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Synthesis of Benzofuran Chains: Monomer to Tetramer†

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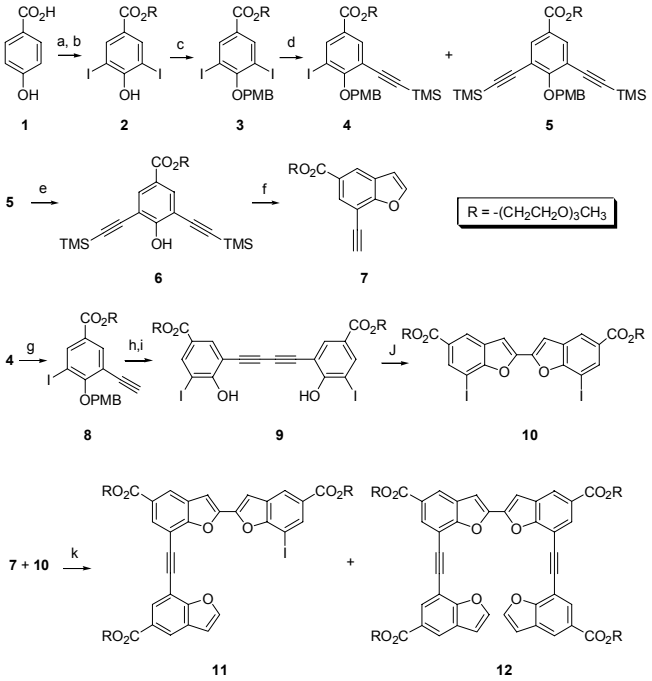
Foldamers are synthetic chain molecules or oligomers capable of folding into ordered arrays like secondary structures of proteins. The folding can be driven by various polar and nonpolar forces including hydrogen bonds, dipole-dipole interactions, π-stacking, and solvophobic interactions. Over the past decade, a variety of foldamers have been described and most of them can be classified into two categories.[1] One is peptidomimetic foldamers derived from unnatural amino acids such as β-amino acids and 2-aminocycloalkanecarboxylic acids. These foldamers provide us an opportunity to gain insight into fundamental principles of the folding of biomacromolecules. Another is aryl strand foldamers prepared from rigid aromatic building blocks, and some of them fold into a helical structure with an internal cavity, thus capable of accommodating a complementary guest.[2]

In recent years, we have prepared a series of oligoindole foldamers which fold into helical structures by forming multiple hydrogen bonds between the indole NHs and an anion in organic media[3] or even in water.[4] Herein, we present the synthesis of benzofuran scaffolds **7** (monomer) and **10** (dimer) which can be used as molecular building blocks for the construction of new aryl stand foldamers capable of folding into a helical conformation by cation binding. In addition, the synthesis of **11** (trimer) and **12** (tetramer) is also described.

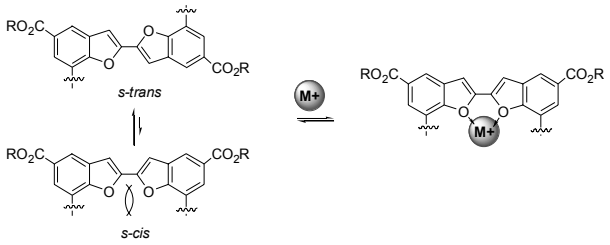
The synthesis began with *p*-hydroxybenzoic acid (**1**) (Scheme 1). Iodination of **1** with NaI/NaOCl under basic conditions[5] afforded 4-hydroxy-3,5-diiodobenzoic acid (80%) which was in turn subjected to esterification with $SOCl_2$/2-[2-(2-methoxyethoxy)ethoxy]ethanol to give the corresponding ester **2** (73%). Here, the side chain of tri(ethylene glycol) unit was introduced to enhance the solubility of longer oligomers **10**-**12**, otherwise insoluble in organic solvents. Then, the hydroxyl group in **2** was first protected with *p*-methoxybenzyl (PMB) chloride in the presence of KI/K_2CO_3 to prevent a complex mixture in the next step of the Pd/CuI-mediated reaction.[6] Here, the PMB group was chosen because it could be selectively removed under mild acidic conditions. Sonogashira coupling[7] of **3** with trimethylsilyl(TMS)-ethyne (1 equiv) provided a mixture of mono- and bis-coupled products **4** (48%) and **5** (23%). After purification by column chromatography (silica gel, hexanes/ethyl acetate, initially 3:2 then 1:2), **5** was dissolved in CH_2Cl_2 containing CF_3COOH (3-5 equiv) and was stirred at room temperature for 3 h to afford **6** in 84% yield. A solution of **6** in THF containing tetrabutylammonium fluoride (TBAF, 3 equiv) was heated at reflux for 7 h to render monomer **7** in 65% yield through two steps; removal of the TMS groups and base-promoted cyclization.[8] It should be noted that this benzofuran formation was attempted with amine bases (diisopropylamine, diisopropylethylamine) and $PdCl_2$, but no product was obtained. When tetrabutylammonium acetate was used as a base, **7** was also formed in a low yield (< 20%).

Next, the TMS group of **4** was removed by treating with TBAF (1.1 equiv) and acetic acid (1.0 equiv) to give **8** (91%). Here, acetic acid was added as a proton source in order to avoid the decomposition of the ester group by hydroxide ions generat-



Scheme 1. Reagents and conditions: (a) NaI (2.1 equiv), NaOH (2.1 equiv), NaOCl (2.1 equiv)/MeOH, rt, 1.5 h, 80%; (b) $SOCl_2$ (2.0 equiv)/CH_2Cl_2, reflux, then $CH_3(OCH_2CH_2)_3OH$ (2.0 equiv), Et_3N/CH_2Cl_2, rt, 73% (2 steps); (c) *p*-methoxybenzyl chloride (1.1 equiv), K_2CO_3 (1.1 equiv), KI (0.3 equiv), DMF, 80 ~ 85 °C, 9 h, 88%; (d) $Pd(PPh_3)_2Cl_2$, CuI, trimethylsilylethyne, Et_3N/THF, 52 ~ 55 °C, 15 h, **4** (48%), **5** (23%); (e) trifluoroacetic acid (3 equiv), CH_2Cl_2, rt, 3 h, 84%; (f) TBAF (3 equiv), THF, reflux, 7 h, 65%; (g) TBAF (1.1 equiv), AcOH (1.0 equiv), THF, rt, 91%; (h) $Cu(OAc)_2$ (1.1 equiv), pyridine, rt, overnight, 81%; (i) trifluoroacetic acid (10 equiv), CH_2Cl_2, rt, 89%; (j) TBAF (3.0 equiv), THF, reflux, 12 h, 59%; (k) the same as d), **11** (44%), **12** (14%).

†This paper is dedicated to Professor Sunggak Kim on the occasion of his honorable retirement.



Scheme 2. Conformational equilibrium between *s-trans* and *s-cis* in the absence and presence of a metal cation.

ed *in situ*. Compound **9** was obtained by oxidative homo-coupling (81% yield) of **8** in the presence of $Cu(OAc)_2$/pyridine, followed by deprotection (89% yield) of the PMB groups with CF_3COOH (10 equiv). Reaction of **9** with TBAF (3 equiv) in THF (reflux, 12 h) resulted in double cyclization to yield dimer **10** in 59% yield.[8] Finally, Sonogashira coupling of **10** with **7** (1 equiv) gave a mixture of trimer **11** and tetramer **12**,[9] which were purified by column chromatography (initially ethyl acetate alone, then ethyl acetate/acetone 1:1) to give 44% and 14% yields, respectively. The low yield of **12** was in part attributed to the highly polar nature of four tri(ethylene glycol) units, causing some loss during purification.

Unlike indole bearing a hydrogen bond donor NH, benzofuran contains an oxygen atom which may function as a hydrogen bond acceptor or as a metal coordination site. According to computer modeling studies, the bi(benzofuran) moiety displays an *s-trans* conformation due to dipole-dipole repulsions but adopts an *s-cis* conformation in the presence of an metal cation (Scheme 2). Moreover, the longer oligomer of **12** can fold into a macrocycle-like structure by cation-dipole interactions between the existing furanyl oxygen atoms and cations such as potassium and cesium. The folding and cation-binding properties of benzofuran-based oligomers in solution are currently under investigation.

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9. Physical and spectroscopic data: **7** (monomer): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (d, J = 1.6 Hz, 1H), 8.18 (d, J = 2.4 Hz, 1H), 7.95 (d, J = 1.6 Hz, 1H), 7.15 (d, J = 2.4 Hz, 1H), 4.64 (s, 1H), 4.39 (m, 3H), 3.75 (m, 3H), 3.58 (m, 3H), 3.56 (m, 6H), 3.38 (m, 3H), 3.17 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.0, 156.6, 148.3, 128.8, 128.0, 125.1, 124.3, 107.9, 106.1, 86.5, 77.0, 71.3, 69.9, 69.7, 69.6, 68.3, 64.3, 58.1; ESI-MASS m/z 355 (MNa^+). **10** (dimer): mp 155 ~ 158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 2H), 8.28 (s, 2H), 7.38 (s, 2H), 4.50 (t, J = 4.0 Hz, 6H), 3.86 (m, 6H), 3.69 (m, 18H), 3.54 (m, 6H), 3.36 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 157.8, 148.4, 147.9, 135.8, 127.1, 127.5, 123.9, 105.9, 74.3, 71.9, 70.6, 70.5, 70.4, 69.1, 64.5, 59.0; ESI-MASS m/z 889 (MNa^+). **11** (trimer): mp 127 ~ 130 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (s, 1H), 8.44 (s, 1H), 8.39 (s, 1H), 8.31 (s, 1H), 8.29 (s, 1H), 8.21 (s, 1H), 7.81 (s, 1H), 7.76 (s, 1H), 7.25 (s, 1H), 4.44 (m, 6H), 3.78 (m, 6H), 3.59 (m, 6H), 3.51 (m, 12H), 3.36 (m, 6H), 3.18 (s, 3H), 3.17 (s, 3H), 3.15 (s, 3H); ESI-MASS m/z 1093 (MNa^+). **12** (tetramer): mp 160 ~ 162 °C ; ^{1}H NMR (400 MHz, $CDCl_3$) 8.40 (s, 4H), 8.34 (s, 4H), 7.85 (s, 2H), 7.47 (s, 2H), 6.94 (s, 2H), 4.55 (m, 6H), 3.89 (m, 6H), 3.75 (m 6H), 3.70 (m, 6H), 3.65 (m, 6H), 3.58 (m, 6H), 3.34 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 165.8, 157.2, 157.0, 148.6, 146.8, 130.7, 129.8, 128.7, 127.7, 126.2, 125.5, 124.5, 124.5, 107.6, 107.3, 107.2, 105.4, 88.4, 87.6, 71.9, 70.7, 70.6, 70.5, 69.2, 69.1, 64.4, 64.3, 59.0; ESI-MASS m/z 1297 (MNa^+).