Synthesis and electrochemical properties of tetrathiafulvalene derived amino acids and peptides

Susan Booth, Emma N. K. Wallace, Kavita Singhal, Philip N. Bartlett and Jeremy D. Kilburn *

Department of Chemistry, University of Southampton, Highfield, Southampton, UK SO17 1BJ

A synthetic route to a tetrathiafulvalene (TTF) derived aspartic acid derivative 18, with suitable orthogonal protecting groups has been developed. The aspartic acid derivative 18 can be used in the synthesis of peptides, as exemplified by the synthesis of di-, tri- and tetra-peptides 21–23. Preliminary electrochemical studies of these novel peptides indicate that they may well undergo conformational reorganisation upon oxidation of the TTF moieties.

Introduction

Organic π-donors based on tetrathiafulvalene (TTF) derivatives and their cation radical salts have been the subject of numerous studies due to their ability to form charge transfer compounds, and their potential as molecular conductors and superconductors.[1] Most of the interesting properties of these materials are, however, exhibited by single crystals and this places limitations on their practical application. Polymeric TTFs are a potential solution to this problem, but most of the polymers reported to date[2] show low conductivity, reflecting the difficulty in preparing materials with control over the stacking interactions of the individual TTF units. Recently considerable attention has also been focused on the incorporation of TTF units into supramolecular architectures and several of these multiple TTF systems have shown interesting electrochemical properties.[3] We reasoned that conducting materials might be prepared by the incorporation of unnatural TTF bearing amino acids into a polypeptide predicted to form regular secondary structural motifs, where the role of the peptide backbone in such materials would be to control the spatial arrangement of the TTF units.[4] For example, in a β-sheet structure layering of the sheets involves interleaving of the amino acid side chain residues perpendicular to the sheet, giving a separation of the side chain residues of approximately 0.36 nm along the axis of an individual peptide strand with slight variations depending on substituent effects, and similar close packing between adjacent peptide strands in the sheet. In one-dimensional organic metals, based upon TTF derivatives, the TTF units are generally observed to arrange themselves in segregated stacks and the separation of TTF units is typically in the range of 0.345–0.365 nm.[5] A β-sheet structure constructed from TTF amino acids could thus provide sheets of extremely tightly ordered TTF molecules with separation ideal for conductivity, after partial oxidation of the TTF units. Interaction between the sheets, and thus the conductivity orthogonal to the plane, might, however, be limited. Alternatively incorporation of TTF bearing amino acids into an α-helical structure might allow the alignment of the TTF units into a conducting stack on one face of the helix[6] or even a helical arrangement of conducting TTF units giving rise to a molecular solenoid! The packing of the individual helical units in the solid state, and hence the degree of interaction between TTF units on adjacent helices, would be influenced by the substitution pattern of the TTF units on the peptide backbone. In addition to the possibility of generating new conducting materials, there has been considerable interest in studying electron transfer processes in proteins, which has been modelled by synthetic peptides derived from amino acids bearing electroactive groups in the side chain residues,[7] but as far as we are aware no such studies using TTF derived amino acids have been reported.

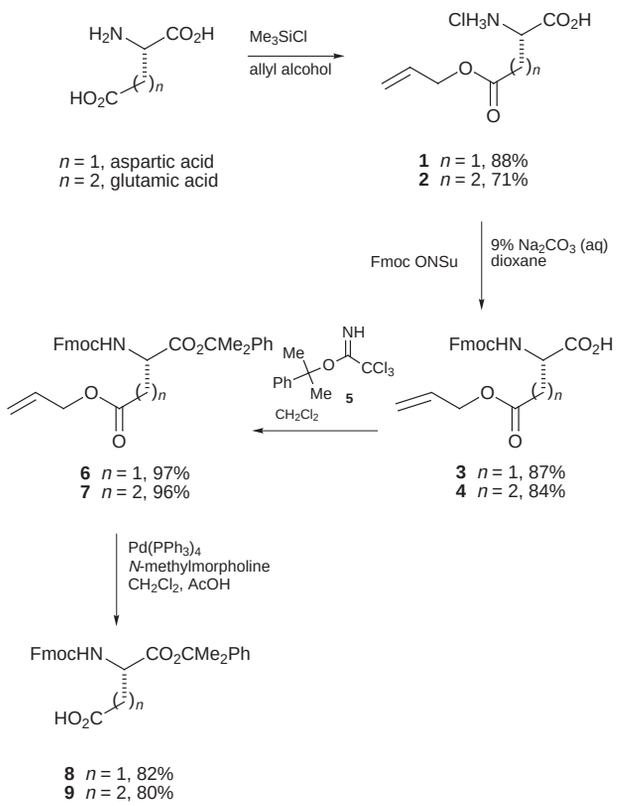
In order to prepare peptides incorporating TTF derived amino acids we set out to establish synthetic routes to suitable, orthogonally protected amino acid derivatives. In this paper we report the synthesis of such unnatural TTF bearing amino acids and their incorporation into small peptide structures. Preliminary electrochemical studies on these new materials are also reported and indicate that on oxidation of the TTF units the higher oligomers may undergo conformational reorganisation in solution, presumably in response to interactions between the oxidised TTF units.

Results and discussion

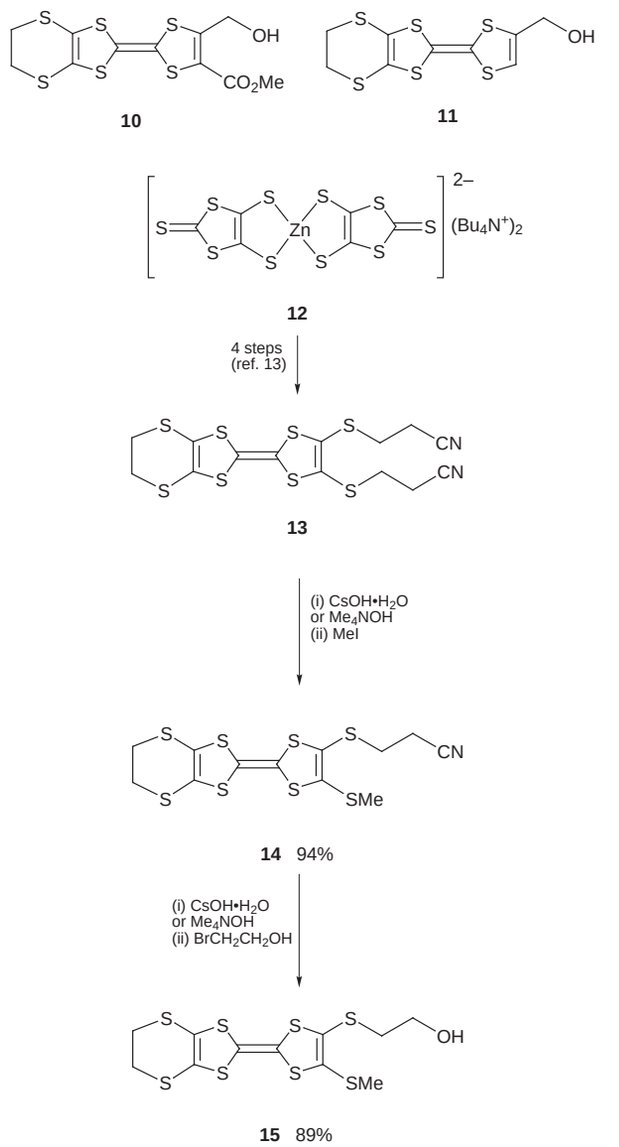
Synthesis

TTF amino acids derived from aspartic and glutamic acid were chosen because of the ability of these amino acids to promote β-sheet formation[8] and the potential ease of attachment of TTF derivatives to the side-chain carboxylates *via* an ester linkage. In order to provide orthogonal protecting groups which would be compatible with the potentially acid-sensitive TTF units, we chose to use fluoren-9-ylmethoxycarbonyl (Fmoc) as the amine protecting group, with the carboxylic acid protected as its 2-phenylpropan-2-yl ester, which requires only weak acid for its cleavage.[9] Protection of the carboxylic acid as its *tert*-butyl ester was avoided because of the strongly acidic conditions required for its removal. Suitably protected aspartic acid and glutamic acid derivatives **8** and **9** were prepared in four steps (Scheme 1). Initial formation of the allyl esters **1** and **2** following the method of Belshaw *et al.*,[10] Fmoc protection of the amino group under standard conditions,[11] and reaction of the resulting acids **3** and **4** with 2-phenylpropan-2-yl 2,2,2-trichloroacetimidate **5**,[9] prepared in one step by the reaction of the sodium salt of 2-phenylpropan-2-ol with trichloroacetamide, afforded the fully protected derivatives **6** and **7**. Palladium(0) catalysed deallylation released the acid side chains to give **8** and **9** respectively.

A series of TTF-alcohols were prepared with a view to linking them to the amino acid derivatives **8** and **9**. Although both alcohols **10** and **11** could be prepared, essentially following literature methods,[12] the overall yields were disappointing. Instead we found that TTF-alcohol **15** could be prepared more readily, and on a large scale, from bis(cyanoethylthio) protected TTF **13** (Scheme 2), described by Becher and co-workers.[13] TTF **13** was prepared in four steps, in good overall yield from Zn(dmit)$_2$(NBu$_4$)$_2$ **12**, itself prepared on a large scale by the sodium metal reduction of carbon disulfide in the presence of DMF.[14]



Scheme 1



Scheme 2

Treatment of **13** with one equivalent of either caesium hydroxide monohydrate or a solution of tetramethylammonium hydroxide in methanol gave the corresponding monothiolate, which was quenched with methyl iodide to give the previously described [13] TTF derivative **14**. Treatment with a further equivalent of base, followed by quenching with 2-bromoethanol, then gave TTF-alcohol **15** in 89% yield.

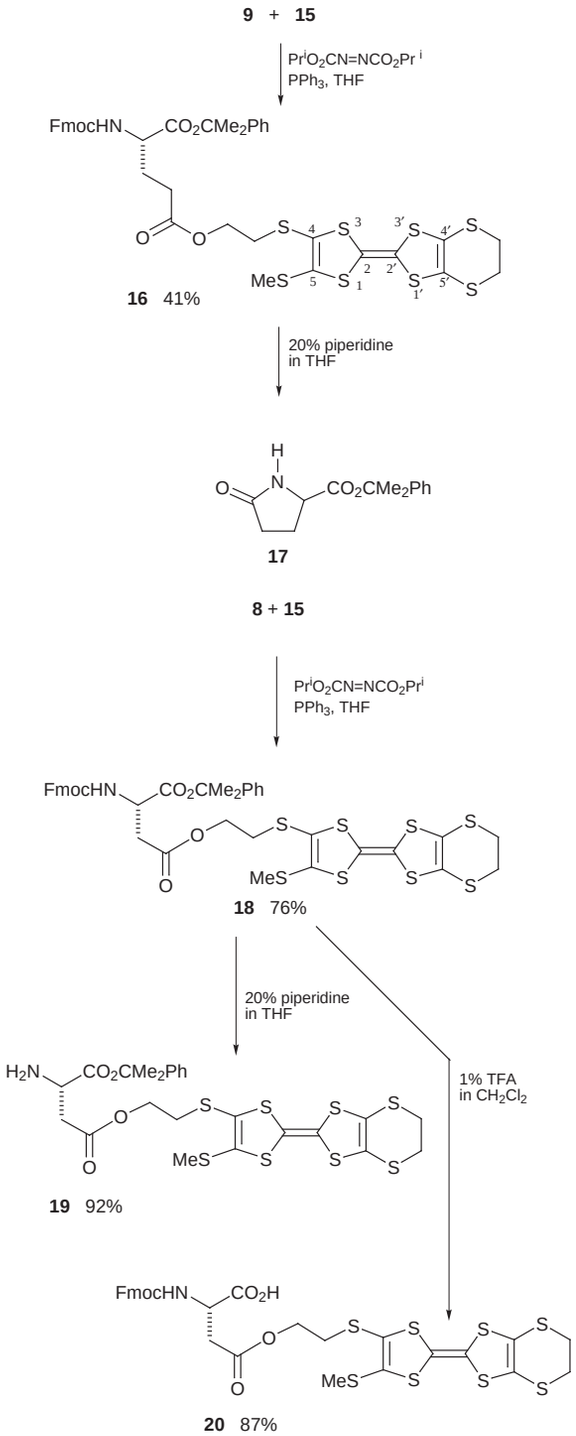
Coupling of amino acids **8** and **9** with TTF-alcohol **15** was best achieved using Mitsunobu conditions [15] [diisopropyl azodicarboxylate (DIAD), PPh_3] which gave the TTF derived amino acids **18** and **16** in 76 and 41% yield, respectively (Scheme 3). Fmoc-Deprotection of **16** and **18** was attempted using a 20% solution of piperidine in THF. Deprotection of glutamic acid derivative **16**, under these conditions, resulted in immediate formation of pyroglutamate derivative **17**, with loss of TTF-alcohol **15**. In the case of aspartic acid derivative **18**, however, Fmoc-deprotection occurred smoothly to afford TTF-amine **19** in 92% yield. Treatment of **18** with 1% TFA in dichloromethane gave the corresponding TTF-acid **20** in 87% yield.[9]

Having successfully developed a route to a TTF bearing amino acid derivative, and having established that the orthogonal protecting groups could be selectively removed, we used these derivatives in the synthesis of a series of di-, tri- and tetra-peptides. Thus, TTF-amine **19** was coupled with TTF-acid **20**, using pyBOP and DIPEA, to afford the dipeptide **21** in 87% yield (Scheme 4). Treatment of dipeptide **21** with 1% TFA in dichloromethane gave the corresponding acid which could again be coupled with TTF-amine **19** using tris(pyrrolidinyl)-benzotriazolyloxyphosphonium hexafluorophosphate (pyBOP) and DIPEA to give tripeptide **22** in 88% yield. Repeating the cycle of acid deprotection (1% TFA in dichloromethane), followed by coupling with TTF-amine **19** (pyBOP, DIPEA) gave tetrapeptide **23** in 85% yield. All the peptides were characterised unambiguously by ^1H and ^{13}C NMR spectroscopy, mass spectrometry, and, with the exception of the tetrapeptide, by microanalysis. Unfortunately at this stage we have been unable to prepare crystalline samples of these materials suitable for X-ray crystallographic studies, and preliminary attempts to prepare solid-state charge transfer salts of these compounds, by controlled oxidation with iodine, led to crude products which could not be purified or recrystallised for conductivity measurements or further studies.

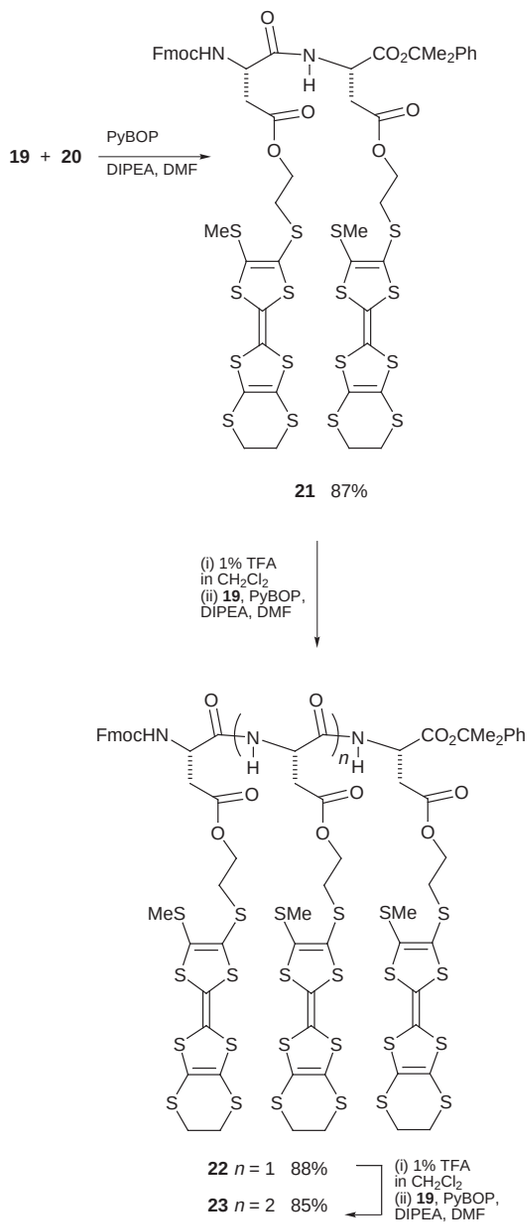
Electrochemical studies

The electrochemistry of the TTF amino acid **18**, dipeptide **21**, tripeptide **22** and tetrapeptide **23** were examined using cyclic voltammetry at a macroscopic platinum electrode and at platinum microelectrodes. The voltammetry for the TTF amino acid **18** in acetonitrile showed two reversible one electron redox processes corresponding to the expected oxidation to the TTF^+ radical cation and to the TTF^{2+} dication [Fig. 1(a)]. This behaviour is identical to that found for unsubstituted TTF except that the redox potentials for the two reactions are shifted anodic by 153 and 47 mV respectively (Table 1), as would be expected for a tetrathioalkyl substituted TTF.[16] At a microelectrode (Fig. 2) the TTF amino acid **18** again showed two reversible one electron waves (as judged by the Tomes criteria [17]) as expected. From the limiting currents at the microelectrode a diffusion coefficient of 1×10^{-5} cm^2 s^{-1} was obtained, 20% less than the corresponding value for TTF [18] and consistent with the increased molecular volume of the TTF amino acid **18** over the parent compound.

In contrast the voltammetry of the di-, tri- and tetra-peptides **21**, **22** and **23**, showed a number of significant differences from the nearly ideally electrochemically reversible behaviour shown



Scheme 3



Scheme 4

Table 1 Cyclic voltammetric data (mid peak potential, $E_{1/2}$, and peak separation, ΔE_p) for TTF amino acid oligomers. Experimental conditions are given in Fig. 1.

	First wave		Second wave	
Compound	$E_{1/2}$/mV *vs.* Ag^+/Ag	ΔE_p/mV	$E_{1/2}$/mV *vs.* Ag^+/Ag	ΔE_p/mV
TTF	−20	70	358	65
TTF amino acid **18**	133	85	405	70
Dipeptide **21**	123	100	433	65
Tripeptide **22**	140	130	453	70
Tetrapeptide **23**	128	130	458	65

by the monomer. First we note that the peak currents increase as expected as the number of redox centres attached to the molecule increases [Fig. 1(b)–(d)]. The cyclic voltammetry at a macroscopic electrode also showed clear broadening of the first redox wave corresponding to the oxidation of the TTF groups to the TTF^+ radical cation but no corresponding broadening of the second wave corresponding to oxidation to the TTF^{2+} dication (Table 1) indicating that the broadening is not due to iR drop. This broadening is independent of the sweep rate over the range 10 to 100 mV s^{-1}. In addition, on going from the monomer to the di-, tri- and tetra-peptides the mid peak potentials for the second oxidation shift to more anodic potentials (Table 1). Examination of the dependence of the peak currents for both the first and second redox processes on the square root of the sweep rate (not shown) revealed that, whereas for the monomeric TTF amino acid **18** there is a linear relationship as expected for an electrochemically reversible reaction, there was increasing deviation from linearity for the di-, tri- and tetra-peptides indicating the presence of an associated chemical reaction accompanying the electron transfer process. Similar deviations from the behaviour expected for a simple sequential electrochemical reaction were evident in the voltammetry for the four species recorded at a microelectrode [Fig. 2(a)–(d)] where the first wave became broader on going from the monomer to the di-, tri- and tetra-peptide. In contrast to the cyclic voltammetry at the macroscopic electrode, however, the limiting

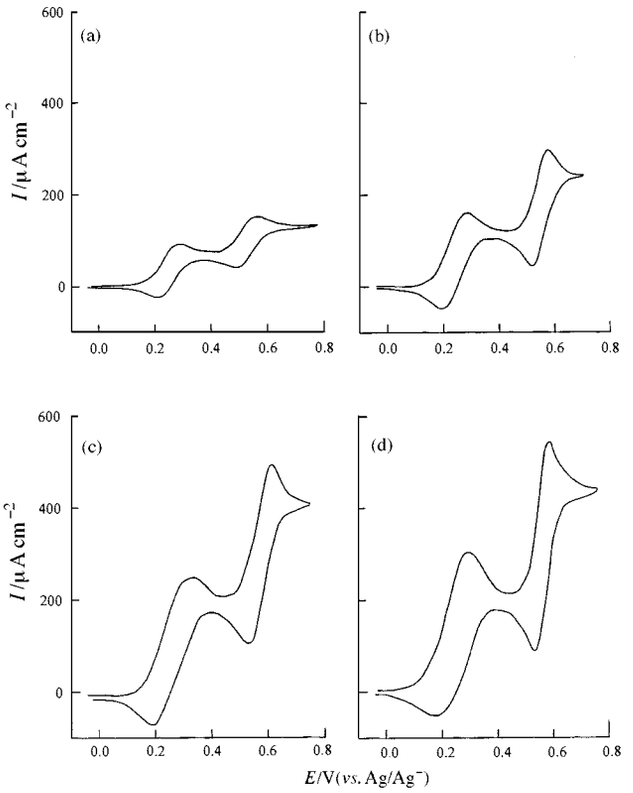


Fig. 1 Cyclic voltammograms at a macroscopic platinum electrode recorded at 20 mV s^{-1} for (a) 1 mmol dm^{-3} TTF amino acid **18** in acetonitrile, (b) 1 mmol dm^{-3} dipeptide **21** in acetonitrile–dichloromethane (4:1), (c) 1 mmol dm^{-3} tripeptide **22** in acetonitrile–dichloromethane (1:1), (d) 1 mmol dm^{-3} tetrapeptide **23** in acetonitrile–dichloromethane (7:3). In all cases the background electrolyte was 0.1 mol dm^{-3} tetraethylammonium tetrafluoroborate.

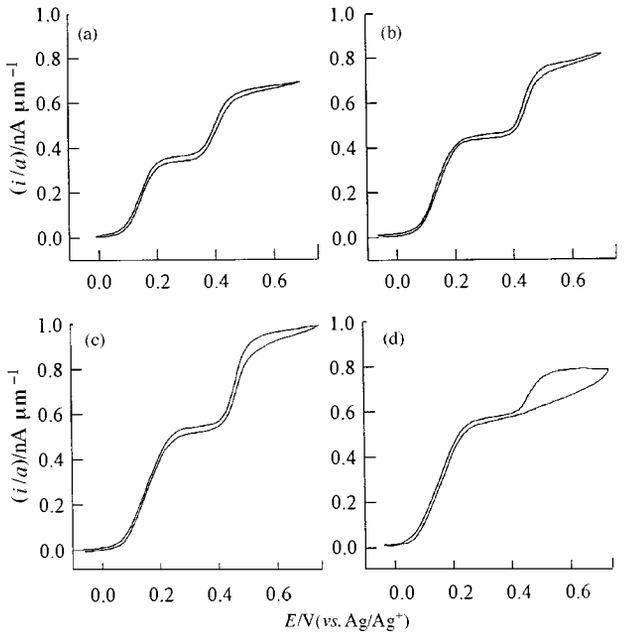


Fig. 2 Voltammograms recorded at 50 mV s^{-1} at platinum microdisc electrodes for (a) 1 mmol dm^{-3} TTF amino acid **18** in acetonitrile at a 13 μm radius electrode, (b) 1 mmol dm^{-3} dipeptide **21** in acetonitrile–dichloromethane (4:1) at a 2.7 μm radius electrode, (c) 1 mmol dm^{-3} tripeptide **22** in acetonitrile–dichloromethane (1:1) at a 2.7 μm radius electrode, (d) 1 mmol dm^{-3} tetrapeptide **23** in acetonitrile–dichloromethane (7:3) at a 2.7 μm radius electrode. In all cases the background electrolyte was 0.1 mol dm^{-3} tetraethylammonium tetrafluoroborate. The currents (i) are normalised with respect to the electrode radius (a) to aid direct comparison.

current associated with the second redox reaction at the microelectrode also decreased with increasing molecular size. Studies of the effect of a 10-fold change in the concentration of the monomer and the di-, tri- and tetra-peptides showed the expected change in the magnitude of the currents, but no changes in the peak potentials or peak separation, clearly indicating that the particular effects seen for the di-, tri- and tetrapeptides arise from intramolecular interactions between the TTF groups, and not from intermolecular interactions or effects of adsorption onto the electrode surface.

These systematic changes, on going from the monomer to the dimer, trimer and tetramer, are consistent with the occurrence of interactions between the TTF moieties within the oligomers. A similar broadening of the first redox wave, in this case accompanied by a sharpening of the second redox wave, has been reported by Kuo *et al.*[19] in studies of TTF immobilised at an electrode surface, and more recently by Bryce and coworkers[20] in a study of the electrochemistry of a TTF dendrimer. In this latter work the changes in the peak widths for the two redox processes were only observed in thin layer voltammetry and not in conventional cyclic voltammetry studies. This difference can be rationalised in terms of the timescales of the two measurements. Thus if structural reorganisation of the system, following oxidation to TTF^{+}, is slow on the timescale of the experiment then the TTF units will behave as non-interacting redox centres. However if there is time during the measurement for structural reorganisation to bring the TTF^{+} groups into a stacked configuration then interaction between the centres will be evident in the voltammetry for both redox process. In the case of the TTF dendrimer the results are consistent with a structural reorganisation which is slow on the cyclic voltammetric timescale (<~1 s^{-1}). In our studies the difference which we observe between the cyclic voltammetry at macroscopic electrodes and at the microelectrode could be explained in terms of a structural reorganisation which is fast on the cyclic voltammetry timescale but which is too slow to occur effectively on the timescale of the microelectrode measurement (<~100 s^{-1}) where the enhanced rate of mass transport at the microdisc means that the TTF species can diffuse away from the electrode before completing the conformational reorganisation.

In conclusion we have developed a synthetic route to a TTF derived aspartic acid derivative, with suitable orthogonal protection to allow this derivative to be used in the synthesis of peptides, as exemplified by the synthesis of a di-, tri- and tetrapeptide. Although we have not been able to prepare characterisable charge transfer salts of these compounds, preliminary electrochemical studies of these materials do indicate that they may well undergo conformational reorganisation upon oxidation of the TTF moieties. Further studies on the electrochemical properties of these materials, and the synthesis of larger peptide structures incorporating the TTF derived amino acid, which may lead to new conducting materials are underway.

Experimental

Melting points were recorded on a Gallenkamp melting point apparatus (MF-370). Infrared spectra were recorded on a Perkin-Elmer 1600 spectrophotometer. ^{1}H NMR Spectra were recorded on a JEOL FX90Q (90 MHz) and a JEOL JNM-GX 270 (270 MHz) instrument; chemical shifts are given in ppm relative to $SiMe_4$ and J values are given in Hz. ^{13}C NMR Spectra were recorded on a JEOL JNM-GX 270 and a Bruker AC 300 instrument. Mass spectra were obtained on a VG Analytical, 70/250/SE, normal geometry double focussing mass spectrometer.

Electrochemical measurements were carried out in acetonitrile (Aldrich HPLC grade, freshly distilled and dried over calcium chloride) or mixtures of acetonitrile and dichloromethane (Fisons), depending on the solubilities of the

compounds. In all cases 0.1 M tetraethylammonium tetrafluoroborate (Fluka >99%) was used as the background electrolyte.

Cyclic voltammetry experiments at macroscopic platinum electrodes were carried out using a conventional three electrode system with a platinum gauze counter and either Ag/0.1 M $AgNO_3$/acetonitrile or Ag/0.01 M $AgNO_3$/acetonitrile reference electrodes (all potential values have been corrected to the same standard value for Ag/0.1 M $AgNO_3$/acetonitrile). For microelectrode measurements a two electrode system was used with the $Ag/AgNO_3$ electrode as the combined counter and reference electrode. All platinum working electrodes were polished with slurries of 1 and 0.3 μm alumina before each experiment.

β-Allyl hydrogen L-aspartate **1** and γ-allyl hydrogen L-glutamate **2** were prepared according to the method of Belshaw *et al.*[9]

β-Allyl hydrogen *N*-(fluoren-9-ylmethoxycarbonyl)-L-aspartate 3

N-(Fluoren-9-ylmethoxycarbonyl)succinimide (4.14 g, 12.28 mmol) in dioxane (25 cm^3) was added to a stirred solution of **1** (3.00 g, 14.32 mmol) and 9% aqueous sodium carbonate (25 cm^3). Stirring at room temperature was continued overnight. The reaction mixture was diluted with water (250 cm^3) and washed with ethyl acetate (3 × 250 cm^3). The aqueous phase was acidified with concentrated hydrochloric acid and extracted with ethyl acetate (2 × 250 cm^3). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography on silica gel with dichloromethane–methanol (19 : 1, v/v) as eluent afforded **3** as a white solid (4.91 g, 87%), mp 105–107 °C [from ethyl acetate–light petroleum (bp 40–60 °C)]; δ_H(300 MHz, $CDCl_3$) 8.84 (br s, 1 H), 7.77 (d, *J* 7.4, 2 H), 7.61 (d, *J* 7.4, 1.1, 2 H), 7.41 (t, *J* 7.4, 2 H), 7.32 (dt, *J* 7.4, 1.1, 2 H), 5.98–5.85 (m, 2 H), 5.34 (d, *J* 17.3, 1 H), 5.27 (d, *J* 10.3, 1 H), 4.74 (dt, *J* 8.5, 4.4, 1 H), 4.64 (d, *J* 5.5, 2 H), 4.46 (dd, *J* 10.7, 7.4, 1 H), 4.38 (dd, *J* 10.7, 7.4, 1 H), 4.24 (t, *J* 7.4, 1 H), 3.14 (dd, *J* 17.6, 4.4, 1 H), 2.95 (dd, *J* 17.6, 4.4, 1 H); δ_C(75.5 MHz, $CDCl_3$) 175.7 (CO), 171.0 (CO), 156.3 (CO), 143.8 (C), 141.5 (C), 131.6 (CH), 127.9 (CH), 127.3 (CH), 125.3 (CH), 120.2 (CH), 119.1 (CH_2), 67.6 (CH_2), 66.1 (CH_2), 50.3 (CH), 47.2 (CH), 36.5 (CH_2); LRMS (FAB) *m/z* 396 (MH^+, 18%) (Found: C, 66.75; H, 5.49; N, 3.53. $C_{22}H_{21}NO_6$ requires C, 66.82; H, 5.36; N, 3.54%).

γ-Allyl hydrogen *N*-(fluoren-9-ylmethoxycarbonyl)-L-glutamate 4

N-(Fluoren-9-ylmethoxycarbonyl)succinimide (6.03 g, 17.9 mmol) in dioxane (50 cm^3) was added to a stirred solution of **2** (5.00 g, 22.4 mmol) and 9% aqueous sodium carbonate (45 cm^3) cooled to 0 °C. The reaction mixture was allowed to warm to room temperature and stirring at this temperature continued overnight. Water (250 cm^3) was added and the aqueous mixture was washed with ethyl acetate (2 × 250 cm^3). The aqueous phase was acidified with concentrated hydrochloric acid and extracted with diethyl ether (2 × 250 cm^3). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on silica gel with dichloromethane–methanol–glacial acetic acid (94 : 5 : 1, v/v) as eluent afforded **4** as a white solid (7.69 g, 84%); δ_H(300 MHz, $CDCl_3$) 8.82 (br s, 1 H), 7.76 (d, *J* 7.4, 2 H), 7.60 (d, *J* 7.4, 2 H), 7.42 (t, *J* 7.4, 2 H), 7.32 (t, *J* 7.4, 2 H), 5.88 (ddt, *J* 17.1, 10.7, 5.8, 1 H), 5.69 (d, *J* 8.1, 1 H), 5.32 (d, *J* 17.1, 1 H), 5.24 (d, *J* 10.1, 1 H), 4.70–4.35 (m, 5 H), 4.22 (t, *J* 7.1, 1 H), 2.60–2.40 (m, 3 H), 2.11 (m, 1 H); δ_C(75.5 MHz, $CDCl_3$) 175.8 (CO), 172.9 (CO), 156.4 (CO), 143.8 (C), 141.5 (C), 132.1 (CH), 127.9 (CH), 127.3 (CH), 125.3 (CH), 120.2 (CH), 118.7 (CH_2), 67.4 (CH_2), 65.7 (CH_2), 53.4 (CH), 47.3 (CH), 30.4 (CH_2), 27.4 (CH_2) (Found: C, 67.25; H, 5.72; N, 3.65. $C_{23}H_{23}NO_6$ requires C, 67.47; H, 5.66; N, 3.42%).

α-(2-Phenylpropan-2-yl) β-allyl *N*-(fluoren-9-ylmethoxycarbonyl)-L-aspartate 6

2-Phenylpropan-2-yl 2,2,2-trichloroacetimidate[8] **5** (1.42 g, 5.06 mmol; 5.3 cm^3 of a 0.96 M solution in cyclohexane) was added to a stirred solution of **3** (1.00 g, 2.53 mmol) in dichloromethane (30 cm^3). Stirring was continued at room temperature overnight. Solvent was evaporated under reduced pressure, the residue diluted with a small amount of dichloromethane and insoluble trichloroacetamidate removed by filtration. Chromatography on silica gel with diethyl ether–light petroleum (bp 40–60 °C) (3 : 7, v/v) afforded **6** as a clear, colourless oil (1.26 g, 97%); ν_{max}(film)/cm^{-1} 3420m, 3065m, 3030m, 2985m, 2945m, 1735s, 1585w, 1505s, 1450m, 1380m, 1340m, 1270m, 1210s; δ_H(300 MHz, $CDCl_3$) 7.78 (d, *J* 7.7, 2 H), 7.60 (d, *J* 7.4, 2 H), 7.43–7.25 (complex m, 9 H), 5.91 (ddt, *J* 17.1, 10.3, 5.8, 1 H), 5.83 (d, *J* 8.4, 1 H), 5.35 (dd, *J* 17.1, 1.5, 1 H), 5.27 (dd, *J* 10.3, 1.5, 1 H), 4.69–4.57 (complex m, 3 H), 4.41 (dd, *J* 10.6, 7.0, 1 H), 4.37 (dd, *J* 10.6, 7.0, 1 H), 4.23 (t, *J* 7.0, 1 H), 3.11 (dd, *J* 16.9, 4.4, 1 H), 2.92 (dd, *J* 16.9, 4.8, 1 H), 1.82 (s, 3 H), 1.80 (s, 3 H); δ_C(75.5 MHz, $CDCl_3$) 170.7 (CO), 169.2 (CO), 156.1 (CO), 145.0 (C), 143.9 (C), 141.4 (C), 131.8 (CH), 128.5 (CH), 127.9 (CH), 127.5 (CH), 127.2 (CH), 125.3 (CH), 124.5 (CH), 120.2 (CH), 119.0 (CH_2), 84.0 (C), 67.4 (CH_2), 65.9 (CH_2), 51.1 (CH), 47.3 (CH), 36.9 (CH_2), 28.6 (CH_3), 28.2 (CH_3); LRMS (FAB) *m/z* 513 (M^+, 1%), 119 (100).

α-(2-Phenylpropan-2-yl) γ-allyl *N*-(fluoren-9-ylmethoxycarbonyl)-L-glutamate 7

2-Phenylpropan-2-yl 2,2,2-trichloroacetimidate[8] **5** (7.51 g, 26.77 mmol; 26 cm^3 of a 0.96 M solution in cyclohexane) was added to a stirred solution of **4** (5.47 g, 13.39 mmol) in dichloromethane (100 cm^3). Stirring was continued at room temperature overnight. The trichloroacetamide side-product was removed by filtration and the filtrate concentrated *in vacuo*. Chromatography on silica gel with diethyl ether–light petroleum (bp 40–60 °C) (3 : 7 v/v) afforded **7** as a clear, colourless oil (6.78 g, 96%); ν_{max}(film)/cm^{-1} 3065m, 2980m, 2945m, 2360w, 2255w, 1955w, 1730s, 1620s, 1450s, 1340m; δ_H(270 MHz, $CDCl_3$) 7.76 (d, *J* 7.3, 2 H), 7.59 (d, *J* 7.5, 2 H), 7.43–7.31 (m, 9 H), 5.94 (ddt, *J* 17.2, 10.8, 5.8, 1 H), 5.39 (br, 1 H), 5.34 (dq, *J* 17.2, 1.5, 1.5, 1 H), 5.26 (dq, *J* 10.8, 1.5, 1.5, 1 H), 4.61 (dt, *J* 5.8, 1.5, 2 H), 4.44–4.37 (m, 3 H), 4.21 (t, *J* 7.0, 1 H), 2.49–2.35 (m, 3 H), 2.01 (m, 1 H), 1.83 (s, 3 H), 1.81 (s, 3 H); δ_C(75.5 MHz, $CDCl_3$) 172.7 (CO), 170.7 (CO), 156.2 (CO), 145.0 (C), 143.9 (C), 141.5 (C), 132.2 (CH), 128.6 (CH), 127.9 (CH), 127.6 (CH), 127.3 (CH), 125.3 (CH), 124.5 (CH), 120.2 (CH), 118.6 (CH_2), 83.8 (C), 67.2 (CH_2), 65.6 (CH_2), 53.9 (CH), 47.3 (CH), 30.3 (CH_2), 28.8 (CH_3), 28.4 (CH_3), 27.9 (CH_3); LRMS (FAB) *m/z* 1077 (2 M^+ + Na, 15%), 550 (M^+ + Na, 100).

α-(2-Phenylpropan-2-yl) hydrogen *N*-(fluoren-9-ylmethoxycarbonyl)-L-aspartate 8

Palladium tetrakis(triphenylphosphine) (324 mg, 0.28 mmol) was added to a degassed solution of **6** (1.44 g, 2.80 mmol) in chloroform–glacial acetic acid–*N*-methylmorpholine (37 : 2 : 1, v/v) (80 cm^3) under a nitrogen atmosphere. Stirring at room temperature under nitrogen was continued overnight, solvent was evaporated under reduced pressure, the residue diluted with dichloromethane (100 cm^3) and washed with 1 M hydrochloric acid (3 × 100 cm^3). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on silica gel with dichloromethane–methanol (39 : 1, v/v) as eluent afforded **8** as a pale yellow viscous oil (1.09 g, 82%); ν_{max}(film)/cm^{-1} 3330br m, 3025m, 2975m, 2360w, 1715s, 1515s, 1450m; δ_H(300 MHz, $CDCl_3$) 7.76 (d, *J* 7.4, 2 H), 7.59 (d, *J* 7.4, 2 H), 7.42–7.28 (complex m, 9 H), 5.79 (d, *J* 8.1, 1 H), 4.65 (dt, *J* 8.1, 4.1, 1 H), 4.42 (dd, *J* 10.3, 7.0, 1 H), 4.36 (dd, *J* 10.3, 7.0, 1 H), 4.22 (t, *J* 7.0, 1 H), 3.14 (dd, *J* 17.5, 4.1, 1 H), 2.95 (dd, *J* 17.5, 4.1, 1 H), 1.81 (s, 3 H), 1.79 (s, 3 H); δ_C(75.5 MHz, $CDCl_3$) 176.1 (CO), 169.1 (CO), 156.2 (CO), 144.9 (C), 143.9 (C), 141.4 (C), 128.5 (CH), 127.9 (CH), 127.6 (CH), 127.3 (CH), 125.3 (CH), 124.5 (CH), 120.2 (CH), 84.2 (C), 67.5 (CH_2), 51.0 (CH), 47.3 (CH), 36.7 (CH_2), 28.6 (CH_3), 28.1 (CH_3); LRMS (FAB) *m/z* 473 (M^+,

2%), 179 (100) (Found: C, 70.91; H, 5.73; N, 2.74. $C_{28}H_{27}NO_6$ requires C, 71.02; H, 5.75; N, 2.96%).

α-(2-Phenylpropan-2-yl) hydrogen *N*-(fluoren-9-ylmethoxycarbonyl)-L-glutamate 9

Palladium tetrakistriphenylphosphine (1.37 g, 1.18 mmol) was added to a degassed solution of **7** (6.25 g, 11.84 mmol) in chloroform–glacial acetic acid–*N*-methylmorpholine (37:2:1, v/v) (360 cm^3) under a nitrogen atmosphere. Stirring at room temperature under nitrogen was continued overnight, solvent was evaporated under reduced pressure, the residue diluted with dichloromethane (250 cm^3) and washed with 1 M hydrochloric acid (3 × 250 cm^3). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on silica gel with a solvent gradient of diethyl ether–light petroleum (bp 40–60 °C)–glacial acetic acid (50:49:1, v/v) up to diethyl ether–glacial acetic acid (99:1, v/v) afforded **9** as a clear, colourless viscous oil (4.62 g, 80%); ν_{max}(film)/cm^{-1} 3335br m, 3020m, 2980m, 2360w, 1720s, 1515s, 1450m, 1340m, 1215s; δ_H(270 MHz, $CDCl_3$) 7.76 (d, *J* 7.5, 2 H), 7.58 (d, *J* 7.3, 2 H), 7.42–7.30 (m, H-2, 9 H), 5.44 (d, *J* 8.1, 1 H), 4.41–4.38 (m, 3 H), 4.22 (t, *J* 7.0, 1 H), 2.51–2.25 (m, 3 H), 2.00 (m, 1 H), 1.81 (s, 3 H), 1.80 (s, 3 H); δ_C(75.5 MHz, $CDCl_3$) 178.3 (CO), 170.6 (CO), 156.3 (CO), 144.9 (C), 143.9 (C), 141.5 (C), 128.6 (CH), 127.9 (CH), 127.6 (CH), 127.3 (CH), 125.3 (CH), 124.5 (CH), 120.2 (CH), 83.9 (C), 67.3 (CH_2), 53.7 (CH), 47.3 (CH), 30.1 (CH_2), 28.7 (CH_3), 28.4 (CH_3), 27.8 (CH_2); LRMS (FAB) *m/z* 487 (M^+, 7%), 179 (100) (Found: C, 71.23; H, 6.03; N, 2.75. $C_{29}H_{29}NO_6$ requires C, 71.44; H, 6.00; N, 2.87%).

4,5-Ethylenedithio-4′-methylthio-5′-(2-hydroxyethylthio)-tetrathiafulvalene 15†

Following the procedure of Becher *et al.*[13] a degassed solution of tetramethylammonium hydroxide (450 mg, 2.08 cm^3 of a 25% solution by wt. of tetramethylammonium hydroxide in methanol, 4.94 mmol) was added dropwise to a degassed solution of 4,5-ethylenedithio-4′-methylthio-5′-(2-cyanoethylthio)-tetrathiafulvalene **14** (1.91 g, 4.49 mmol) in dry THF (50 cm^3). Stirring at room temperature was continued for 1 h after which time a degassed solution of 2-bromoethanol (617 mg, 4.94 mmol) in dry THF (5 cm^3) was added in one portion. Stirring at room temperature was continued overnight. Solvent was evaporated under reduced pressure and the residue partitioned between water and dichloromethane. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on silica gel with ethyl acetate–light petroleum (bp 40–60 °C) (1:1, v/v) afforded **15** as a red–brown solid (1.66 g, 89%); ν_{max}(CH_2Cl_2)/cm^{-1} 3605br m, 3045w, 2925w, 2875w, 1810w, 1730w, 1415m, 1385w, 1285m, 1055s; δ_H(270 MHz, $CDCl_3$) 3.85 (br, 2 H), 3.30 (s, 4 H), 2.94 (t, *J* 7.0, 2 H), 2.45 (s, 3 H); δ_C(75.5 MHz, $CDCl_3$) 133.6 (C), 122.7 (C), 114.1 (C), 114.0 (C), 60.1 (C), 39.4 (CH_2), 30.4 (CH_2), 19.5 (CH_2) (Found: C, 31.70; H, 2.89. $C_{11}H_{12}OS_8$ requires C, 31.70; H, 2.90%).

α-(2-Phenylpropan-2-yl) γ-[4′,5′-ethylenedithio-5-(methylthio)-tetrathiafulvalen-4-ylthioethyl] *N*-(fluoren-9-ylmethoxycarbonyl)-L-glutamate 16[16]

Diisopropyl azodicarboxylate (73 mg, 0.36 mmol) in dry THF (2 cm^3) was added dropwise to a solution of **9** (117 mg, 0.24 mmol), **15** (100 mg, 0.24 mmol) and triphenylphosphine (95 mg, 0.36 mmol) in dry THF (5 cm^3) cooled to 0 °C under a nitrogen atmosphere. Stirring at room temperature was continued for 48 h. THF was evaporated *in vacuo*, the residue diluted with dichloromethane (50 cm^3) and the solution washed with saturated aqueous sodium hydrogen carbonate (2 × 50 cm^3). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography on silica gel with dichloromethane–light petroleum (bp 40–60 °C) (4:1, v/v) as eluent afforded **16** (88 mg, 41%) as an orange foam; ν_{max}(film)/cm^{-1} 3350m, 2010–2925w, 1730s, 1515m, 1445m, 1265m, 1210m; δ_H(300 MHz, $CDCl_3$) 7.69 (d, *J* 7.4, 2 H), 7.51 (d, *J* 7.4, 2 H), 7.38–7.19 (complex m, 9 H), 5.31 (br, 1 H), 4.39–4.28 (complex m, 3 H), 4.24–4.09 (complex m, 3 H), 3.21 (s, 4 H), 2.96 (t, *J* 6.7, 2 H), 2.51–2.16 (complex m, 6 H), 2.00 (m, 1 H), 1.76 (s, 3 H), 1.75 (s, 3 H); δ_C(75.5 MHz, $CDCl_3$) 172.6 (CO), 170.5 (CO), 156.1 (CO), 145.0 (C), 143.9 (C), 141.5 (C), 132.7 (C), 128.6 (CH), 127.9 (CH), 127.6 (CH), 127.3 (CH), 125.3 (CH), 124.5 (CH), 123.1 (C), 120.2 (CH), 114.1 (C), 83.8 (C), 67.3 (CH_2), 63.2 (CH_2), 53.8 (CH), 47.4 (CH), 34.6 (CH_2), 30.4 (CH_2), 28.7 (CH_3), 28.4 (CH_3), 19.3 (CH_3); LRMS *m/z* (FAB) 885 (M^+, 42%), 119 (100) (Found: M^+, 885.0506. $C_{40}H_{39}NO_6S_8$ requires M^+, 885.0543).

α-(2-Phenylpropan-2-yl) β-[4′,5′-ethylenedithio-5-(methylthio)-tetrathiafulvalen-4-ylthioethyl] *N*-(fluoren-9-ylmethoxycarbonyl)-L-aspartate 18[16]

Diisopropyl azodicarboxylate (64 mg, 0.32 mmol) in dry THF (2 cm^3) was added *via* a syringe to a solution of **8** (100 mg, 0.21 mmol), **15** (88 mg, 0.21 mmol) and triphenylphosphine (83 mg, 0.32 mmol) in dry THF (5 cm^3) under a nitrogen atmosphere. Stirring at room temperature was continued overnight. THF was evaporated *in vacuo*. Chromatography on silica gel with ethyl acetate–light petroleum (bp 40–60 °C) (9:16, v/v) as eluent afforded **18** as an orange foam (139 mg, 76%); ν_{max}(CH_2Cl_2)/cm^{-1} 3415w, 2930w, 2360w, 1730s, 1505m, 1340w, 1210m; δ_H(300 MHz, $CDCl_3$) 7.85 (d, *J* 7.4, 2 H), 7.70 (d, *J* 7.4, 2 H), 7.44–7.21 (complex m, 9 H), 4.66 (m, 1 H), 4.37 (d, *J* 6.6, 2 H), 4.30 (t, *J* 6.6, 2 H), 4.25 (t, *J* 6.6, 1 H), 3.39 (s, 4 H), 3.10 (t, *J* 6.6, 2 H), 2.96 (m, 2 H), 2.46 (s, 3 H), 1.76 (s, 6 H); δ_C(75.5 MHz, CD_3COCD_3) 170.6 (CO), 169.7 (CO), 156.6 (CO), 146.3 (C), 144.8 (C), 141.8 (C), 133.7 (C), 133.6 (C), 129.7 (C), 129.5 (C), 128.8 (CH), 128.3 (CH), 127.8 (CH), 127.6 (CH), 125.9 (CH), 125.1 (CH), 120.6 (CH), 83.5 (C), 67.2 (CH_2), 63.7 (CH_2), 52.0 (CH), 47.8 (CH), 37.0 (CH_2), 30.6 (CH_2), 28.6 (CH_3), 19.0 (CH_3); LRMS (FAB) *m/z* 871 (M^+, 100%) (Found: C, 52.84; H, 4.28; N, 1.79. $C_{39}H_{37}NO_6S_8$ requires C, 53.24; H, 4.28; N, 1.61%).

α-(2-Phenylpropan-2-yl) β-[4′,5′-ethylenedithio-5-(methylthio)-tetrathiafulvalen-4-ylthioethyl] L-aspartate 19[17]

The protected amino acid **18** (756 mg, 0.868 mmol) was stirred at room temperature under a nitrogen atmosphere in a piperidine–THF (1:20, v/v) solution (20 cm^3) for 3 min. Solvent was evaporated under reduced pressure. Chromatography on silica gel with dichloromethane–methanol (99:1, v/v) as eluent afforded **19** as an orange oil (520 mg, 92%); δ_H(300 MHz, $CDCl_3$) 7.36–7.25 (complex m, 5 H), 4.27 (t, *J* 6.6, 2 H), 3.81 (dd, *J* 7.3, 5.0, 1 H), 3.32 (s, 4 H), 3.00 (t, *J* 6.6, 2 H), 2.85 (dd, *J* 16.2, 5.0, 1 H), 2.70 (dd, *J* 16.2, 7.3, 1 H), 2.43 (s, 3 H), 1.80 (s, 3 H), 1.79 (s, 3 H); δ_C(75.5 MHz, $CDCl_3$) 172.7 (CO), 171.1 (CO), 145.3 (C), 128.5 (CH), 127.4 (CH), 124.4 (CH), 82.9 (C), 63.2 (CH_2), 51.9 (CH), 39.2 (CH_2), 34.5 (CH_2), 30.4 (CH_2), 28.7 (CH_3), 28.6 (CH_3), 19.4 (CH_3) [Found (FAB-MS): MH^+, 649.9756. $C_{24}H_{27}NO_4S_8$ requires *M*H, 649.9784].

β-[4′,5′-Ethylenedithio-5-(methylthio)tetrathiafulvalen-4-ylthioethyl] hydrogen *N*-(fluoren-9-ylmethoxycarbonyl)-L-aspartate 20[8]

The protected amino acid **18** (100 mg, 0.115 mmol) was stirred in a solution of trifluoroacetic acid–dichloromethane (1:99, v/v) (50 cm^3) for 5 min. 10% Aqueous sodium hydrogen carbonate (50 cm^3) was added and the mixture extracted with dichloromethane (2 × 50 cm^3). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography on silica gel with dichloromethane–methanol–acetic acid (95:4:1, v/v) as eluent afforded **20** as an orange oil (76 mg, 87%); ν_{max}(CH_2Cl_2)/cm^{-1} 3515br m, 2545w,

† The numbering system used for these TTF compounds is shown for compound **16** in Scheme 3.

2360w, 1730s, 1510w; δ_H(300 MHz, CD_3COCD_3) 7.83 (d, *J* 7.4, 2 H), 7.69 (d, *J* 7.4, 2 H), 7.40 (t, *J* 7.4, 2 H), 7.31 (t, *J* 7.4, 2 H), 6.81 (d, *J* 8.8, 1 H), 4.69 (dt, *J* 8.8, 6.4, 1 H), 4.36 (d, *J* 7.4, 2 H), 4.31–4.22 (complex m, 3 H), 3.34 (s, 4 H), 3.10 (t, *J* 6.4, 2 H), 2.97 (m, *J* 5.1, 2 H), 2.46 (s, 3 H); δ_C(75.5 MHz, CD_3COCD_3) 172.3 (CO), 170.8 (CO), 156.7 (CO), 144.8 (C), 141.8 (C), 133.5 (C), 128.4 (CH), 127.8 (CH), 126.0 (CH), 123.4 (C), 120.7 (CH), 114.2 (C), 108.1 (C), 67.2 (CH_2), 63.7 (CH_2), 51.3 (CH), 47.8 (CH), 37.0 (CH_2), 30.7 (CH_2), 19.2 (CH_3); LRMS *m/z* (ES^+) 776 (M^+ + Na, 25%), 753 (M^+, 30) [Found (ES^+): M^+, 752.9642. $C_{30}H_{27}NO_6S_8$ requires M^+, 752.9604].

Dipeptide 21

DIPEA (36 mg, 0.277 mmol) in dry DMF (1 cm^3) was added dropwise to a solution of **19** (150 mg, 0.231 mmol), **20** (174 mg, 0.231 mmol) and pyBOP (144 mg, 0.277 mmol) in dry DMF (10 cm^3). Stirring at room temperature was continued overnight under a nitrogen atmosphere. The reaction mixture was diluted with dichloromethane (100 cm^3) and the organic phase washed with water to remove DMF. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on silica gel with dichloromethane–methanol (99:1, v/v) as eluent afforded **21** as an orange foam (279 mg, 87%); ν_{max}(CH_2Cl_2)/cm^{-1} 3740m, 3415w, 3045w, 2930w, 1735s, 1685w, 1450m, 1415w, 1390w, 1355w, 1265m, 1215m; δ_H(300 MHz, $CDCl_3$) 7.71 (d, *J* 7.7, 2 H), 7.54 (d, *J* 7.0, 2 H), 7.38–7.10 (complex m, 9 H), 5.96 (d, *J* 5.9, 1 H), 4.76 (m, 1 H), 4.59 (m, 1 H), 4.33 (m, 2 H), 4.20 (complex m, 5 H), 3.22 (s, 8 H), 3.03–2.65 (complex m, 8 H), 2.36 (s, 3 H), 2.33 (s, 3 H), 1.72 (s, 6 H); δ_C(75.5 MHz, $CDCl_3$) 171.2 (CO), 170.3 (CO), 170.1 (CO), 168.4 (CO), 155.9 (CO), 144.8 (C), 143.7 (C), 141.3 (C), 133.4 (CO), 133.1 (CO), 129.2 (CO), 129.1 (CO), 128.4 (CH), 127.8 (CH), 127.4 (CH), 127.2 (CH), 125.3 (CH), 124.4 (CH), 122.2 (C), 120.1 (CH), 113.9 (C), 113.2 (C), 109.9 (C), 83.9 (C), 67.4 (CH_2), 63.3 (CH_2), 51.0 (CH), 49.4 (CH), 47.1 (CH), 36.3 (CH_2), 36.1 (CH_2), 34.2 (CH_2), 30.3 (CH_2), 28.4 (CH_3), 28.3 (CH_3), 19.2 (CH_3); LRMS (FAB) *m/z* 1386 (M + 2, 9%), 119 (100) (Found: C, 46.94; H, 3.77; N, 1.86. $C_{54}H_{52}N_2O_9S_{16}$ requires C, 46.79; H, 3.78; N, 2.02%).

Tripeptide 22

Dipeptide **21** (300 mg, 0.217 mmol) was stirred in a solution of trifluoroacetic acid–dichloromethane (1:99, v/v) (40 cm^3) for 1 h. 10% Aqueous sodium hydrogen carbonate (50 cm^3) was added and the mixture extracted with dichloromethane (2 × 50 cm^3). The sodium salt of the dipeptide acid was seen as an insoluble brown gum in the aqueous phase. The aqueous phase was acidified with aqueous 1 M HCl and the free acid extracted into dichloromethane. The organic phases were combined, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography on silica gel with dichloromethane–methanol (98:2, v/v) as eluent afforded the dipeptide acid as an orange glass (210 mg, 77%) which was used directly in the next reaction. Thus DIPEA (13 mg, 0.104 mmol) in dry DMF (1 cm^3) was added dropwise to a solution of the dipeptide acid (110 mg, 0.0869 mmol), amine **19** (56 mg, 0.0869 mmol) and pyBOP (54 mg, 0.104 mmol) in dry DMF (10 cm^3). Stirring at room temperature under nitrogen was continued overnight. The reaction mixture was poured into water and the resultant solid filtered, dissolved in dichloromethane, dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on silica gel with dichloromethane–methanol (99:1, v/v) as eluent afforded **22** as an orange glass (146 mg, 88%); ν_{max}(CH_2Cl_2)/cm^{-1} 2930w, 2400w, 1730s, 1680m, 1495s, 1355w, 1290m; δ_H(270 MHz, CD_3COCD_3) 7.71 (d, *J* 7.3, 2 H), 7.55 (d, *J* 6.7, 2 H), 7.48–7.15 (complex m, 9 H), 6.75 (d, *J* 5.7, 1/3 H), 4.77 (br, 2 H), 4.50 (br, 1 H), 4.32 (m, 2 H), 4.18 (br, 7 H), 3.28 (s, 12 H), 2.91–2.78 (br m, 21 H), 1.69 (s, 6 H); δ_C(75.5 MHz, $CDCl_3$) 171.1, 170.3, 170.1, 169.6, 168.4, 156.1, 144.8, 143.7, 141.2, 133.0, 132.7, 128.3, 127.8, 127.1, 125.1, 124.3, 122.4, 122.2, 120.0, 113.8, 113.7, 113.2, 83.5, 67.3, 63.2 (br), 51.3, 49.4, 47.0, 36.0, 35.6, 34.3, 34.1, 31.4, 30.2, 28.4, 28.2, 19.1; LRMS *m/z* (ES^+) 1896 (M^+, 28%) (isotopic substitution pattern was in accordance with $C_{69}H_{67}N_3O_{12}S_{24}$) (Found: C, 73.39; H, 6.10; N, 3.52. $C_{69}H_{67}N_3O_{12}S_{24}$ requires C, 73.32; H, 5.97; N, 3.72%).

Tetrapeptide 23

Tripeptide **22** (95 mg, 0.05 mmol) was stirred in a solution of trifluoroacetic acid–dichloromethane (1:99, v/v) (10 cm^3) for 30 min. The reaction mixture was diluted with dichloromethane (50 cm^3) and washed with saturated aqueous sodium hydrogen carbonate (50 cm^3). The sodium salt of the tripeptide acid formed an insoluble brown gum in the aqueous phase which was acidified with 1 M aqueous HCl and the free acid was extracted into dichloromethane. The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give the tripeptide acid which was used directly in the next reaction. Thus the tripeptide acid (89 mg, 0.05 mmol), amine **19** (33 mg, 0.05 mmol) and pyBOP (31 mg, 0.06 mmol) were dissolved in dry DMF (5 cm^3). DIPEA (9 mg, 0.06 mmol) in DMF (1 cm^3) was added dropwise. Stirring at room temperature under nitrogen was continued overnight. The reaction mixture was poured into water and washed with dichloromethane (50 cm^3). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* and the resultant oil was triturated with methanol to remove any remaining DMF. Chromatography on silica gel with dichloromethane–acetonitrile (95:5, v/v) as eluent afforded **23** as an orange glass (102 mg, 85%); ν_{max}(CH_2Cl_2)/cm^{-1} 2925w, 1730s, 1685s, 1500s, 1450w, 1415w, 1390w, 1355w, 1290m; δ_H(270 MHz, CD_3COCD_3) 7.70 (d, *J* 7.3, 2 H), 7.54 (d, *J* 6.8, 2 H), 7.35–7.26 (complex m, 9 H), 4.79–4.58 (br, 3 H), 4.44 (br, 1 H), 4.32 (m, 2 H), 4.09 (br, 9 H), 3.26 (s, 16 H), 2.84–2.78 (br m, 16 H), 2.61 (s, 12 H), 1.69 (s, 6 H); δ_C(75.5 MHz, $CDCl_3$) 171.5, 171.4, 171.2, 170.7, 170.3, 169.9, 169.6, 168.5, 156.2, 145.1, 143.8, 141.5, 132.8, 132.6, 128.5, 128.0, 127.3, 125.3, 124.5, 120.2, 118.1, 116.8, 83.8, 67.6, 63.9 (br), 51.3, 50.1, 49.6, 47.3, 36.3, 35.7, 30.5, 28.6, 28.4, 19.6 (br); LRMS *m/z* (FAB) 2409 (M^+) (isotopic substitution pattern was in accordance with $C_{84}H_{82}N_4O_{15}S_{32}$).

Acknowledgements

We thank the EPSRC for funding this work (GR/H23427) and Dr S. V. Kelkar for preliminary work on the synthesis of compounds **10** and **11**.

References

1 F. Wudl, D. Wobschall and E. J. Hufnagel, *J. Am. Chem. Soc.*, 1972, **94**, 671; J. Ferraris, D. O. Cowan, V. V. Walatka and J. H. Perlstein, *ibid.*, 1972, **94**, 3372; J. M. Williams, A. J. Schultz, U. Geiser, K. D. Carlson, A. Kini, H. H. Wang, W.-K. Kwok, M.-H. Whangbo and J. E. Schirber, *Science*, 1991, **252**, 1502; M. R. Bryce, *J. Mater. Chem.*, 1995, **5**, 1481.
2 S. Frenzel, S. Arndt, R. M. Gregorious and K. Mullen, *J. Mater. Chem.*, 1995, **5**, 1529 and references therein.
3 (*a*) J. Becher, Z. T. Li, P. Blanchard, N. Svenstrup, J. Lau, M. B. Nielsen and P. Leriche, *Pure Appl. Chem.*, 1997, **69**, 465; (*b*) T. Jørgensen, T. K. Hansen and J. Becher, *Chem. Soc. Rev.*, 1994, **23**, 41; (*c*) R. P. Parg, J. D. Kilburn, M. C. Petty, C. Pearson and T. G. Ryan, *J. Mater. Chem.*, 1995, **5**, 1609.
4 S. Kothakota, T. L. Mason, D. A. Tirrell and M. J. Fournier, *J. Am. Chem. Soc.*, 1995, **117**, 536.
5 K. Bechgaard, T. J. Kistenmacher, A. N. Bloch and D. O. Cowan, *Acta Crystallogr.*, 1977, **B33**, 417; G. Schukat, A. M. Richter and E. Fanghanel, *Sulfur Rep.*, 1987, **7**, 155.
6 For example, an α-helical peptide incorporating crown ether derived amino acids produces an ion channel from the aligned crown ether units, J.-C. Meillon and N. Voyer, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 967; N. Voyer and M. Robitaille, *J. Am. Chem. Soc.*, 1995, **117**, 6599.
7 M. A. Fox, *Acc. Chem. Res.*, 1992, **25**, 569.
8 G. E. Schulz and R. H. Schirmer, *Principles of Protein Structure*,

Springer-Verlag, New York, 1979, pp. 66–129; A. G. Walton, *Polypeptides and Protein Structure*, Elsevier, New York, 1981, pp. 50–68.
9 C. Yue, J. Thierry and P. Potier, *Tetrahedron Lett.*, 1993, **34**, 323; H. P. Wessel, T. Iversen and D. R. Bundle, *J. Chem. Soc.*, *Perkin Trans. 1*, 1985, 2247.
10 P. J. Belshaw, S. Mzengeza and G. A. Lajoie, *Synth. Commun.*, 1990, **20**, 3157.
11 A. Paquet, *Can. J. Chem.*, 1982, **60**, 976.
12 P. Blanchard, M. Sallé, G. Duguay, M. Jubault and A. Gorgues, *Tetrahedron Lett.*, 1992, **33**, 2685; see also ref. 3(*c*).
13 K. B. Simonsen, N. Svenstrup, J. Lau, P. Mørk, G. J. Kristensen and J. Becher, *Synthesis*, 1996, 407; N. Svenstrup, K. M. Rasmussen, T. K. Hansen and J. Becher, *Synthesis*, 1994, 809.
14 G. Steimecke, H. Sieler, R. Kimse and E. Hoyer, *Phosphorus Sulfur Relat. Elem.*, 1979, **7**, 49; K. S. Varma, A. Bury, N. J. Harris and A. E. Underhill, *Synthesis*, 1987, 837.
15 O. Mitsunobu, J. Kimura, K. Iizumu and N. Yanagida, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 510.
16 D. L. Lichtenberger, R. L. Johnston, K. Hinkelmann, T. Suzuki and F. Wudl, *J. Am. Chem. Soc.*, 1990, **112**, 3302.
17 P. H. Reiger, *Electrochemistry*, Chapman and Hall, New York, 2nd edn., 1994, p. 158.
18 J. D. Norton, W. E. Benson, H. S. White, B. P. Pendley and H. D. Abruña, *Anal. Chem.*, 1991, **63**, 1909.
19 K. Kuo, P. R. Moses, J. R. Lenhard, D. C. Green and R. W. Murray, *Anal. Chem.*, 1979, **51**, 745.
20 C. S. Wang, M. R. Bryce, A. S. Batsanov, L. M. Goldenberg and J. A. K. Howard, *J. Mater. Chem.*, 1997, **7**, 1189.

Paper 8/00759D
Received 28*th January* 1998
Accepted 27*th February* 1998