

The delicate balance between gelation and crystallisation: structural and computational investigations

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SUPPORTING INFORMATION

Synthesis of dipeptides and precursors.

***tert*-Butyl 2-(naphthalen-1-yloxy)acetate:** 1-Naphthol (7.20 g, 0.050 mol) was dissolved in acetone (100 mL). Potassium carbonate (20.7 g, 0.15 mol) was added, followed by *tert*-butyl chloroacetate (7.85 mL, 0.055 mol) and the solution heated to reflux for 24 hours. After cooling, chloroform (200 mL) was added and the solution washed well with water, dried with magnesium sulfate and the solvent removed *in vacuo*. The crude mixture was purified by column chromatography using ethyl acetate / hexane as an eluent (15/85 v/v) to afford the title compound as a colourless oil (9.52 g, 74 %). ¹H NMR (CDCl₃) 8.38 (d, ArH, 1H, ³J_{HH} = 6.2 Hz), 7.77 (d, ArH, 1H, ³J_{HH} = 6.2 Hz, 7.48 (m, ArH, 3H), 7.31 (t, ArH, 1H, ³J_{HH} = 7.9 Hz), 6.68 (d, ArH, 1H, ³J_{HH} = 7.6 Hz), 4.68 (s, OCH₂, 2H), 1.49 (s, C(CH₃)₃, 9H) ppm. ¹³C NMR (CDCl₃) 168.3, 154.2, 135.0, 127.8, 126.9, 126.0, 125.9, 125.8, 122.6, 121.6, 105.4, 82.7, 66.5, 28.5 ppm. MS (CI) 276 ([M+NH₄]⁺). Analysis calculated for C₁₆H₁₈O₃: C, 74.40 %; H, 7.02 %. Found: C, 74.69 %; H, 7.04 %.

2-(Naphthalen-1-yloxy)acetic acid: *tert*-Butyl 2-(naphthalen-1-yloxy)acetate (9.5 g, 0.037 mol) was dissolved in chloroform (25 mL). Trifluoroacetic acid (3 mL) was added and the solution stirred overnight. The solvent was then removed *in vacuo* and the solid afforded

washed well with hexanes to afford 2-(naphthalen-1-yloxy)acetic acid in an 87 % yield. ^1H NMR (DMSO) 8.22 (d, ArH, 1H, $^3J_{\text{HH}} = 6.7$ Hz), 7.88 (d, ArH, 1H, $^3J_{\text{HH}} = 5.8$ Hz), 7.52 (m, ArH, 3H), 7.41 (t, ArH, 1H, $^3J_{\text{HH}} = 7.9$ Hz), 6.88 (d, ArH, 1H, $^3J_{\text{HH}} = 7.7$ Hz), 4.69 (s, OCH_2 , 2H) ppm. ^{13}C NMR (DMSO) 170.4, 153.6, 134.3, 127.8, 126.9, 126.4, 125.7, 125.2, 121.9, 120.8, 105.7, 65.2 ppm. MS (CI) 220 ($[\text{M}+\text{NH}_4]^+$). Analysis calculated for $\text{C}_{12}\text{H}_{10}\text{O}_3$: C, 71.28 %; H, 4.98 %. Found: C, 70.88 %; H, 5.04 %.

Dipeptide Synthesis. The dipeptides were prepared via sequential coupling of C-ethyl protected amino acids to 2-(naphthalen-1-yloxy)acetic acid using standard coupling methodologies. In a typical procedure, to a stirred solution of 2-(naphthalen-1-yloxy)acetic acid (0.50 g, 2.49 mmol) in chloroform (20 mL) was added *N*-methylmorpholine (0.41 mL, 3.8 mmol), and *iso*-butylchloroformate (0.33 mL, 2.5 mmol) at 0 °C. The solution was stirred at 0 °C for 5 minutes. A solution of alanine ethyl ester (0.38 g, 2.5 mmol) and *N*-methylmorpholine (0.41 mL, 3.8 mmol) in chloroform (20 mL) was added. The solution was allowed to warm to room temperature and stirring continued overnight. The solution was washed sequentially with distilled water, dilute aqueous acid, aqueous potassium carbonate solution and distilled water, dried over magnesium sulfate, and the solvent removed *in vacuo*. The amino acids or peptides were recovered in yields of between 85 and 97 %.

To deprotect the C-terminus, lithium hydroxide (0.2 g) was added to a solution of the ethyl-protected amino acid of dipeptide (0.5 g) in a THF:water solution (3:1 mixture, 25mL) and the solution stirred for 18 hours. After this time, distilled water (100mL) was added. Hydrochloric acid (1.0M) was added drop-wise until the pH was lowered to pH 4-5. In most cases, the amino acid or dipeptide precipitated from solution and was collected by filtration. If not, the solution was then placed in a separating funnel, extracted with chloroform (3 × 150mL), dried over magnesium sulfate, and the solvent removed *in vacuo*. After drying, final isolated yields were between 67 and 94 %.

Ethyl 2-(2-(naphthalen-1-yloxy)acetamido)acetate: ^1H NMR (CDCl_3) 8.27 (d, ArH, 1H, $^3J_{\text{HH}} = 7.6$ Hz), 7.83 (d, ArH, 1H, $^3J_{\text{HH}} = 7.8$ Hz), 7.54 (m, ArH, 3H), 7.40 (t, ArH, 1H, $^3J_{\text{HH}} = 7.7$ Hz), 7.25 (bs, NH, 1H), 6.81 (d, ArH, 1H, $^3J_{\text{HH}} = 7.7$ Hz), 4.73 (s, ArOCH_2 , 2H), 4.24 (q, OCH_2 , 2H, $^3J_{\text{HH}} = 7.2$ Hz), 4.15 (d, NHCH_2 , 2H, $^3J_{\text{HH}} = 5.4$ Hz), 1.30 (t, CH_2CH_3 , 3H, $^3J_{\text{HH}} = 7.2$ Hz) ppm. ^{13}C NMR (CDCl_3) 169.8, 168.9, 153.3, 135.0, 128.2, 127.2, 126.3, 126.1,

125.6, 122.3, 121.8, 106.1, 68.0, 62.1, 41.4, 14.5 ppm. MS (CI) 288 ($[\text{MH}]^+$). Analysis calculated for $\text{C}_{16}\text{H}_{17}\text{NO}_4$: C, 66.89 %; H, 5.96 %; N, 4.88 %. Found: C, 66.63 %; H, 6.02 %; N, 4.81 %.

Ethyl 2-(2-(naphthalen-1-yloxy)acetamido)propanoate: ^1H NMR (CDCl_3) 8.26 (d, ArH, 1H, $^3J_{\text{HH}} = 7.9$ Hz), 7.82 (d, ArH, 1H, $^3J_{\text{HH}} = 7.3$ Hz), 7.53 (m, ArH and NH, 3H), 7.37 (t, ArH, 1H, $^3J_{\text{HH}} = 7.9$ Hz), 7.33 (bs, NH, 1H), 6.80 (d, ArH, 1H, $^3J_{\text{HH}} = 7.6$ Hz), 4.69 (m, CHNH , 1H), 4.68 (d, OCH_2 , 2H, $^3J_{\text{HH}} = 4.2$ Hz), 4.22 (q, CH_2CH_3 , 2H, $^3J_{\text{HH}} = 7.1$ Hz), 1.48 (d, CHCH_3 , 3H, $^3J_{\text{HH}} = 7.1$ Hz), 1.28 (t, CH_2CH_3 , 3H, $^3J_{\text{HH}} = 7.1$ Hz) ppm. ^{13}C NMR (CDCl_3) 172.9, 168.1, 153.3, 135.0, 128.2, 127.1, 126.3, 126.1, 125.6, 122.3, 121.8, 106.1, 68.1, 62.1, 48.3, 18.9, 14.3 ppm. MS (CI) 302 ($[\text{MH}]^+$). Analysis calculated for $\text{C}_{17}\text{H}_{19}\text{NO}_4$: C, 67.76 %; H, 6.36 %; N, 4.65 %. Found: C, 67.53 %; H, 6.40 %; N, 4.61 %.

2-(2-(Naphthalen-1-yloxy)acetamido)acetic acid: ^1H NMR (DMSO) 8.42 (m, ArH, 2H), 7.89 (d, ArH, 1H, $^3J_{\text{HH}} = 6.7$ Hz), 7.54 (m, ArH, 2H), 7.42 (t, ArH, 1H, $^3J_{\text{HH}} = 7.7$ Hz), 6.96 (d, ArH, 1H, $^3J_{\text{HH}} = 7.7$ Hz), 4.74 (s, OCH_2 , 2H), 3.90 (d, NHCH_2 , 2H, $^3J_{\text{HH}} = 6.0$ Hz) ppm. ^{13}C NMR (DMSO) 171.4, 168.3, 153.4, 134.4, 127.8, 126.9, 126.4, 125.7, 125.1, 122.4, 121.1, 106.2, 67.6, 40.9 ppm. MS (CI) 277 ($[\text{M}+\text{NH}_4]^+$). Analysis calculated for $\text{C}_{14}\text{H}_{13}\text{NO}_4$: C, 64.86 %; H, 5.05 %; N, 5.40 %. Found: C, 64.90 %; H, 5.05 %; N, 5.38 %.

2-(2-(Naphthalen-1-yloxy)acetamido)propanoic acid: ^1H NMR (DMSO) 8.48 (d, ArH, 1H, $^3J_{\text{HH}} = 7.5$ Hz), 8.31 (m, NH, 1H), 7.89 (d, ArH, 1H, $^3J_{\text{HH}} = 9.5$ Hz), 7.54 (m, ArH, 3H), 7.40 (t, ArH, 1H, $^3J_{\text{HH}} = 8.0$ Hz), 6.92 (d, ArH, 1H, $^3J_{\text{HH}} = 7.6$ Hz), 4.73 (d, OCH_2 , 2H, $^3J_{\text{HH}} = 3.1$ Hz), 4.36 (m, CHNH , 1H), 1.36 (d, CHCH_3 , 3H, $^3J_{\text{HH}} = 7.3$ Hz) ppm. ^{13}C NMR (DMSO) 174.2, 167.6, 153.6, 134.4, 127.8, 126.9, 126.4, 125.7, 125.1, 122.3, 121.0, 106.1, 67.5, 47.7, 17.5 ppm. MS (CI) 291 ($[\text{M}+\text{NH}_4]^+$). Analysis calculated for $\text{C}_{15}\text{H}_{15}\text{NO}_4$: C, 65.93 %; H, 5.53 %; N, 5.13 %. Found: C, 66.36 %; H, 5.58 %; N, 4.88 %.

Ethyl 2-(2-(2-(naphthalen-1-yloxy)acetamido)acetamido)propanoate: ^1H NMR (CDCl_3) 8.27 (d, ArH, 1H, $^3J_{\text{HH}} = 9.5$ Hz), 7.80 (d, ArH, 1H, $^3J_{\text{HH}} = 6.9$ Hz), 7.51 (m, ArH and NH, 4H), 7.36 (t, ArH, 1H, $^3J_{\text{HH}} = 7.9$ Hz), 6.90 (bs, NH, 1H), 6.77 (d, ArH, 1H, $^3J_{\text{HH}} = 7.7$ Hz), 4.69 (s, OCH_2 , 2H), 4.58 (m, CHNH , 1H), 4.18 (q, CH_2CH_3 , 2H, $^3J_{\text{HH}} = 7.1$ Hz), 4.10 (d, CHNH , 1H, $^3J_{\text{HH}} = 5.4$ Hz), 1.41 (d, CHCH_3 , 3H, $^3J_{\text{HH}} = 7.2$ Hz), 1.27 (t, CH_2CH_3 , 3H, $^3J_{\text{HH}} =$

7.1 Hz) ppm. MS (CI) 359 ($[\text{MH}]^+$). Analysis calculated for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_5$: C, 63.68 %; H, 6.19 %; N, 7.82 %. Found: C, 63.49 %; H, 6.18 %; N, 7.79 %.

Ethyl 2-(2-(2-(naphthalen-1-yloxy)acetamido)propanamido)acetate: ^1H NMR (CDCl_3) 8.24 (d, ArH, 1H, $^3J_{\text{HH}} = 7.9$ Hz), 7.82 (d, ArH, 1H, $^3J_{\text{HH}} = 7.3$ Hz), 7.54 (m, ArH, 3H, 7.37 (t, ArH, 1H, $^3J_{\text{HH}} = 8.0$ Hz), 7.29 (bd, NH, 1H, $^3J_{\text{HH}} = 7.8$ Hz), 6.81 (d, ArH, 1H, $^3J_{\text{HH}} = 7.6$ Hz), 6.66 (bs, NH, 1H), 4.71 (s, OCH_2 , 2H), 4.70 (m, CHNH , 1H), 4.21 (q, CH_2CH_3 , 2H, $^3J_{\text{HH}} = 7.1$ Hz), 4.04 (d, CHNH , 1H, $^3J_{\text{HH}} = 5.3$ Hz), 1.48 (d, CHCH_3 , 3H, $^3J_{\text{HH}} = 7.0$ Hz), 1.28 (t, CH_2CH_3 , 3H, $^3J_{\text{HH}} = 7.1$ Hz) ppm. ^{13}C NMR (CDCl_3) 172.2, 169.9, 168.8, 153.3, 135.0, 128.1, 127.2, 126.4, 126.0, 125.6, 122.4, 121.8, 106.1, 68.1, 62.0, 48.8, 41.8, 18.6, 14.5 ppm. MS (CI) 359 ($[\text{MH}]^+$). Analysis calculated for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_5$: C, 63.68 %; H, 6.19 %; N, 7.82 %. Found: C, 63.64 %; H, 6.18 %; N, 7.80 %.

(R)-2-(2-(2-(Naphthalen-1-yloxy)acetamido)acetamido)propanoic acid, Dipeptide 1: ^1H NMR (DMSO) 8.39 (d, NH, 1H, $^3J_{\text{HH}} = 7.0$ Hz), 8.33 (dd, ArH, 1H, $^3J_{\text{HH}} = 11.4$ Hz, $^3J_{\text{HH}} = 5.7$ Hz), 8.24 (d, NH, 1H, $^3J_{\text{HH}} = 7.3$ Hz), 7.89 (d, ArH, 1H, $^3J_{\text{HH}} = 6.5$ Hz), 7.54 (m, ArH, 3H), 7.42 (t, ArH, 1H, $^3J_{\text{HH}} = 7.8$ Hz), 6.96 (d, ArH, 1H, $^3J_{\text{HH}} = 7.6$ Hz), 4.74 (s, OCH_2 , 2H), 4.26 (m, CHNH , 1H), 3.87 (m, CH_2NH , 2H), 1.28 (d, CH_3 , 3H, $^3J_{\text{HH}} = 7.3$ Hz) ppm. ^{13}C NMR (DMSO) 174.3, 168.6, 168.1, 153.5, 134.4, 127.8, 126.9, 126.5, 125.7, 125.1, 122.4, 121.1, 106.1, 67.6, 47.9, 47.9, 17.7 ppm. MS (CI) 348 ($[\text{M}+\text{NH}_4]^+$). Analysis calculated for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_5$: C, 61.81 %; H, 5.49 %; N, 8.48 %. Found: C, 62.25 %; H, 5.36 %; N, 8.49 %.

2-(2-(2-(Naphthalen-1-yloxy)acetamido)propanamido)acetic acid, Dipeptide 2: ^1H NMR (DMSO) 8.32 (t, NH, 1H, $^3J_{\text{HH}} = 6.0$ Hz), 8.25 (d, NH, 1H, $^3J_{\text{HH}} = 5.2$ Hz), 7.85 (d, ArH, 1H, $^3J_{\text{HH}} = 8.9$ Hz), 7.83 (d, ArH, 1H, $^3J_{\text{HH}} = 8.2$ Hz), 7.79 (d, ArH, 1H, $^3J_{\text{HH}} = 8.2$ Hz), 7.47 (t, ArH, 1H, $^3J_{\text{HH}} = 8.3$ Hz), 7.37 (t, ArH, 1H, $^3J_{\text{HH}} = 7.0$ Hz), 7.30 (d, ArH, 1H, $^3J_{\text{HH}} = 2.5$ Hz), 7.26 (d, ArH, 1H, $^3J_{\text{HH}} = 8.9$ Hz), 4.65 (d, OCH_2 , 2H, $^3J_{\text{HH}} = 2.0$ Hz), 4.45 (m, CHNH , 1H), 5.76 (t, CH_2NH , 2H, $^3J_{\text{HH}} = 6.1$ Hz), 1.29 (d, CHCH_3 , 3H, $^3J_{\text{HH}} = 7.1$ Hz) ppm. ^{13}C NMR (DMSO) 172.4, 171.4, 167.4, 153.5, 134.4, 127.8, 126.9, 126.5, 125.8, 125.1, 122.1, 121.0, 106.1, 67.4, 48.1, 41.5, 18.9 ppm. MS (CI) 331 ($[\text{MH}]^+$). Analysis calculated for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_5$: C, 61.81 %; H, 5.49 %; N, 8.48 %. Found: C, 61.70 %; H, 5.47 %; N, 8.45 %.