Cyclic Trimers of Chiral Furan Amino Acids

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Abstract: Chiral furan amino acids were synthesized as novel peptide building blocks. Cyclooligomerization of these monomers by a single-step process led to the selective formation of chiral C_3-symmetric cyclic trimers, which were studied for their structures and properties, like anion binding and antimicrobial activities.

Key words: chiral furan amino acids, anion binding, synthetic receptors, cyclic trimers, antimicrobial

Cyclization of linear peptides or covalent bridging of their constituent amino acids at appropriate places is a widely used method to constrain their conformational degrees of freedom, preorganize their ligand binding elements and induce desirable structural biases essential for their biological activities, such as transporting ions or molecules across membranes through tubular structures,[1] anion binding by directed hydrogen bonding interactions,[2] and acting as receptors to various other hosts.[3] In this context, many structurally rigid molecular scaffolds have been designed to create varieties of amide-linked artificial cyclic receptors containing predisposed cavities that could be moulded to precise dimensions providing attractive tools to chemists to carry out in vitro studies of molecular recognition processes of biological systems with the ultimate aim of developing their therapeutic applications.[4–6] Recently, we developed a novel furan amino acid, 5-(aminomethyl)-2-furancarboxylic acid (**1a**) and prepared its trimer, an 18-membered cyclic oligopeptide **2a**,[7] which was found to be an excellent receptor for carboxylate binding.[8] Studies on the binding of amino acid carboxylates by multiple hydrogen bonding receptors have gained increasing importance in recent years,[9] especially due to the alarming emergence of vancomycin resistant strains.[10] The presence of multidentate H-bonding sites in **2a** made it an ideal receptor for carboxylate anion. The synthesis of **2a** was achieved by a high-yielding cyclotrimerization reaction of the unfunctionalized furan amino acid **1a** with BOP reagent using DIPEA as base and DMF as solvent. It avoids the lengthy step-wise assembling of linear precursors, conventionally followed for making such cyclic products. An extension of this work by us led to the synthesis of cyclic homooligomers of furanoid sugar amino acids that showed interesting structures and properties.[11] Also, similar one-pot cyclooligomerizations of five-membered heterocyclic ring containing amino acids using various reagents have been carried out by many others (Figure 1).[12]

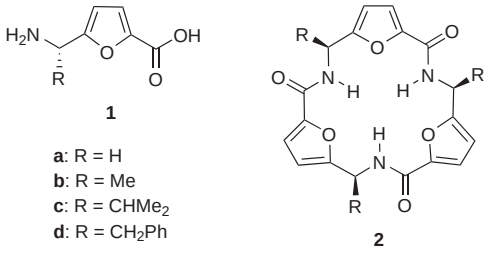

Figure 1

As part of our ongoing project on the development of novel cyclic oligomers of various multi-functional monomeric building blocks, we were interested in developing optically active furan amino acids **1b**–**d** to prepare their cyclooligomers **2b**–**d**, respectively. It was felt by us that introduction of a chiral center in the amino terminus of **1a** can give rise to an additional combinatorial site in this bifunctional building block that will allow to mimic the side-chains of natural amino acids influencing the hydrophobicity/hydrophilicity of the resulting peptidomimetic molecules. In this paper, we describe the stereoselective synthesis of chiral furan amino acids, 5-(1-aminoalkyl)-2-furoic acids **1b**–**d**, in enantiomerically pure forms starting from their corresponding chiral amino aldehydes. Cyclotrimerization of these monomers by the above-mentioned single-step process led to chiral C_3-symmetric cyclic products **2b**–**d**, which were studied for their anion binding properties. These molecules were also tested for their antimicrobial properties and showed significant activities against some Gram-positive and Gram-negative bacteria.

The details of the synthesis of compounds **2b**–**d** are shown in Scheme 1. The starting materials in this scheme were chiral *N*-Boc-amino aldehyde **3** derived from the corresponding amino acid[13] and the 3,4-*O*-isopropylidene-1,1-dibromobut-1-en-3,4-diol (**4**) that was prepared from (*R*)-glyceraldehyde acetonide.[14] Chiral purity of the starting *N*-Boc-amino aldehyde **3** is very critical in this scheme. This was ascertained in the beginning by measuring its optical rotation and comparing with reported values. Treatment of **3** with the Li-acetylide prepared in situ by reacting **4** with *n*-BuLi, gave the propargyl alcohol adduct **5** as a mixture of isomers. *Cis*-hydrogenation of **5** using P2-Ni[15] provided the *cis*-allylic alcohol inter-

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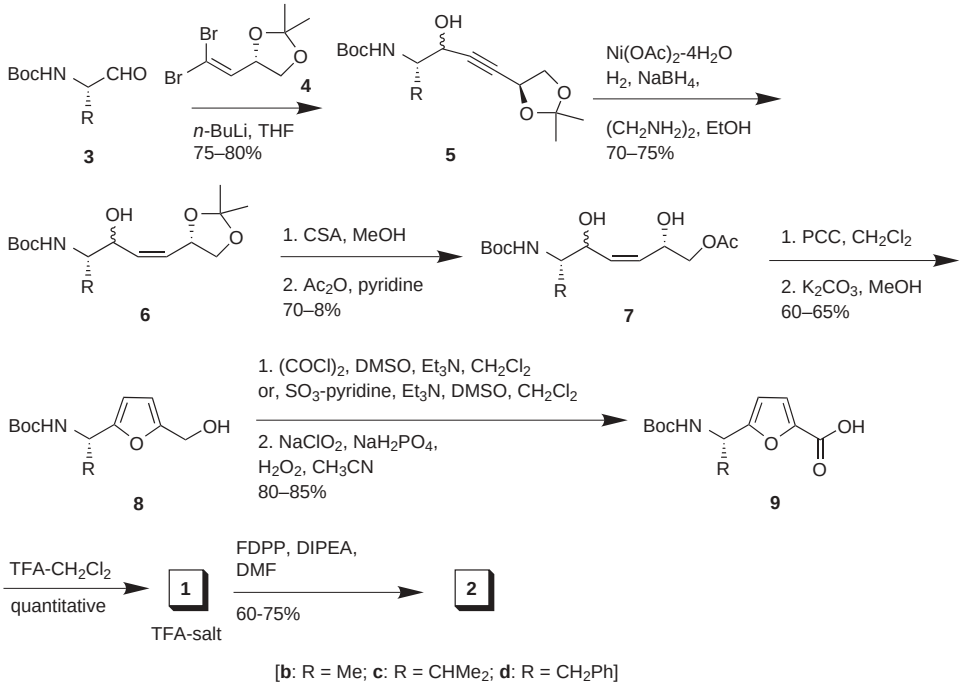

Scheme 1 Synthesis of chiral furan amino acids **1b–d** and their cyclic trimers **2b–d**.

mediate **6**. Treatment of **6** with acid led to the deprotection of the acetonide and the primary hydroxyl was selectively protected as acetate to get the '*cis*-2-butene-1,4-diol' intermediate **7**. The resulting '*cis*-2-butene-1,4-diol' moiety of **7** was next transformed into a furan ring on oxidation with pyridinium chlorochromate (PCC),[16] which was followed by the treatment of the intermediate with anhydrous K_2CO_3 to deprotect the acetate to give the chiral furanyl alcohol intermediate **8**. Finally, a two-step oxidation process, (i) Swern oxidation (**8a**) or oxidation by SO_3–pyridine complex (**8b**,**c**) to an aldehyde, and (ii) oxidation of the aldehyde to acid using $NaClO_2$–H_2O_2, converted the primary hydroxyl group of **8** into the acid functionality to furnish Boc-protected intermediate **9**. Deprotection of the Boc group using trifluoroacetic acid (TFA) in CH_2Cl_2 gave the TFA salts of **1**, which were directly subjected to cyclooligomerization reaction. Treatment of the TFA salt of **1** dissolved in amine-free DMF with pentafluorophenyl diphenylphosphinate (FDPP) followed by the slow addition of DIPEA provided the cyclic trimer **2** selectively.[17] The choice of FDPP over BOP reagent was made as the former was found to give slightly better yields of the cyclized products.[12l]

Detailed theoretical studies were carried out to examine the selective formation of the cyclic trimer in these cyclooligomerization reactions using the unsubstituted 5-(aminomethyl)-2-furancarboxylic acid (**1a**). Ab initio calculations at HF 6-31G** levels revealed that while the formation of the higher order cyclized oligopeptides, $[HN\text{-}CH_2\text{-}(furan)\text{-}CO]_n$ with n = 3,4, is energetically favorable, that of the cyclic dimer is thermodynamically unfavorable. The difference in the free energy between the monomer and the oligomer is significantly more favorable for the trimer than the dimer. Solvation by DMF showed enhancement of this preference further as seen in greater difference in the free energy, and even in the electronic energy, of the monomer and the trimer than that of the monomer and the dimer. Interestingly, the formation of the tetramer is also found favorable, indeed a little more so than the trimer. That it is not formed experimentally implies that calculations on isolated systems are not sufficient to understand the chemistry of such a large system. However, calculation for solvation by DMF for the formation of the tetramer is yet to be done to draw the final conclusion.[18]

The ^{1}H NMR spectra of **2b–d** in different solvents, DMSO-d_6, CD_3CN and $CDCl_3$, showed perfect C_3-symmetric structures[19] with signals from a single unit. The NH signal appeared at δ = 8.36 ppm with a ^3J of 8.9 Hz for **2b** and at δ = 8.15 ppm with a ^3J of 10.4 Hz for **2c** in DMSO-d_6. The NH signal of **2d** appeared at δ = 8.49 ppm with a coupling constant of J = 8.9 Hz in DMSO-d_6 and at δ = 6.78 ppm with J = 9.4 Hz coupling in $CDCl_3$. Energy minimization of these compounds were carried out using MOPAC in CS Chem3D (Pro, version 5.0). The energy-minimized structures thus obtained (Figure 2) displayed tripod bowl shaped structures for **2b–d** with *s-cis* orientation of all the amide carbonyls and NH bonds pointing to the same side of the side-chains. The H-N-Cα-H torsional angle in both **2b** and **2d** is ca 175°, while the same in **2c** is ca 180° (*trans*), which are in conformity with the observed ^3J values. The bulkier Cβ substituents in **2c** made the approach of guests to its NH groups sterically more demanding than in **2b** and **2d**. It is to be noted here that the H-N-Cα-H torsional angle in the energy-minimized structure of **2a** was ca 120° supported by a ^3J of 5.6 Hz.[7]

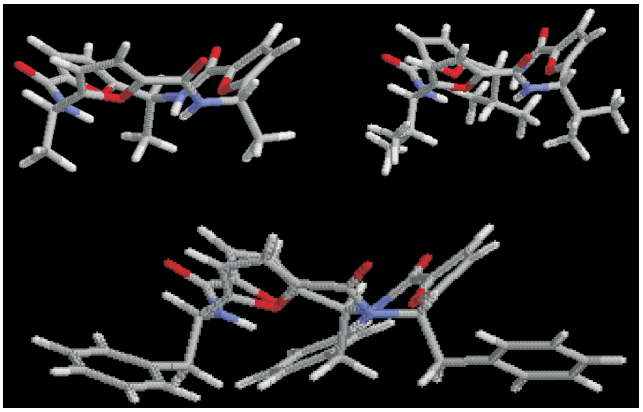

Figure 2 Energy-minimized structures of **2b** (top left), **2c** (top right) and **2d** (bottom).

The average distance between any one of the three ring oxygens and its adjacent amide protons in **2b**–**d** is ca 2.4–2.5 Å indicating the possibilities of the existence of a network of intramolecular NH → O(ring) H-bonds where each amide proton is hydrogen bonded to two adjacent furan oxygens and vice versa. This is supported by the observed low-field chemical shifts of the amide protons, >8 ppm in DMSO-d_6 and at ca 6.7 ppm in nonpolar $CDCl_3$.

The binding capabilities of one of these cyclic peptides **2d** with various anions were measured by the ^{1}H NMR titration method[20] using their tetra-*n*-butylammonium (TBA) salts in CD_3CN and DMSO-d_6. Addition of an excess of TBA salt (ca. 10–12 equiv) to a solution of the host caused downfield shifts of the amide proton resonance with $\Delta\delta_{max}$ = 2.74 ppm using tetra-*n*-butylammonium acetate (TBAA) and 2.29 ppm with tetra-*n*-butylammonium chloride (TBACl) in CD_3CN, suggesting the formation of very tightly bound H-bonded complexes. With tetra-*n*-butylammonium iodide (TBAI), the amide proton shift was moderate (1.05 ppm) suggesting weak binding. Binding studies with another carboxylate anion, the tetra-*n*-butylammonium salt of Ac-D-Ala-D-Ala-O$^-$ (TBAX), were carried out in DMSO-d_6, a strong H-bonding solvent, due to its poor solubility in CD_3CN. The downfield shift of the amide proton signal in this case was smaller than those with TBAA and TBACl in CD_3CN, with a $\Delta\delta_{max}$ of 1.04 ppm suggestive of moderate binding.

The symmetries of the molecules as well as the ^3J couplings of their amide signals remained intact even after binding with the anions that caused downfield shifts only for the amide protons leaving other proton shifts unchanged. This indicates that the binding with various anions did not disturb the symmetry of the host or its structure. Furthermore, loss of extended conjugation was expected to prevent any out of plane bending of the amide moieties. Similar binding studies with **2c** using various anions did not show any shift of its amide proton resonance indicating inaccessibility of its binding site due to the presence of bulky *iso*propyl groups in the molecule.

Following the procedure reported by Kelly et al.,[21] NMR titrations were carried out by adding increasing amounts of TBA salts to a solution of **2d** in CD_3CN at 21 °C. A graph between the chemical shift differences ($\Delta\delta_{obs}$) and [guest]/[host] was plotted (Figure 3). The stoichiometry of complexation of **2d** with various anions was determined by using Job's method of continuous variations[22] (Figure 3) that showed a maximum at ca 0.5 mole fraction in each case, confirming the formation of a 1:1 complex.

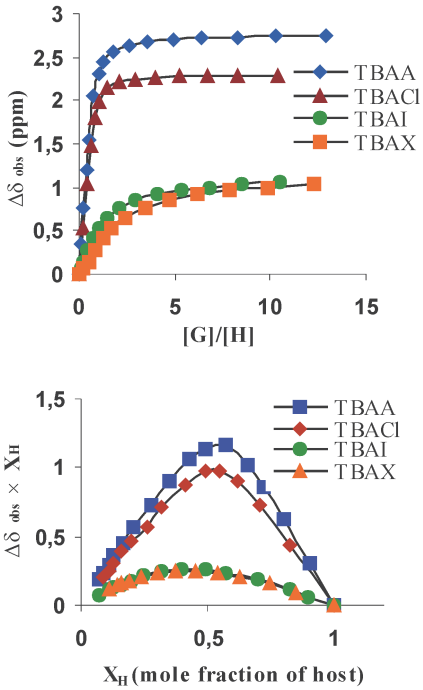

Figure 3 ^{1}H NMR titration plots (top) and Job plots (bottom) for the complexation of **2d** (host) with tetra-*n*-butylammonium (TBA) salts of acetate (A), chloride, iodide and Ac-D-Ala-D-Ala-O$^-$ (X), in CD_3CN solution for the first three and DMSO-d_6 for the last one.

The association constant (K_a) measured by NMR titration method[21,23] are shown in Table 1. While the association constants for tetra-*n*-butylammonium acetate (TBAA) and tetra-*n*-butylammonium chloride (TBACl) were high, binding with iodide (entry 3, Table 1) was weak, may be, due to its bulkier size. In polar solvent DMSO-d_6, moderate association constant was observed with TBA[Ac-(D-Ala)$_2$] (entry 4, Table 1) in spite of the solvent molecules also competing for the H-bonding sites.

Table 1 Association Constants (K_a) (M^{-1}) of **2d** with Different TBA Salts

Entry	Salts	K_a (M^{-1})·10^{-3} (stand. dev.)
1	TBAA[a]	5.50 (± 1.30)
2	TBACl[a]	8.46 (± 1.18)
3	TBAI[a]	0.47 (± 0.06)
4	TBA[Ac-(D-Ala)$_2$][b]	1.78 (± 0.06)

[a] CD_3CN.
[b] DMSO-d_6.

The strong binding of **2d** with various anions, especially with carboxylates, encouraged us to test these cyclic peptides for their antimicrobial activities. The antimicrobial activities of the cyclic peptides **2b**–**d** were evaluated by Agar diffusion assay using nutrient medium.[24] Compounds **2c** and **2d** were excellently active against *Escherichia coli*. In case of *Pseudomonas aeruginosa*, compound **2c** showed relatively higher degree of activity compared to **2b**, whereas compound **2d** was inactive against the same microorganism in comparison with the standard streptomycin.

Compounds **2c** and **2d** have comparable activities against Gram-positive bacteria like *Bacillus cereus* with the standard streptomycin. The cyclic peptides **2b**–**d** were, otherwise, inactive against most of the Gram-positive bacteria for which they were tested.

Compound **2b** displayed very mild activity against fungi like *Candida albicans* with standard nistatin. The other two cyclic peptides **2c** and **2d** did not have any antifungal activity.[25]

In conclusion, the novel oligopeptide-based macrocyclic synthetic receptors **2b**–**d**, prepared from a new class of chiral building blocks, chiral furan amino acids **1b**–**d**, demonstrate excellent binding capabilities with various anions and show encouraging biological activities that may find many useful applications.

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(17) Selected physical data of **2b**: R_f = 0.4 (silica, 8% MeOH in $CHCl_3$); $[\alpha]_D^{29}$ –33.9 (*c* 0.115, MeOH). ^{1}H NMR (200 MHz, DMSO-d_6): δ = 8.37 (d, *J* = 9.52 Hz, 1 H, N*H*), 7.02 (d, *J* = 2.93 Hz, 1 H, furan ring proton), 6.51 (d, *J* = 2.97 Hz, 1 H, furan ring proton), 5.41 (dq, *J* = 9.52, 7.32 Hz, 1 H, C-*H*), 1.54 (d, *J* = 7.32 Hz, 3 H, C*β*-H_3). MS (LSI-MS): *m/z* = 412 $[M + H]^+$.
Selected physical data of **2c**: R_f = 0.5 (silica, 8% MeOH in $CHCl_3$); $[\alpha]_D^{29}$ –36.4 (*c* 0.055, MeOH). ^{1}H NMR (200 MHz, DMSO-d_6): δ = 8.17 (d, *J* = 10.41 Hz, 1 H, N*H*), 6.98 (d, *J* = 2.97 Hz, 1 H, furan ring proton), 6.49 (d, *J* = 2.97 Hz, 1 H, furan ring proton), 4.91 (dd, *J* = 10.41, 9.66 Hz, 1 H, C*α*-*H*), 2.04 (m, 1 H, C*β*-*H*), 1.04 (d, *J* = 6.69 Hz, 3 H, C*γ*-H_3), 0.86 (d, *J* = 6.69 Hz, 3 H, C*γ*-H'_3). MS (ESI): *m/z* = 496 $[M + H]^+$, 518 $[M + Na]^+$, 519 $[M + Na + H]^+$.
Selected physical data of **2d**: R_f = 0.5 (silica, 7% MeOH in $CHCl_3$); $[\alpha]_D^{29}$ –100.0 (*c* 0.070, MeCN). ^{1}H NMR (200 MHz, DMSO-d_6): δ = 8.43 (d, *J* = 8.92 Hz, 1 H, N*H*), 7.17 (m, 5 H, aromatic protons), 6.83 (d, *J* = 2.97 Hz, 1 H, furan ring proton), 6.15 (d, *J* = 2.97 Hz, 1 H, furan ring proton), 5.46 (ddd, *J* = 8.92, 8.18 Hz, 1 H, C*α*-*H*), 3.19 (m, 2 H, C*β*-H_2). MS (LSI-MS): *m/z* = 640 $[M + H]^+$, 662 $[M + Na]^+$.

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