Synthetically Accessible, Tunable, Low-Molecular-Weight Oligopeptide Organogelators

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SUPPLEMENTARY INFORMATION

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1. Sample Mass Spectrometric Analysis of Oligopeptides

Fig. S1. ESMS of an oligolysine initiated by adventitious water, with *m/z* peaks for four, five, six, seven and eight lysine repeat units.

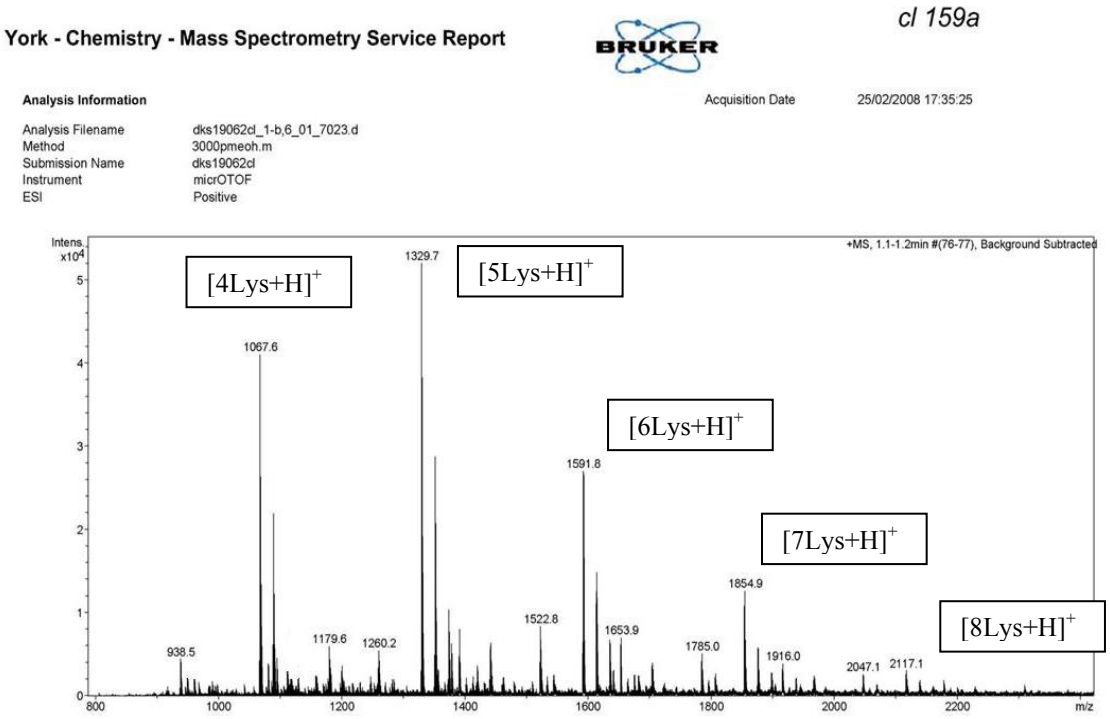


Fig. S2. ESMS of oligolysine attached to initiator **3**, with *m/z* peaks for four, five, six, seven and eight lysine repeat units attached to the amine on the initiator.

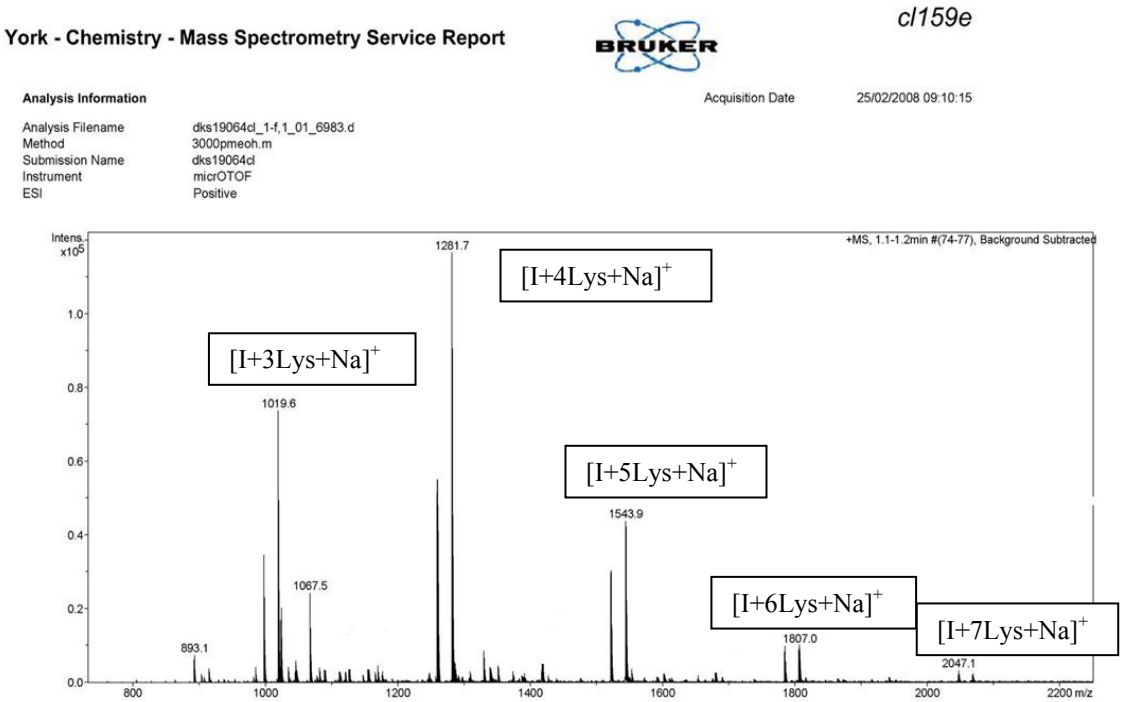


Fig. S3. ESMS of an oligolysine attached to initiator **4** (product **4-Lys-B**), oligomerised from a 1:4 mixture (initator:lysine-NCA), with *m/z* peaks for two and three lysine repeat units attached to the initiator.

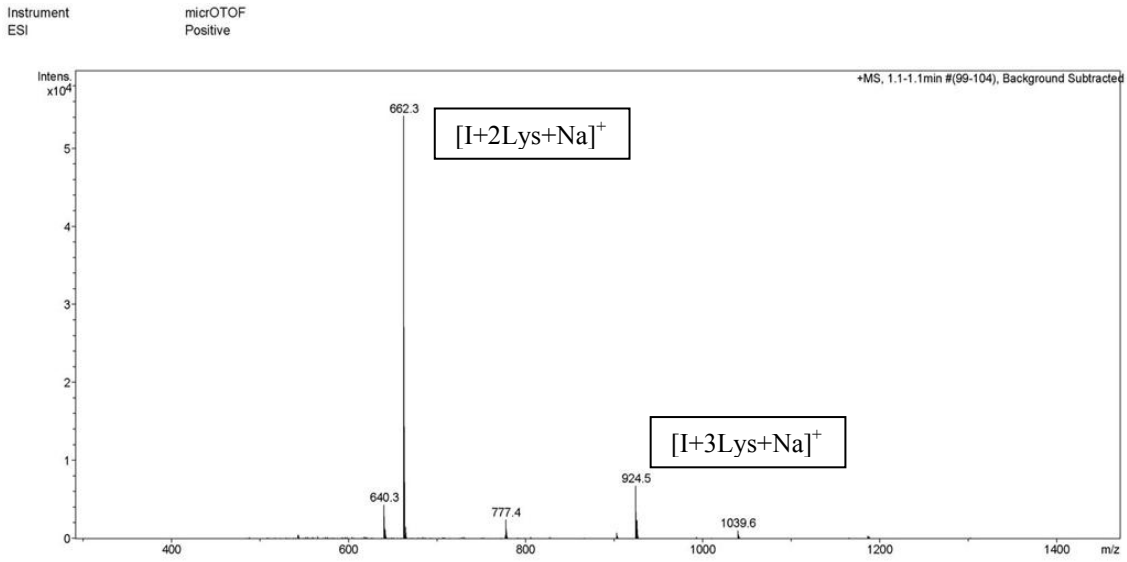
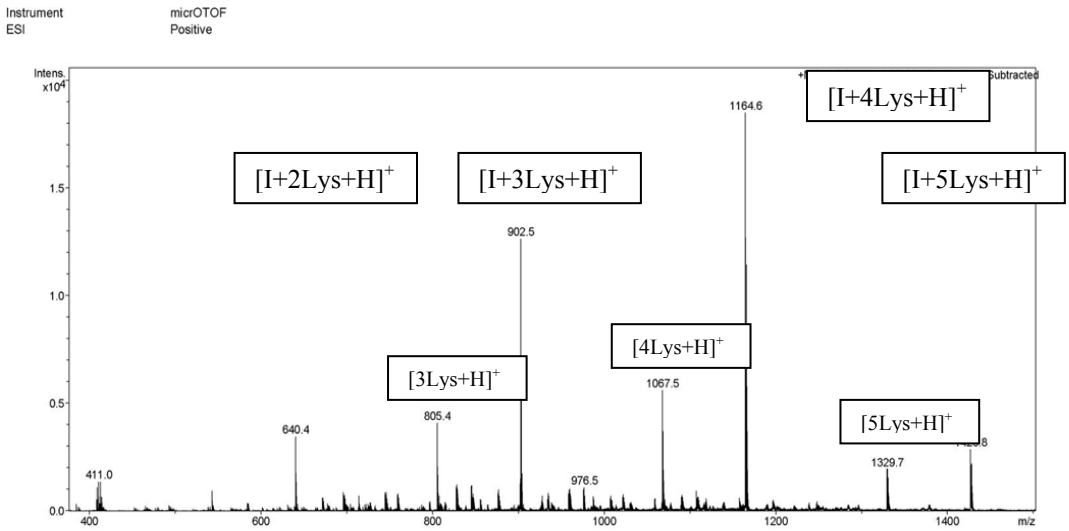


Fig. S4. ESMS of an oligolysine attached to initiator **4** (product **4-Lys-B**), oligomerised from a 1:10 mixture (initator:lysine-NCA), demonstrating *m/z* peaks for two, three, four and five lysine repeat units attached to the initiator and some oligolysines initiated by adventitious water.



2. SEM Imaging of Oligopeptide Xerogels

Fig S5. SEM image of xerogel formed by compound **4-Lys-A** (15 mg) dried from 1,2-dichlorobenzene (0.5 mL).

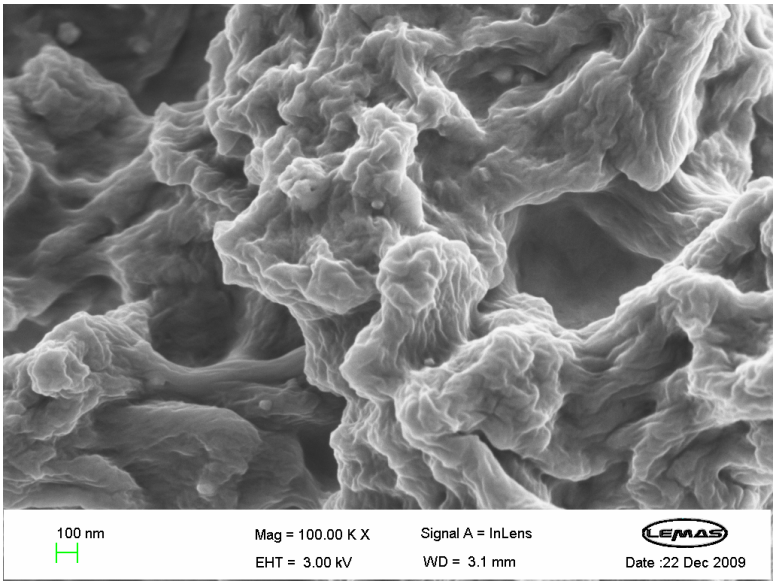
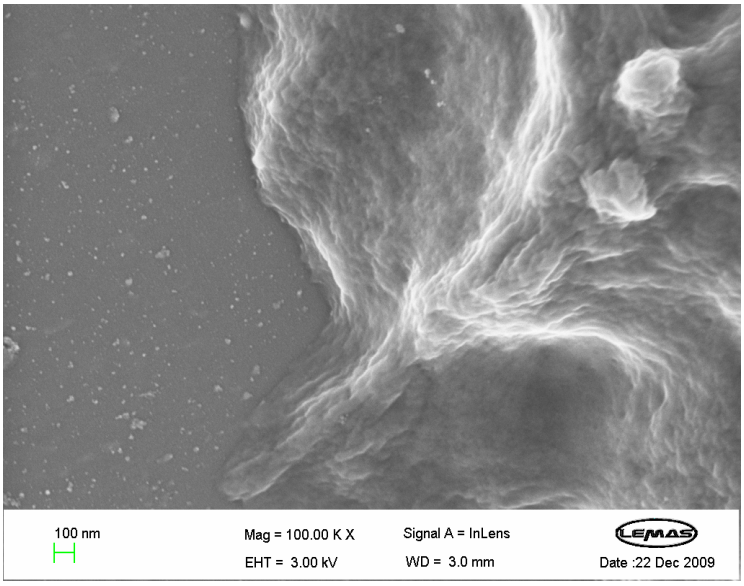


Fig S6. SEM image of xerogel formed by compound **4-Lys-A** (15 mg) dried from 1,2-dichlorobenzene (0.5 mL).



3 Experimental Procedures

3.1 Synthetic Methods and Characterisation Data

Synthesis of N$^{\varepsilon}$-benzyloxycarbonyl-L-lysine-N-carboxyanhydride.[1] *N*$^{\varepsilon}$-benzyloxycarbonyl-L-lysine (3.00 g, 10.68 mmol) was suspended in dry THF (50 mL) under an argon atmosphere over molecular sieves, and the temperature was increased to 55°C. Triphosgene (1.06 g, 3.56 mmol, caution – toxic) was dissolved in dry THF (5 mL) under argon atmosphere and added slowly to the reaction mixture. The reaction mixture was stirred at 60°C for 4 h, and then cooled to ambient temperature and a 10-fold excess of *n*-hexane was added to precipitate the product. The white compound **3.9** was obtained by filtration and dried under vacuum, with a 2.76 g yield (84%). ^{1}H NMR (DMSO-d_6) δ_H 9.13 (1H, s, NH_α), 7.33 (6H, m, C_6H_5), 7.33 (1H, s, N*HZ*), 4.99 (2H, s, C$H_2C_6H_5$), 4.44-4.41 (1H, m, CH_α), 2.97 (2H, dd, CH_2NHZ, *J* = 5.7 Hz, *J* = 4 Hz), 1.77-1.60 (2H, m, $CH_\alpha CH_2$), 1.50-1.28 (4H, m, CH_2-CH_2). ^{13}C NMR (DMSO-d_6) δ_C 171.7 ($CH_\alpha CO$), 156.1($COOCH_2C_6H_5$), 152.0 (*C*ONH), 137.3, 128.4, 127.7 (C_6H_5), 65.1 ($CH_2C_6H_5$), 57.0 (CH_α), 40.1 (CH_2NHZ), 30.6, 28.8, 21.6 ($CH_\alpha CH_2 CH_2 CH_2$). ESI-MS (*m/z*) calc. for $C_{15}H_{18}N_2NaO_5$ $[M+Na]^+$ 329.1108; found 329.1109 (100%).

General procedure for the ring opening polymerisation of *N*$^{\varepsilon}$-carboxybenzyloxy-L-lysine *N*-carboxyanhydride. The relevant initiator (0.272 mmol, 0.167 equiv) was placed in a dried flask and dried in the vacuum oven overnight. Gelators were then synthesized by adding the *N*$^{\varepsilon}$-benzyloxycarbonyl-L-lysine *N*-carboxyanhydride (0.50 g, 1.63 mmol, 1 eq.) solubilised in extra dry DMF (10 mL) under argon atmosphere dropwise to a solution of the appropriate amine or diamine in dry DMF (20 mL) under an argon atmosphere. The mixture was stirred for 5 d at room temperature. The DMF was removed by vacuum distillation. The solid products were dissolved in a minimum of DMF and the desired products were precipitated by addition of diethyl ether. The products were obtained as white to beige powders which were easy to manipulate.

Gelator 1-Lys$_n$. The general procedure was followed using octadecylamine as the amine. The product was obtained as a white solid in a yield of 383 mg (65 wt%). ^{1}H NMR (DMSO-d_6) δ_H 8.26 (1H, br, NH_αCO), 8.08 (1H, br, NH_αCO), 7.96 (1H, br,

N*H*$_\alpha$CO), 7.79 (1H, br, N*H*$_\alpha$CO), 7.33 (20H, s, C_6H_5), 7.24 (4H, br, N*H*Z), 4.99 (8H, s, C*H*$_2$C$_6$H$_5$), 4.27-4.12 (4H, m, C*H*$_\alpha$), 2.94 (8H, br, C*H*$_2$Z), 1.63-1.51 (8H, m, CH$_\alpha$C*H*$_2$), 1.47-1.16 (52H, m, C*H*$_2$, C*H*$_3$). ESI-MS (*m/z*) calc. for $C_{74}H_{111}N_9NaO_{12}$ (**1-Lys$_4$**) $[M+Na]^+$ 1340.8244; found 1340.8195 (53%, $[M+Na]^+$), 1318.8377 (42%, $[M+H]^+$) – other mass spectral peaks were present – see Table S1.

Gelator 2-Lys$_n$. The general procedure was followed using 4,4'-diaminodiphenylmethane as the diamine. The product was obtained as a beige solid in a yield of 343 mg (61 wt%). ^{1}H NMR (DMSO-*d*$_6$) δ_H 8.33 (1H, br, N*H*$_\alpha$CO), 7.96 (3H, br, N*H*$_\alpha$CO), 7.27 (4H, d, C$_6$*H*$_4$, *J* = 8.4 Hz), 7.33 (20H, s, C_6H_5), 7.24 (4H, br, N*H*Z), 6.83 (4H, d, C$_6$*H*$_4$, *J* = 8.4 Hz), 4.99 (8H, s, C*H*$_2$C$_6$H$_5$), 4.30-4.07 (4H, m, C*H*$_\alpha$), 3.67 (2H, s, C*H*$_2$(C$_6$H$_4$)$_2$), 2.94 (8H, br, C*H*$_2$Z), 1.65-1.16 (24H, m, C*H*$_2$). ESI-MS (*m/z*) calc. for $C_{69}H_{87}N_{10}O_{12}$ (**2-Lys$_4$**) $[M+H]^+$ 1247.6499; found 1247.6478 (100%, $[M+H]^+$), 1269.6322 (80%, $[M+Na]^+$) – other mass spectral peaks were present – see Table S1.

Gelator 3-Lys$_n$. The general procedure was followed using 4,4'-diaminodicyclohexylmethane as the diamine. The product was obtained as a white solid in a yield of 458 mg (80 wt%). ^{1}H NMR (DMSO-*d*$_6$) δ_H 8.31 (2H, br, N*H*$_\alpha$CO), 7.86 (2H, br, N*H*$_\alpha$CO), 7.34 (20H, s, C_6H_5), 7.24 (4H, br, N*H*Z), 4.99 (8H, s, C*H*$_2$C$_6$H$_5$), 4.28-4.17 (4H, m, C*H*$_\alpha$), 3.65 (1H, br, C*H*NH), 3.34 (1H, br, C*H*NH), 2.95 (8H, br, C*H*$_2$Z), 1.71-1.08 (24H, m, C*H*$_2$, C$_6$*H*$_{10}$). ESI-MS (*m/z*) calc. for $C_{69}H_{98}N_{10}NaO_{12}$ (**3-Lys$_4$**) $[M+Na]^+$ 1281.7558; found 1281.7234 (100%, $[M+Na]^+$), 1259.7429 (50%, $[M+H]^+$) – other mass spectral peaks were present – see Table S1.

Gelator 4-Lys$_n$. The general procedure was followed using *trans*-aminocyclohexanol as the amine. The product was obtained as a white solid in a yield of 413 mg (77 wt%). ^{1}H NMR (DMSO-*d*$_6$) δ_H 7.96 (4H, br, N*H*$_\alpha$CO), 7.34 (20H, s, C_6H_5), 7.24 (4H, br, N*H*Z), 4.99 (8H, s, C*H*$_2$C$_6$H$_5$), 4.54 (1H, br, C*H*NH), 4.27-4.19 (4H, m, C*H*$_\alpha$), 3.45 (1H, br, C*H*OH), 2.94 (8H, br, C*H*$_2$Z), 1.76-1.14 (24H, m, C*H*$_2$, C$_6$*H*$_{10}$). ESI-MS (*m/z*) calc. for $C_{62}H_{85}N_9NaO_{13}$ (**4-Lys$_n$**) requires $[M+Na]^+$ 1186.6159; found 1186.6166 (20%, $[M+Na]^+$), 1164.6332 (12%, $[M+H]^+$) – other mass spectral peaks were present – see Table S1.

Gelator 5-Lys$_n$. The general procedure was followed using 1-(3-aminopropyl)-2-pyrrolidinone as the amine. The product was obtained as a white solid in a yield of 177 mg (32 wt%). ^{1}H NMR (DMSO-d_6) δ_H 8.09 (1H, br, N*H*CO), 7.91 (3H, br, N*H*CO), 7.33 (20H, s, C_6H_5), 7.23 (4H, br, N*H*Z), 4.99 (8H, s, C$H_2C_6H_5$), 4.30 (1H, br, CH_α), 4.20 (2H, br, CH_α), 4.10 (2H, br, CH_2NR_2), 2.94 (8H, br, CH_2Z), 1.60-1.18 (24H, m, CH_2, C_4H_6NO). ESI-MS (*m/z*) calc. for $C_{63}H_{86}N_{10}NaO_{13}$ (**5-Lys$_4$**) $[M+Na]^+$ 1213.6268; found 1213.6279 (40%, $[M+Na]^+$), 1191.6467 (12%, $[M+Na]^+$).

Gelator 6-Lys$_n$. The general procedure was followed using 4-(2-aminoethyl)morpholine as the amine. The product was obtained as a white solid in a yield of 389 mg (72 wt%). ^{1}H NMR (DMSO-d_6) δ_H 8.44 (1H, br, N*H*CO), 7.91 (3H, br, N*H*CO), 7.33 (20H, s, C_6H_5), 7.23 (4H, br, N*H*Z), 4.99 (8H, s, C$H_2C_6H_5$), 4.30 (1H, br, CH_α), 4.20 (2H, br, CH_α), 4.10 (1H, br, CH_α), 2.94 (8H, br, CH_2Z), 1.60-1.20 (24H, m, CH_2, C_4H_4NO). ESI-MS (*m/z*) calc. for $C_{62}H_{86}N_{10}O_{13}$ (**6-Lys$_4$**) requires $[M+H]^+$ 1179.41; found 1179.6 (4%, $[M+H]^+$).

3.2 Mass Spectral Data

Table S1. Table of the composition of the mixtures obtained by ROP. Figures provided are *m/z* values, relative intensities are provided in brackets.

Initiators		1	2	3	4	5	6
Oligolysines (Lys_n)	4	-	1067 ($3.5x10^4$)	1067 ($0.22x10^5$)	-	1067.5 ($1.2x10^4$)	1067.5 ($5.8 x10^4$)
	5	-	1329 ($3.5 x10^4$)	-	-	1329.7 ($1.2 x10^4$)	1329.7 ($6.6 x10^4$)
	6	-	1591 ($1.6x10^4$)	-	-	1591.9 ($0.8 x10^4$)	1591.8 ($3.6 x10^4$)
	7	-	1854 ($0.5x10^4$)	-	-	1875.9 ($0.2 x10^4$)	1854.9 ($1.6 x10^4$)
	8	-	-	-	-	-	2117.1 ($0.4 x10^4$)
Lysine atatached to initiator ($l\text{-}Lys_n$)	2	816.6 ($1.8x10^5$)	-	-	662.4 ($1x10^5$)	689.4 ($7.5 x10^4$)	917.4 ($0.6 x10^4$)
	3	1078.7 ($1.7x10^5$)	985.5 ($6x10^4$)	1019.6 ($0.7 x10^5$)	924.5 ($0.6 x10^5$)	951.5 ($5.5 x10^4$)	1179.6 ($0.6 x10^4$)
	4	1340.8 ($0.95x10^5$)	1247.6 ($9x10^4$)	1281.7 ($1.2x10^5$)	1186.6 ($0.2x10^5$)	1213.6 ($3 x10^4$)	1441.7 ($0.25x10^4$)
	5	1582.0 ($0.22x10^5$)	1510 ($5x10^4$)	1543.9 ($0.4x10^5$)	1449.7 ($0.05x10^5$)	1475.8 ($1x10^4$)	1704.8 ($0.15x10^4$)
	6	1844.1 ($0.8x10^5$)	1772 ($2x10^4$)	1807.0 ($1. ? x10^5$)	-	1737.9 ($0.25x10^4$)	1966.9 ($0.1 x10^4$)
	7	-	2035 ($1x10^4$)	2047 ($0.5x10^5$)	-	2001.0 ($0.2 x10^4$)	-
	8	-	2297 ($0.5x10^4$)	-	-	2263.1 ($0.05x10^4$)	-

3.3 Procedure for Making Gels

An accurately measured mass of gelator was weighed out into a 2 ml glass vial. The solvent (0.5 ml) was then added using a Gilson pipette. The sample was sonicated for 30 minutes and heated with a heat gun until a homogeneous solution had been obtained which was then left to cool down. All gels were left over night to set.

3.4 Procedure for the Measurement of T_{gel} Values

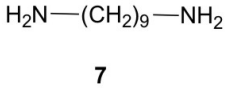
Once the gel as formed, in a 2 mL glass sample vial, it was placed into a high precision thermoregulated oil bath and the temperature was increased at the rate of 0.5°C.min^{-1}. The temperature at which solvent started to leach from the sample was recorded as the T_{gel} value, which reflects the onset temperature of the gel-sol transition.

3.5 Procedure for the Preparation of SEM Samples

A small amount of gel sample was removed from its glass vial with a spatula and it was spread thinly onto an aluminum stub and left to dry overnight under ambient conditions in a fume hood. Before imaging, the sample was covered in a thin layer (4 nm) of Pd/Pt busing an Agar sputter coater before being placed in the microscope.

4 Other Initiators

Ring opening polymerisation was also investigated with initators **7-10**.



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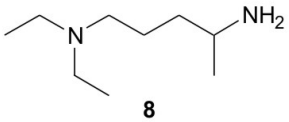

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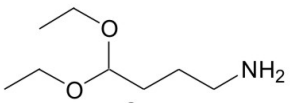

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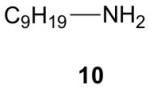

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Initiators **9** and **10** gave products that could not be precipitated – presumably indicating ineffective oligomerisation. ESMS of the crude solid products formed from initiators **7** and **8** showed that these initiators did not form **I-Lys$_n$** but instead only had ESMS peaks for unattached oligo-lysine (**Lys$_n$**) – oligomerisation was initiated with adventitious water, possibly because these initiators were difficult to dry fully.

5 References

1. J. Lee, S.-J. Lee, J.-Y. Choi, J. Y. Yoo and C.-H. Ahn, *Eur. J. Pharm. Sci.* **2005**, *24*, 441.