at room temperature. The solvent and excess oxalyl chloride were then removed, and the resulting diacid chloride was dissolved in CH_2Cl_2 (5 mL). This solution was then added concurrently to a pre-cooled solution of diamine salt **1** (50.0 mg, 0.039 mmol) in CH_2Cl_2 (70 mL) containing DIEA (54.9 mg, 0.42 mmol) at 0 °C. The reaction was stirred in an ice bath for 2 h, warmed up to room temperature, stirred overnight and then heated under reflux for 2 h. After quenching with CH_3OH and removing the solvent, the residue was triturated with CH_3OH and EtOAc. Filtration provided the crude product.

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