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H-bonding directed one-step synthesis of novel macrocyclic peptides from ε-aminoquinolinecarboxylic acid

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ABSTRACT

Two macrocyclic peptides **1a** and **1b** were synthesized directly from ε-aminoquinolinecarboxylic acid **2a** and **2b**, respectively. The preorganization of the uncyclized intermediates mediated by hydrogen bonding assisted the cyclization. The structures of **1a** and **1b** were characterized by ^{1}H and ^{13}C NMR spectroscopy and MALDI-TOF MS analysis. Solid state structure of **1a** was investigated by single crystal X-ray studies. Their aggregation behaviors in solution were studied by both variable concentration and temperature ^{1}H NMR experiments.

Macrocycles are fascinating supramolecular building blocks to chemists because of their applications in the fields of biomimics and materials chemistry.[1] For instance, over the past decade, *m*-arylene ethylene-based macrocycles were widely studied in the fabrication of functional materials.[2] Aryl amide-linked have also received remarkable attention for their applications in the field of peptidomimics. Gong[3] and Li and co-workers[4] demonstrated that their macrocyclic oligoamides were able to selectively bind guandinium ions and fullerenes, respectively. In particular, Gong and co-workers recently reported large transmembrane conductances of transmembrane pores formed by aromatic oligoamide macrocycles.[5] However, most of these macrocycles were prepared via multi-step coupling reactions,[4,6] which are laborious in preparation and separation. To avoid these synthetic workload, one-step cyclization appears to be an appealing method to obtain such macrocycles. Moreover, unlike the intensively studied aliphatic macrocyclic peptides with tubular assemblies employed as versatile functional materials,[7] the aromatic cyclic counterparts seem to be less investigated. Huc and co-workers[8] recently reported the synthesis of aromatic cyclic δ-peptides based on δ-Aqc (Fig. 1) in one-step cyclization. These aromatic cyclic peptides act not only as a molecular clip to interact with small guests, but also as a new class of G-quadruplex ligands. These investigations inspired us to develop a new class of aromatic cyclic peptides and to seek their potential functions.

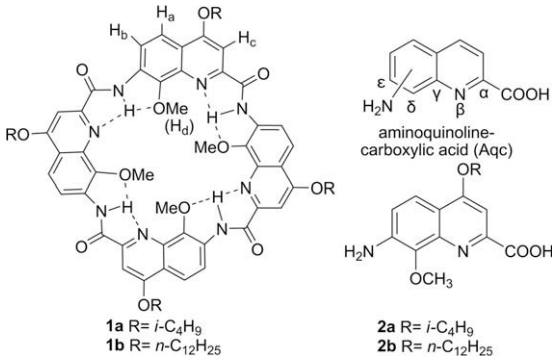

Figure 1. Structures of macrocyclic peptides **1** and their precursors **2**.

Recently, we have reported that aromatic ε-peptides based on ε-aminoquinolinecarboxylic acid (ε-Aqc) adopted helical structures assisted by hydrogen bonds.[9] Crystal structure of the tetramer demonstrates that four monomeric units are required for a helical turn, in which the two ends of the tetramer are placed in closed proximity. It is expected that such a helical conformation of tetramer should facilitate its cyclization into corresponding macrocyles. Herein, we present such one-step synthesis of two macrocyclic peptides **1a** and **1b** (Fig. 1) based on ε-Aqc. We also

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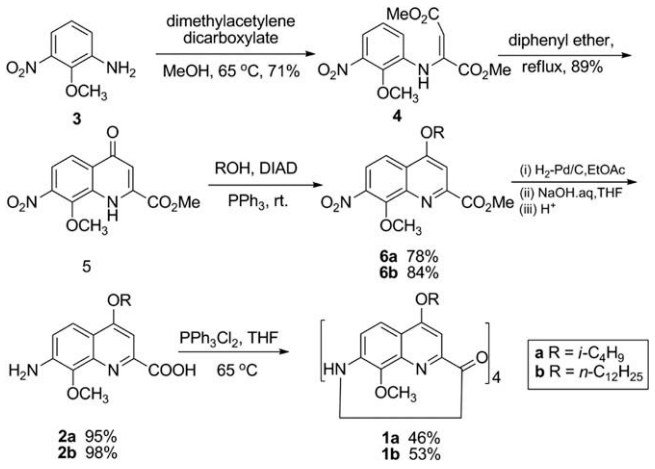

Scheme 1. Synthesis of macrocyclic peptides **1a** and **1b**.

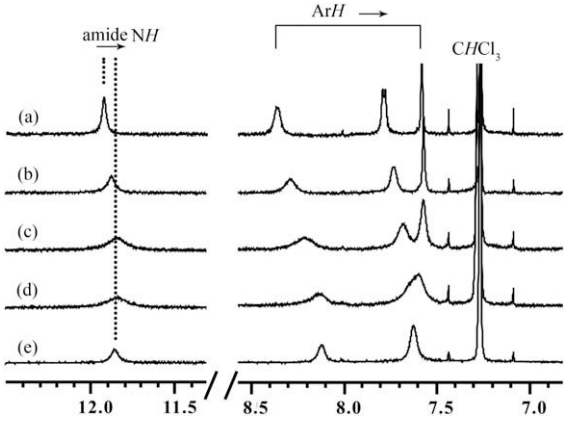

Figure 2. Part of the variable temperature ^{1}H NMR (600 MHz) of **1b** in $CDCl_3$ (1 mM). (a) 293 K; (b) 273 K; (c) 258 K; (d) 243 K; (e) 228 K.

report the crystal structure of **1a** and stacking studies of **1a** and **1b** in solution via both variable temperature and concentration ^{1}H NMR studies.

The synthesis of macrocyclic peptides **1a** and **1b** is outlined in Scheme 1. 2-methoxyl-3-nitroaniline **3** reacted with dimethyl acetylenedicarboxylate by Michael condensation[10] to obtain **4**, which underwent cyclization under pyrolytic conditions to give **5**. Compound **5** reacted with corresponding alcohols by Mitsunobu reaction to yield **6a** or **6b**, which was followed by subsequent hydrogenation and saponification, and acidification to give the amino acid **2a** or **2b**. For the one-step cyclization, in the presence of dichlorotriphenylphosphorane,[11] **2a** or **2b** in dry THF was converted into the corresponding acid chloride in situ, which was converted into a dimeric peptide intermediate upon reacting with the ε-amino group of the other quinoline. As illustrated in Figure 1, the dimer adopted a crescent conformation stabilized by two five-membered rings H-bonds in which the amide hydrogen, the methoxyl group, and the nitrogen atom in the quinoline ring were involved. The longer peptide intermediates were produced in a similar way and eventually cyclized into the expected macrocycles in moderate yields.[12] In our experiments, we also tried other coupling reagents such as thionyl chloride, oxalyl chloride, and PyBOP as well. Unfortunately, we failed to obtain the target macrocycle **1a** or **1b**. It could be ascribed to the low nucleophilicity of the amine group.

Macrocyclic peptides **1a** and **1b** have been characterized by ^{1}H and ^{13}C NMR spectroscopy as well as by MALDI-TOF Mass Spectroscopic analysis. In addition, the solid state structure of **1a** was confirmed by X-ray analysis. ^{1}H NMR signals of quinoline ring protons were equivalent, which is reminiscent of the case in the macrocyclic δ-Aqc peptides.[8a]

Firstly, we investigated the stacking properties of our macrocyclic peptides in $CDCl_3$ via variable temperature ^{1}H NMR experiments. For **1a** at concentrations of 10 mM and 1 mM, all protons shift to upfield upon decreasing temperature from 293 K to 258 K, but this trend was reversed as the temperature was lowered from 258 K to 223 K (Figs. S1 and S2). We postulated that low solubility of **1a** in $CDCl_3$ likely accounted for this phenomenon. To ascertain our assumption, we synthesized the macrocyclic peptide **1b** and investigated its behavior under identical variable temperature ^{1}H NMR experimental conditions. At the concentration of 10 mM, the trend in proton shifts was similar to that observed for the macrocycle **1a** at the same concentration (Fig. S3). However, at the concentration of 1 mM, the upfield shift of all the protons in **1b** at reducing temperatures from 293 K to 243 K was accompanied by signal broadening and a sort of coalescence (Fig. 2). It was calculated that, H_a, H_b, and the protons of the methoxyl groups (H_d) shifted upfield by a value of 0.22, 0.19, and 0.05 ppm, respectively. This indicates that the macrocyclic peptide **1b** with more lipophilic side chains would possess increased solubility in chloroform.

The stacking properties of macrocyclic peptides **1a** and **1b** were also investigated by the concentration-dependent ^{1}H NMR experiments at ambient temperature. In the concentration range between 1 and 20 mM in $CDCl_3$, all proton signals shifted asymptotically toward higher field with increasing concentration (Figs. S4 and S5). As shown in Figure 3a and b, each proton in both cases showed the same trend and the protons of the quinoline rings (H_a, H_b, and H_c) shifted more upfield than H_d. Specifically, H_a, H_b, H_c, and H_d of **1a** (Fig. 3a) shifted to higher field by values

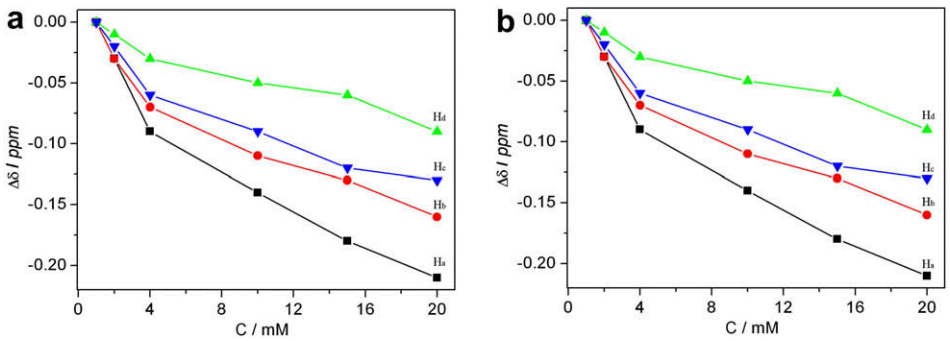

Figure 3. Proton chemical shift changes of the macrocycles in the concentration-dependent ^{1}H NMR (400 MHz): (a) **1a**; (b) **1b**, $\Delta\delta = \delta_c - \delta_{1\ mM}$.

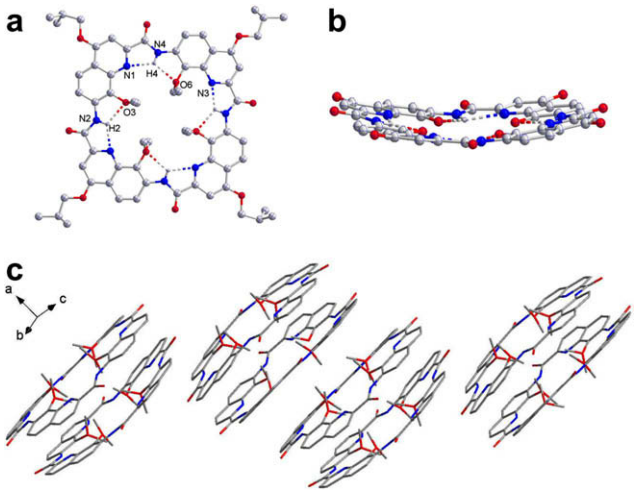

Figure 4. Crystal structures of macrocycle 1a (a) top view, (b) side view, (c) stacking view. (side chains and hydrogen atoms irrelevant to hydrogen bonds in (b) and (c) were all removed for clarity).

of 0.26, 0.21, 0.16, and 0.09 ppm, respectively, while for **1b** (Fig. 3b), each signal changed in the same trend by upfield shifts of 0.33, 0.25, 0.19, and 0.10 ppm, respectively. The chemical shift changes were probably caused by the intermolecular aromatic stacking interactions. It is noteworthy that the protons of macrocyclic peptide **1b** shifted more than their counterparts in **1a**, which might be attributed to the stronger aromatic stacking interactions aided by the capabilities of the longer side chains of **1b** to intertwine, intermolecularly.

The crystals suitable for X-ray diffraction analysis were grown by slow evaporation of solvent from chloroform–methanol–toluene solution.[13] The solid state structure is presented in Figure 4. Macrocycle **1a** consisted of an almost flat disc in the crystal structure. As expected, the four amide protons were all involved in intramolecular three-center hydrogen bonding. The disordered methoxyl groups pointed to either surfaces of the disc while all the amide oxygen atoms pointed outwards from the circumference. The four quinoline rings were not all coplanar in general. Two quinoline rings in each independent crystallographic unit were held in the same plane via the hydrogen bonding [N4···N1 2.592(2) Å, N4···O6 2.647(3) Å], and associated with the other pair, which are tilted out of plane, by similar intramolecular interaction [N2···N3 2.572(9) Å, N2···O3 2.651(6) Å, dihedral angle 16.2°] to create the dish-like conformation. Unexpectedly, along *a* axis, two macrocyclic dishes initially assembled together to form a dimeric unit by stable face-to-face aromatic π–π stacking interactions[14] with slight slippage, centroid distances of 3.722(2) and 3.654(2) Å. Furthermore, partial face-to-face π–π interactions (centroid distances of 3.584(2) Å) of the dimers prevented the column-pattern stacking observed in other macrocycles, but in agreement with the reported macrocycles containing methoxyl groups.[4]

In conclusion, two novel shape-persistent macrocyclic peptides were synthesized directly from ε-aminoquinoline-carboxylic acid in one step with moderate yields. In this process, hydrogen bonding interactions were rationalized to play an important role of assisting the oligoamide intermediates to fold and facilitated cyclization. We believe that our synthetic method of preparing the cyclic peptides could provide an expedient route in the development of such macrocycles. Currently, we are exploring Aqc-based macrocyclic peptides possessing different functionalities with an aim to investigate their interactions with different guest molecules.

Acknowledgments

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Supplementary data

Supplementary data associated (synthetic procedures of compound **1**–**7** and relevant ^{1}H and ^{13}C NMR spectra, variable temperature and concentration ^{1}H NMR spectra of **1a** and **1b**, and crystallographic data of **1a** (CIF file)) with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.207.

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12. *General synthetic procedure for the macrocycles*: To a stirred solution of compound **2a** or **2b** (1.0 mmol) in dry THF (30 mL), under an atmosphere of argon was added dichlorotriphenylphosphorane (1.33 g, 4.0 mmol) and the solution was heated to reflux for 8–14 h. The solvent was evaporated under reduced pressure and the residue was further purified by silica gel column chromatography to yield the macrocycles **1a** or **1b**. **1a**: white powder, mp >300 °C. ^{1}H NMR (400 MHz, 4 mM, $CDCl_3$): 11.63 (s, 4H), 8.10 (d, J = 8.9 Hz, 4H), 7.64 (d, J = 8.9 Hz, 4H), 7.55 (s, 4H), 4.36 (s, 12H), 4.30 (d, J = 6.2 Hz, 8H), 2.52–2.46 (m, 4H), 1.38 (d, J = 6.6 Hz, 24H). ^{13}C NMR (100 MHz, 20 mM, $CDCl_3$): 163.9, 161.2, 150.0, 141.5, 140.0, 131.6, 118.8, 117.7, 117.3, 97.1, 75.4, 63.1, 28.7, 19.6. MALDI-TOF MS: m/z calcd for $[M+H]^+$ 1089.5, found 1089.8; $[M+Na]^+$ 1111.5, found 1111.7. **1b**: pale yellow powder, mp = 198–200 °C. ^{1}H NMR (600 MHz, 10 mM, $CDCl_3$): δ 11.69 (s, 4H), 8.18 (d, J = 8.4 Hz, 4H), 7.65 (d, J = 8.4 Hz 4H), 7.50 (s, 4H), 4.50 (s, 8H), 4.39 (s, 12H), 2.14–2.17 (m, 8H), 1.77–1.80 (m, 8H), 1.58–1.60 (m, 8H), 1.36 (br m, 56H), 0.88–0.91 (t, 12H). ^{13}C NMR (100 MHz, 10 mM, $CDCl_3$): δ 164.0, 161.3, 150.1, 141.9, 140.2, 131.9, 119.0, 117.9, 117.7, 97.1, 69.4, 63.1, 32.1, 31.0, 30.0, 29.9, 29.8, 29.6, 29.5, 26.5, 22.9, 14.3. MALDI-TOF MS: m/z calcd for $[M+H]^+$ 1537.0, found 1537.8; $[M+Na]^+$ 1559.0, found 1559.8.
13. *Crystal data of* **1a**: $C_{61}H_{65}Cl_3N_8O_{12}$, M = 1208.56, orthorhombic, F*ddd*, a = 25.347(5), b = 28.709(6), c = 36.676(7) Å, V = 26689(9) Å^3, Z = 16, Dc = 1.203 Mg/m^3, T = 113 K, crystal size 0.20 × 0.20 × 0.20 mm^3, R = 0.1309, wR_2 = 0.3641 [I>2σ(I)], GOF on F^2 = 1.482, μ = 0.199 mm^{-1}, CCDC-715184.
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