Solid phase synthesis of liquid crystalline oligopeptides

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Structurally well-defined liquid crystalline oligopeptides based upon a side-chain mesogenically substituted L-lysine residue are prepared *via* solid phase peptide synthesis (SPPS).

In the last few years, liquid crystalline polymers (LCPs) have attracted ever increasing attention because of their unique balance of properties and potential applications in a number of areas. The polydisperse nature of these materials, arising from the particular polymerisation methods used for their synthesis, can have a considerable influence upon their liquid crystalline properties, therefore there is considerable interest in the use of 'living' polymerisation approaches to prepare monodisperse LCPs with well defined molecular architectures, and hence well defined properties.[1,2]

Although the ability of synthetic polypeptides such as poly(γ-benzyl-L-glutamate) to form liquid crystalline phases in solution has been known since the early 1950s,[3] it has only been in the last few years that analogues capable of forming thermotropic phases have been prepared. The first examples were based upon poly(γ-alkyl-L-glutamate),[4] but more recent systems have also incorporated mesogenic groups into the glutamate side-chains.[5] These polypeptides owe their thermotropic nature not only to the rigid-rod character of the α-helical main-chain, but also to the ability of the side-chains to plasticize the main-chain and act as a 'pseudo-solvent'. They are attracting considerable attention for a variety of potential applications.[6]

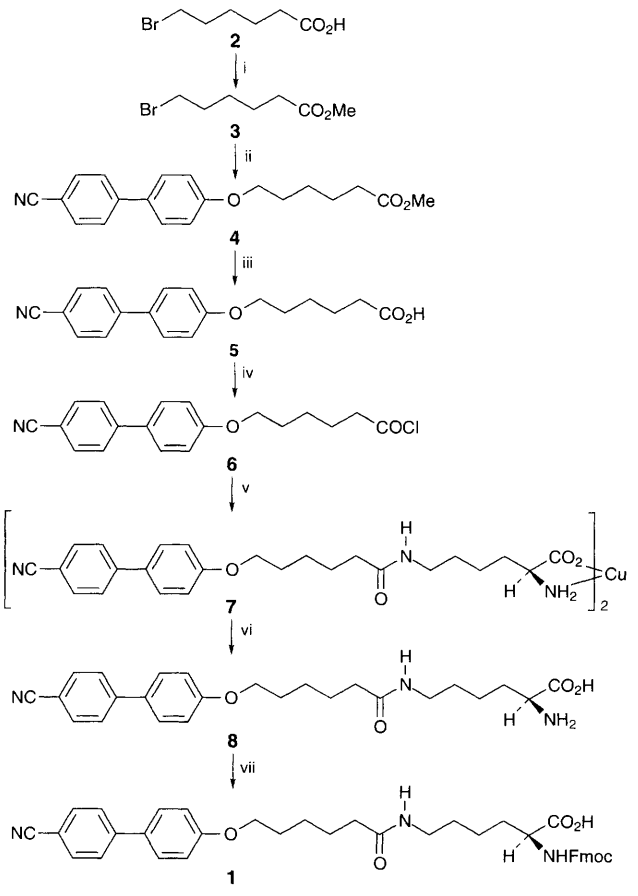
The usual methods for the preparation of these polypeptides involve either the modification of a pre-formed polypeptide through *trans*-esterification or the polymerization of an *N*-carboxy anhydride (NCA).[6] Both of these methods, however, yield materials characterized by relatively broad molecular weight distributions, so limiting their potential usefulness. There is also limited scope for tailoring these properties through control of the chemical structure.

The technique of solid phase peptide synthesis (SPPS), first demonstrated by Merrifield in 1963,[7] is now one of the most important methods for the rapid synthesis of peptides, small proteins and indeed DNA fragments. The methodology is also being rapidly modified for use in various combinatorial synthesis programmes.[8–10] While SPPS has been used widely to prepare many biologically important molecules, to our knowledge, there has been no premeditated attempt to use this approach to synthesize a structurally well-defined liquid crystalline material with potential materials applications.

We evolved a solid phase strategy for synthesizing structurally well-defined oligopeptides based upon the mesogenically substituted L-lysine residue [Fmoc-Lys(M)-OH] **1**. The route to **1** is shown in Scheme 1. ^{1}H NMR, micro-analytical and IR data of compounds **1–8** were consistent with the proposed structures. The oligopeptides **9–11** [H-(Lys(M))$_n$-NH$_2$: n = 2(**9**), 3(**10**) or 4(**11**)], designed so that each residue in the sequence was mesogenically substituted, were prepared by conventional solid phase peptide synthesis on a modified Rink type resin using Fmoc chemistry and PyBOP coupling protocols.† The cleaved oligopeptides were characterized by electrospray mass spectrometry,‡ and were found to be sufficiently pure so as to not require further purification. The ability to couple efficiently these amino acid residues with such large side-chain substituents is particularly notable, and is already allowing us to prepare larger peptides in good yields.

Liquid crystal characterization of the oligopeptides was carried out by hot-stage polarized optical microscopy.§ All three oligopeptides were found to form liquid crystalline phases upon heating.¶ Initial observations suggest that these phases are nematic, but further, more detailed, characterisation is required to confirm this. Interestingly, whereas oligopeptides **9** and **10** display enantiotropic behaviour, oligopeptide **11** shows monotropic behaviour.

We believe that this approach offers considerable potential for the construction of structurally well-defined supramolecular materials with characteristics that can be tuned through control of the particular amino acid sequences and the pendant mesogenic structures. In particular, we are interested in systems which can take full advantage of the helical and β-sheet conformations available to the oligopeptide main-chain. This approach might also be extended to non-peptide main-chains.



Scheme 1 *Reagents and conditions*: i, MeOH/H_2SO_4; ii, NCC_6H_4 C_6H_4OH/K_2CO_3; iii, KOH; iv, $SOCl_2$; v, $CuLys_2$/NaOH; vi, EDTA.2Na$^+$; vii, Fmoc-Cl/Na_2CO_3

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Footnotes

† The oligopeptides were prepared using a Novasyn Crystal solid phase peptide synthesizer, Novasyn PR500 resin and PyBOP coupling chemistry. Each residue was double coupled using a two-fold excess of amino acid. Cleavage was with 10% TFA in CH_2Cl_2 for 90 min.

‡ ES-MS data. Peptide **9**, *M* 856.2, found at 857.2 ($M + H^+$). Peptide **10**, M = 1275.7, found at 639.0 ($M + 2H^+$), 650.0 ($M + H^+ + Na^+$), 1276.3 ($M + H^+$) and 1298.2 ($M + Na^+$). Peptide **11**, M = 1695.3, found at 848.5 ($M + 2H^+$), 859.4 ($M + H^+ + Na^+$), 867.5 ($M + H^+ + K^+$) and 870.4 ($M + 2Na^+$).

§ Microscopy was carried out on an Olympus CH-2 microscope fitted with a JVC TK-1085E colour video camera attachment and a Mettler FP5 hot-stage.

¶ Peptide **9**: k 142 °C lc 173 °C i. Peptide **10**: k 163 °C lc 190 °C i. Peptide **11**: k 204 °C i 175 °C lc.

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