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Cyclic trimer of 5-(aminomethyl)-2-furancarboxylic acid as a novel synthetic receptor for carboxylate recognition

Tushar K. Chakraborty,* Subhasish Tapadar and S. Kiran Kumar

Indian Institute of Chemical Technology, Hyderabad 500 007, India

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Abstract—A novel 18-membered cyclic oligopeptide **1** based on 5-(aminomethyl)-2-furancarboxylic acid (**2**), is developed as an excellent receptor for carboxylate binding having an association constant of 8.64×10^3 M^{-1} for tetrabutylammonium acetate in CD_3CN. The synthesis of **1** was achieved by a high-yielding cyclotrimerization reaction of the unfunctionalized furan amino acid **2**.

The creation of structurally rigid molecular frameworks with predisposed cavities of precise dimensions provides attractive tools for chemists to carry out in vitro studies of molecular recognition processes of biological systems with the ultimate aim of developing their therapeutic applications.[1–3] Cyclic peptides with restricted conformational degrees of freedom, especially those based on constrained molecular scaffolds or unnatural amino acids represent a notable class of such compounds that are being extensively studied as hosts for various guests.[4] The introduction of unnatural components in these designs also leads to their improved pharmacokinetic properties. We report here the synthesis of a novel 18-membered cyclic oligopeptide **1** prepared from a new monomeric building block based on the furan amino acid, 5-(aminomethyl)-2-furancarboxylic acid (**2**, Faa) and demonstrate that it is an excellent artificial receptor for carboxylate binding.[5] Studies on the binding of amino acid carboxylates by multiple hydrogen bonding receptors have gained increasing importance in recent years,[6] especially due to the alarming emergence of vancomycin resistant strains.[7] The presence of multidentate H-bonding sites in **1** was expected to make it an ideal receptor for various carboxylate ligands.

Scheme 1 outlines the synthesis of **1** and **2**. Acid treatment of D-fructose (**3**), following a reported procedure,[8] gave 5-(chloromethyl)-2-furancarboxaldehyde (**4**) in 80% yield. Jones' oxidation of **4** was followed by esterification of the resulting acid using CH_2N_2 to give the corresponding methyl ester **5** in 85% yield.[9] The chloromethyl substituent was next transformed into a Boc-protected aminomethyl moiety in three steps: displacement by azide, selective azide reduction and finally, in-situ protection using Boc_2O giving the protected Faa **6** in 80% overall yield.[9] Saponification of **6** was followed by Boc deprotection to give **7** that is the TFA salt of **2**. A solution of **7** in amine-free dry DMF (10^{-2} M) was treated with benzotriazol-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate (BOP reagent) at 0°C, followed by the slow addition of Et_3N.[10] After the reaction was over, it was subjected to aqueous work-up and finally, chromatographic purification furnished the cyclic trimer **1** in 65% yield from **6**.[11]

The ^1H NMR spectra of **1** in different solvents, DMSO-d_6, CD_3CN and $CDCl_3$, showed a perfect C_3 symmetric structure[12] with only four signals from the four different types of protons attached to each unit. Energy minimization of **1** was carried out using Sybyl 6.7 program on a Silicon Graphics O2 workstation. The Tripos force field with default parameters was used and minimizations were done first with steepest decent, followed by conjugate gradient methods for a maximum of 2000 iterations each or RMS deviation of 0.001 kcal/mol, whichever was earlier. The energy-minimized structure thus obtained (Fig. 1) displayed a near-planar geometry with *s-cis* orientation of all the amide carbonyls. The average distance between any one of the three ring oxygens and its adjacent amide protons is ~2.1 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 sup-

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* Corresponding author. E-mail: chakraborty@iict.ap.nic.in

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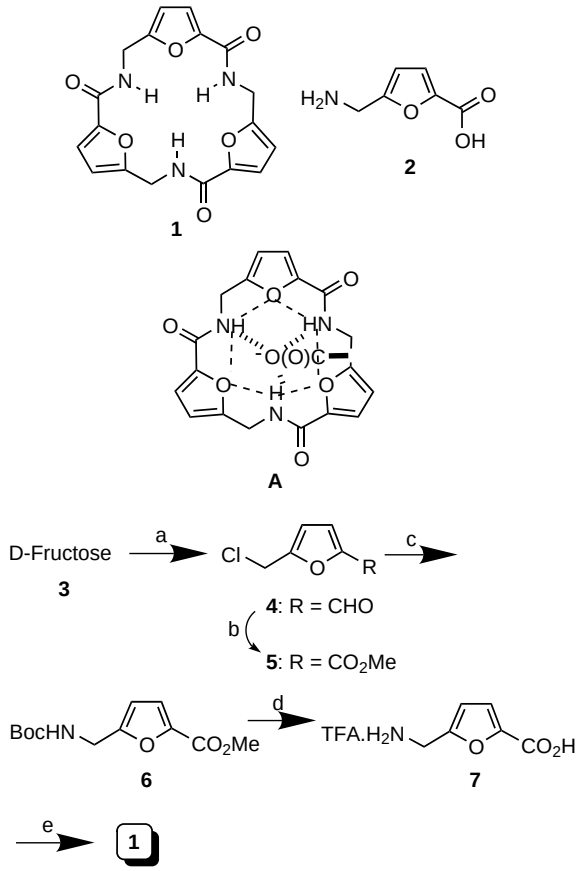

Scheme 1. Synthesis of **1**. *Reagents and conditions*: (a) $MgCl_2{\cdot}6H_2O$, HCl, toluene, 75°C, 1.5 h, 80% (Ref. 8); (b) (i) Jones' oxidation; (ii) CH_2N_2, Et_2O, 85%; (c) (i) NaN_3, DMF, 65°C, 1 h; (ii) Ph_3P, MeOH, rt, 2 h; (iii) Boc_2O, rt, 10 min, 80% (three steps); (d) (i) LiOH, THF–MeOH–H_2O (3:1:1), 0°C, 2 h, quantitative; (ii) trifluoroacetic acid (TFA), CH_2Cl_2, 0°C to rt, 30 min, quantitative; (e) BOP reagent, Et_3N, DMF, rt, 12 h, 65%.

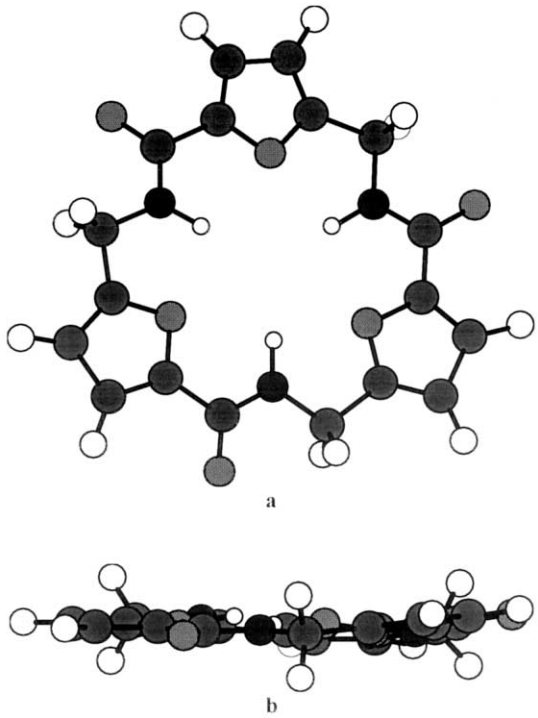

Figure 1. Energy minimized (Tripos, Sybyl 6.7) structure of **1** viewed from top (*a*) and along the plane of the molecule (*b*).

ported by the observed low-field chemical shift of the amide proton in nonpolar solvent, δ 6.75 in $CDCl_3$. The planar structure of the molecule with extended conjugation between the furan rings and their adjacent amide moieties and the convergence of all three hydrogen bond donors inside the ring make compound **1** a tailor-made receptor for carboxylate binding as shown schematically in structure **A**.

The binding capability of **1** with a carboxylate anion was measured by the ^1H NMR titration method[13] using tetrabutylammonium acetate (TBAA) in CD_3CN. Addition of an excess of TBAA to a CD_3CN solution of **1** caused huge a downfield shift (2.46 ppm) of the host amide proton resonance, suggesting the formation of a very tightly-bound H-bonded complex.[14] The symmetry of the molecule remained intact even after binding with the carboxylate that caused the downfield shift only for the amide proton leaving other proton shifts unchanged. This indicates that the binding of **1**, having three H-bond donors, with carboxylate anion maintained a dynamic equilibrium that did not disturb the symmetry of the host. Although, the structure of the carboxylate-bound complex **A** or the orientations of the amide protons in it are not known, loss of extended conjugation was expected to prevent any out of plane bending of the amide moieties, unless it was getting compensated by the binding energy.

Following the procedure reported by Kelly et al.,[15] NMR titrations were carried out by adding increasing amounts of TBAA to a solution of **1** in CD_3CN at 21°C. While the initial chemical shift of the host amide proton was 7.55 ppm, at the saturation point it shifted to 10.01 ppm. A graph between chemical shift differences ($\Delta\delta_{obs}$) and [guest]/[host] was plotted (Fig. 2(a)). The stoichiometry of complexation of **1** with TBAA was determined by using Job's method of continuous variations[16] (Fig. 2(b)) that showed a maximum at 0.5 mole fraction, confirming the formation of a 1:1 complex. The association constant (K_a) measured by NMR titration method[15,17] was 8.64×10^3 M^{-1} ($<\pm14\%$) in CD_3CN.

In conclusion, the novel oligopeptide-based macrocyclic synthetic receptor **1**,[18] prepared from a new building block-furan amino acid **2**, demonstrates excellent binding capability with carboxylates that will find many useful applications, especially, in the synthetic and mechanistic studies on many structurally similar C_3-symmetric and pseudo C_3-symmetric natural products.[10a,19]

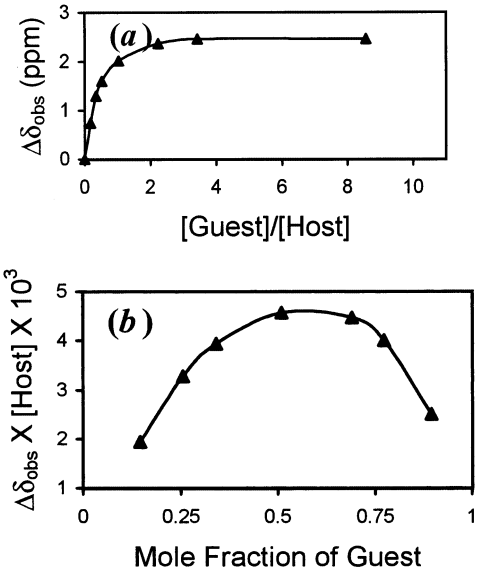

Figure 2. ^{1}H NMR titration curve (*a*) and Job plot (*b*) for the complexation of **1** (host) with TBAA in CD_3CN.

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9. Data for **5**: R_f=0.55 (silica gel, 30% EtOAc in petroleum ether); IR (neat): ν_{max} 3137, 1728, 1600, 760 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.11 (d, J=4.65 Hz, 1H); 6.49 (d, J=4.65 Hz, 1H); 4.58 (s, 2H); 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.58, 153.98, 144.63, 118.63, 111.25, 51.84, 36.50; MS (EI): m/z (%): 174 (12) [M$^+$]; HRMS (EI): calcd for $C_7H_7ClO_3$ [M$^+$]: 174.0084, found: 174.0088.
   Data for **6**: R_f=0.4 (silica gel, 30% EtOAc in petroleum ether); IR (neat): ν_{max} 3356, 1717 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.04 (d, J=4.65 Hz, 1H), 6.31 (d, J=4.65 Hz, 1H), 4.91 (bs, 1H), 4.31 (d, J=7.1 Hz, 2H), 3.85 (s, 3H), 1.44 (s, 9H); ^{13}C ($CDCl_3$, 50 MHz): δ 158.89, 156.81, 155.40, 143.74, 118.82, 108.84, 79.87, 51.61, 37.93, 28.23; MS (LSIMS): m/z (%): 279 (25) [M$^+$+H+Na]; HRMS (LSIMS): calcd for $C_{12}H_{18}NO_5$ [M$^+$+H]: 256.1185, found: 256.1186.
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11. Synthesis of **1** from **6**. To a stirred solution of **6** (1 g, 3.92 mmol) in THF–MeOH–H_2O (3:1:1, 15 mL), $LiOH{\cdot}H_2O$ (493.9 mg, 11.76 mmol) was added. After being stirred at room temperature for 1 h, the reaction mixture was acidified with 1 M HCl (pH 2), extracted with ethyl acetate, washed, dried (Na_2SO_4) and concentrated in vacuo. The crude acid was dissolved in dry CH_2Cl_2 (6 mL), cooled to 0°C and TFA (4 mL) was added. After being stirred at room temperature for 2 h, the solvent was evaporated in vacuo and the residue was used directly in the next step.
    The crude amino acid salt was dissolved in amine free dry DMF (392 mL, 10^{-2} M) and cooled to 0°C. BOP reagent (2.42 g, 5.49 mmol) was added to it and stirred for 15 min at the same temperature. Next, Et_3N (2.73 mL, 19.6 mmol) was slowly added to the reaction mixture over a period of 15 min. After the addition was over, it was stirred at room temperature for 12 h. DMF was removed under reduced pressure, the residue extracted with 10% methanol in ethyl acetate, washed with aqueous 10% citric acid solution, water, brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (SiO_2, 4–8% Methanol in $CHCl_3$) afforded **1** (314 mg, 65% from **6**) as a white solid. Data for **1**: R_f=0.4 (silica, 60% EtOAc in petroleum ether); IR

(KBr): ν_{max} 3402, 3269, 1651, 1561, 1502, 1292 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.52 (t, $J=5.6$ Hz, 3H, N*H*), 6.99 (d, $J=3.5$ Hz, 3H, furan*H*), 6.5 (d, $J=3.5$ Hz, 3 H, furan*H*), 4.62 (d, $J=5.6$ Hz, 6H, furan-CH_2NHCO); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 156.97, 152.83, 146.49, 114.76, 108.53, 35.11; MS (LSIMS): m/z (%): 370 (8) [M^++H]; MS (MALDI): m/z 370 (50) [M^++H]; HRMS (LSIMS): calcd for $C_{18}H_{16}N_3O_6$ [M^++H]: 370.1039, found: 370.1041.

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