Synthesis of N-derivatised pyrroles: precursors to highly functionalised electropolymers

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We describe the synthesis and characterisation of 13 new pyrrole derivatives which provide routes to amino acid, di- and tri-peptide functionalised electropolymers directly or *via* post-polymerisational chemistry.

Introduction

Tailored electropolymers possessing functional groups which: (i) specifically interact with biological molecules such as redox cofactors,[1] small peptides,[2] oligonucleotides[3] or enzymes,[4] (ii) allow the *de novo* building of biological structures on conducting surfaces, (iii) provide redox control of the binding or release of a bioactive molecule, (iv) provide chiral interfaces[5] or (v) confer biocompatibility, are attracting widespread interest as advanced materials. Applications and potential uses include biosensing, electrocatalysis and redox addressable libraries.[6,7]

Pyrroles substituted either at the N- or 3-position generally undergo facile electropolymerisation on conducting substrates to give adherent functionalised films.[8] However, where the substituent is sensitive to the oxidative conditions of the electropolymerisation or inhibits this process, introduction of the functional group after polymerisation is demanded. This can be achieved by pre-forming polymers which possess reactive groups such as active esters or (protected) amines that couple with appropriately functionalised molecules.

Amino acid residues are widely involved in the binding of metal ions in redox active and catalytic metallo-proteins, in particular cysteine, methionine and histidine.[9] Here we report the synthesis of monomeric precursors which allow the introduction of these groups within conducting films pre- or post-electropolymerisation.

Results and discussion

Amine, and protected amine functionalised monomers

In earlier work we have shown that various pyrroles functionalised with active ester groups such as pentafluorophenolate, *N*-hydroxysuccinimide or 2,4-dinitrophenolate, electropolymerise to give reactive films which undergo efficient conversion to amide (or ester) derivatives.[10] We have examined the possibility of a complementary approach; the adaptation of amine protection–deprotection strategies, that form the basis of Merrifield chemistry, to electropolymers. Fig. 1 lists the monomers **1**–**4** which were synthesised for this purpose. 3-(Pyrrol-1-yl)propylamine **1** was prepared by a straightforward reduction of 3-(pyrrol-1-yl)propionitrile with $LiAlH_4$.[11] It was readily converted to the protected Boc **2**, Fmoc **3** and 6-nitroveratryloxycarbonyl (Nvoc) **4** derivatives by the appropriate reagents, as described in the Experimental section. The pyrroles **2**–**4** undergo facile electropolymerisation at potentials around 1.0 V *versus* saturated calomel electrode (SCE) to give stable, adherent conducting films (see Table 1); **1** must be electropolymerised in the protonated form to circumvent the nucleophilic amine group attacking pyrrole radical cations.[7]

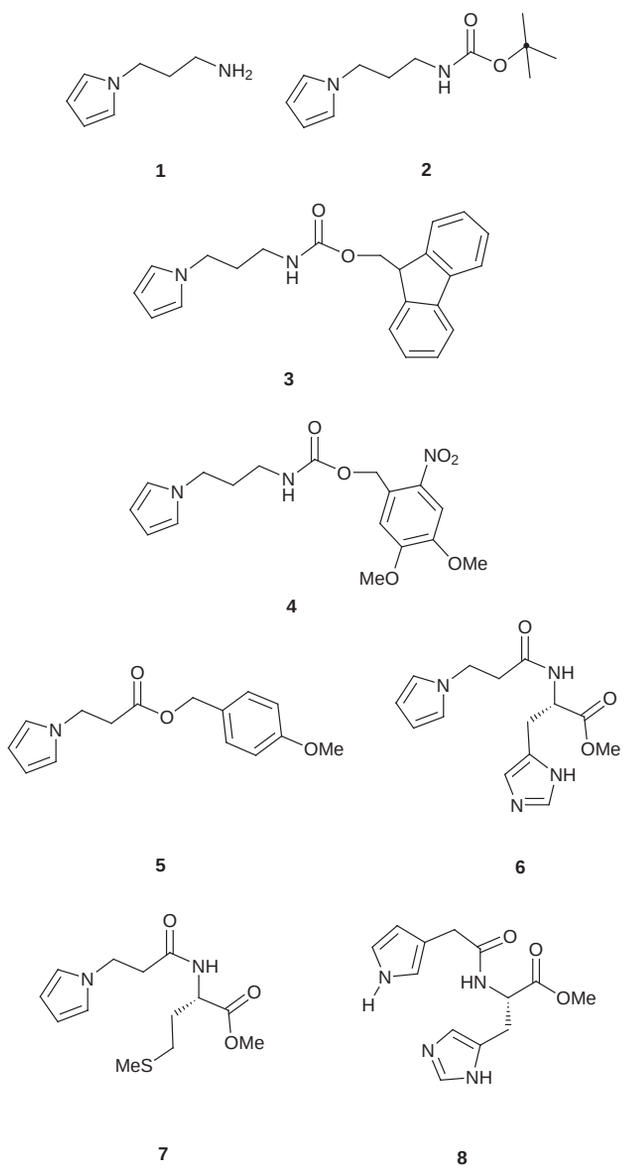


Fig. 1 Amino-, benzyl- and amino acid functionalised pyrrole monomers.

Poly(**2**) cannot be deprotected with TFA, whereas poly(**3**)

Table 1 Mid-point potentials and FT-IR spectroscopic characteristics of the electropolymer films. All mid-point potentials were measured from cyclic voltammograms of *ca.* 1 μm thick films recorded at 50 mV s^{-1}

Polymer	Electropolymer $(E_p^{ox} + E_p^{red})/2$ *vs.* SCE	Characteristic FT-IR frequencies of polymer film
1–H^+	+0.50	3250 (NH_3^+), 1109 (B–F)
2	+0.58	3401 (NH), 1710 (C=O), 1274 (C–N), 1135 (C–O)
3	+0.60	1725 (C=O), 1250 (C–N), 1135 (C–O)
4	+0.63	1718 (C=O), 1520 (NO), 1329 (NO), 1273 (C–N)
5	+0.60	1728 (C=O), 1247, 1168
6	+0.64	1744 (C=O ester), 1666 (C=O amide)
8	+0.18	1740 (C=O ester), 1645 (C=O amide)
9	+0.64	3361 (NH), 1740 (C=O ester), 1669 (C=O amide)
10	+0.60	1735 (C=O acid), 1655 (C=ONH), 1514 (C=ONH)
11	+0.63	1781 (C=O ester), 1663 (C=ONH), 1510 (C=ONH), 997 (C–F)
14/H^+	+0.66	1737 (C=O ester), 1662 (C=ONH), 1060 (B–F)

and poly(**4**) are readily deprotected by piperidine and photolytically, respectively.[7] The reason for the failure to deprotect the Boc derivative presumably rests with the inability of TFA to penetrate the polymer film. This is not exceptional. We find that the carboxylate protected derivative 4-methoxybenzyl 3-(pyrrol-1-yl)propanoate **5** can be electropolymerised but cannot be deprotected by TFA even under forcing conditions.

One might expect that poly(**1**) formed either directly, or by deprotection of poly(**3**) or poly(**4**), would show similar reactivity. However this is not the case.[7] Formed directly from the amine, the polymer is quite unreactive whereas deprotection of poly(**3**) or poly(**4**) affords polymers which react with active esters. The difference in polymer reactivity probably lies with the difference in access to the amine groups and is explained by the deprotection affording molecular cavities around these groups with the loss of the bulky Fmoc and Nvoc groups producing a more open polymer network.

Amino acid and peptide functionalised monomers

L-Histidine methyl ester and L-methionine methyl ester *N*-pyrrole derivatives (**6** and **7** respectively) were synthesised by reacting 3-(pyrrol-1-yl)propionic acid[12] with the amino acid using 1,1′-carbonyldiimidazole (CDI) as coupling reagent, Fig. 1.

N-[3-(Pyrrol-1-yl)propanoyl]-L-histidine methyl ester **6** is readily electropolymerised in the presence of HBF_4 which prevents nucleophilic attack by the imidazole ring on the oxidised pyrrole intermediates. We have also synthesised a 3-pyrrole derivative, the pyrrol-3-ylacetyl-L-histidine methyl ester **8**, using the same procedures but with pyrrol-3-ylacetic acid[13] as the precursor, Fig. 1. It also undergoes facile polymerisation in the protonated form, Table 1.

All attempts to electropolymerise the *N*-[3-(pyrrol-1-yl)-propanoyl]-L-methionine methyl ester **7**, employing a variety of electrolytes, solvents and conditions have failed. However we have shown in earlier work that poly(**7**) can be formed by the post-polymerisation reaction of poly[2,4-dinitrophenyl-3-(pyrrol-1-yl)propanoate] with L-methionine methyl ester.[10]

Cystine functionalised electropolymer films can be accessed *via* electropolymerisation of the appropriate cystine monomer followed by cleavage of the disulfide bridge with basic 1,4-dithio-L-threitol solution.[1] The carboxylic function of cystine has to be blocked before coupling to the pyrrole and we have generally utilised Me or Et ester cystine derivatives. However to enable further structural elaboration, or to introduce acidic or chelating carboxylate functions into a cysteinyl electropolymer, an allyl ester protecting group can be employed as described by Waldmann and Kunz.[14] *N*,*N*′-Bis[3-(pyrrol-1-yl)-propanoyl]-L-cystine diallyl ester **9** was synthesised by amide formation between L-cystine bisallyl ester bis(toluene-4-sulfonate) and 3-pyrrol-1-ylpropionic acid using CDI as coupling reagent as outlined in Scheme 1 and described in the Experimental section. Deprotection of the allyl ester groups was carried out under mild palladium catalysed conditions with pyrrolidine acting as a base[15] to form the *N*,*N*′-bis[3-(pyrrol-1-yl)propanoyl]-L-cystine **10**, Scheme 1. The monomer was esterified with pentafluorophenol to form the active ester *N*,*N*′-bis[3-(pyrrol-1-yl)-propanoyl]-L-cystine bis(pentafluorophenyl) ester **11**. All three monomers (**9**–**11**) are readily electropolymerised to form stable films, see Table 1. Fig. 2 shows the potentiodynamic growth of poly(**10**) which typifies that of all the N-substituted pyrroles.

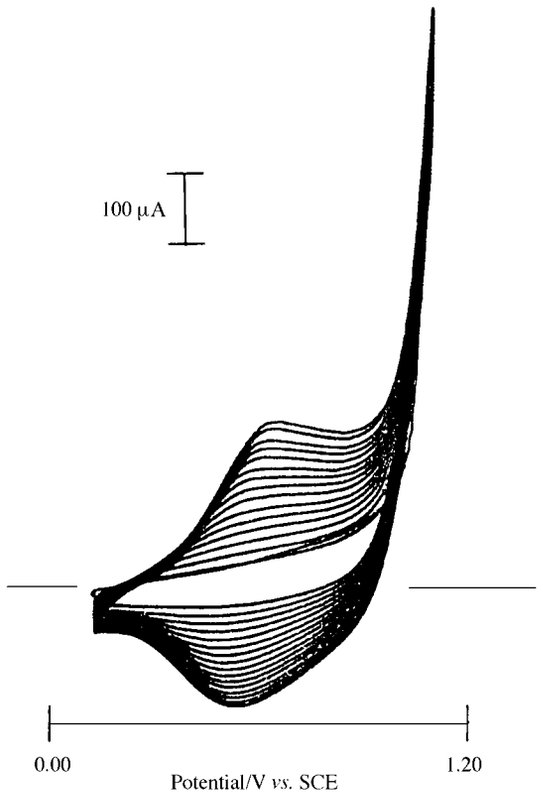
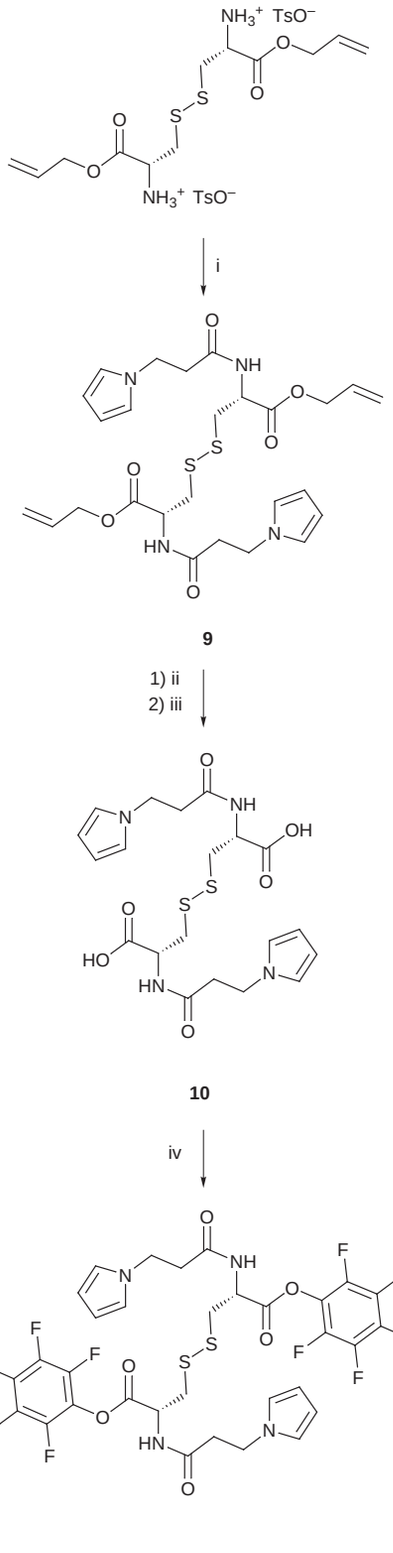


Fig. 2 Potentiodynamic growth of poly(**10**). The polymer was grown on a polished Pt disk, area = 0.64 cm^2 by cycling the potential between 0.16 and 0.88 V *versus* SCE at 100 mV s^{-1} in 0.2 M $[NBu_4][BF_4]$–MeCN containing the monomer **10**, *ca.* 10 mM.

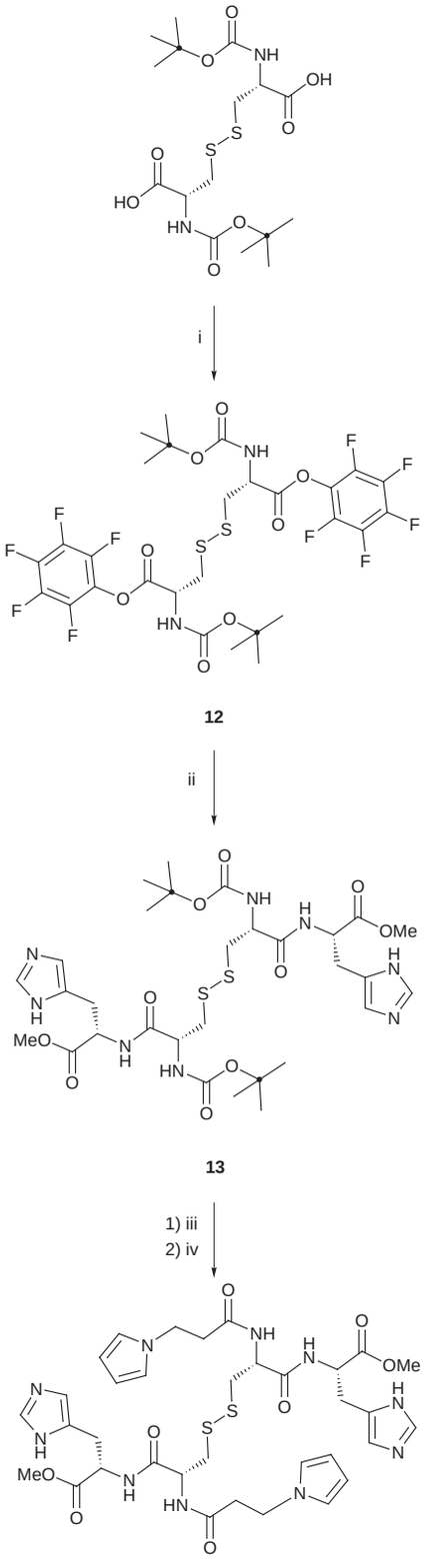
The tripeptide [*N*,*N*′-bis[3-(pyrrol-1-yl)propanoyl]-L-cystinyl]-di-L-histidine dimethyl ester **14** was synthesised by the route outlined in Scheme 2 *via* the precursors *N*,*N*′-bis(*tert*-butoxycarbonyl)-L-cystine bis(pentafluorophenyl) ester **12** and [*N*,*N*′-bis(*tert*-butoxycarbonyl)-L-cystinyl]-di-L-histidine dimethyl ester **13**, the synthesis and characterisation of which are given in the Experimental section. The route *via* the active ester **12** was found to give a cleaner synthesis than direct coupling with CDI or DCC. The tripeptide **14** undergoes facile electropolymerisation at the surface of a platinum disc electrode and diffuse reflectance FT-IR spectroscopy confirmed the presence of the cystine and histidine moieties within the polymer film, Table 1.

Direct *versus* post-polymerisation synthesis

In earlier work we have shown that to support ion transport

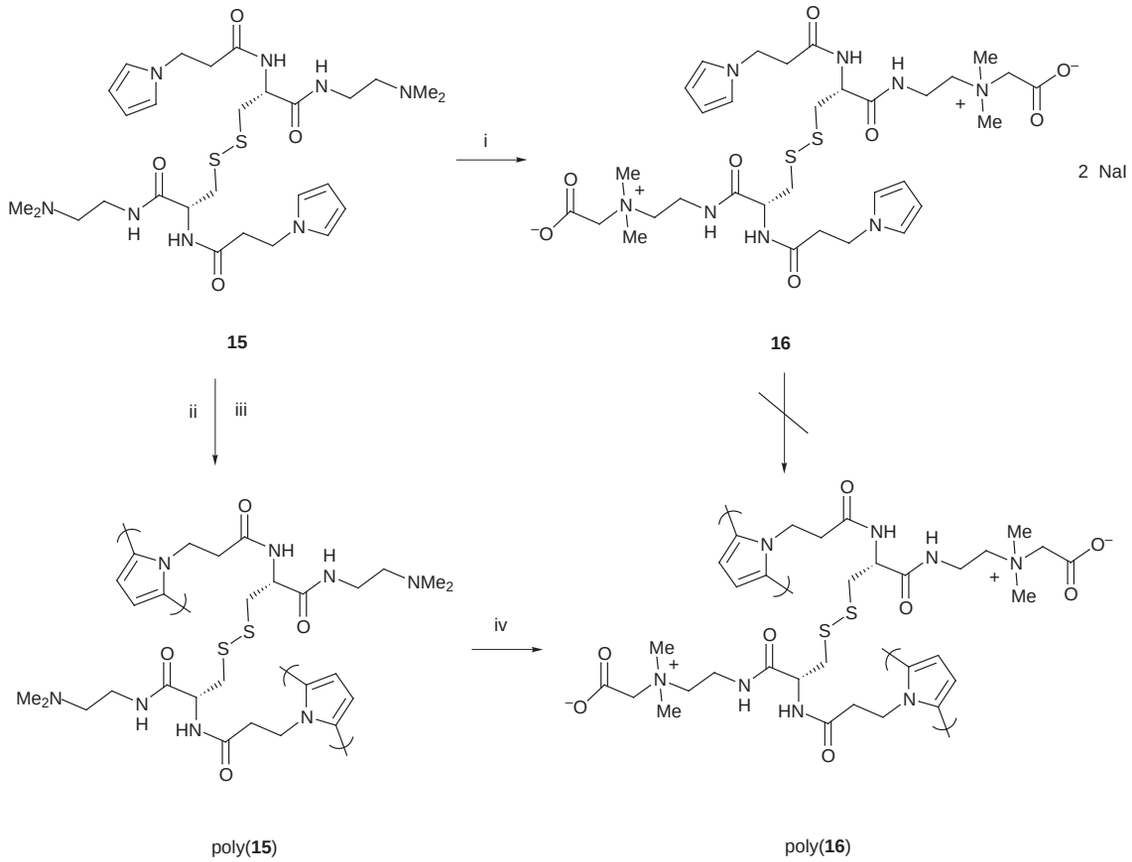


Scheme 1 Synthesis of *N*-pyrrole cystinyl derivatives: allyl ester **9**, carboxylic acid **10** and pentafluorophenolate **11**. *Reagents and conditions*: (i) 3-(pyrrol-1-yl)propionic acid, CDI, THF, Et_3N, 48 h at ambient temperature and 6 h at 50 °C; (ii) PPh_3, $Pd(PPh_3)_4$, pyrrolidine, MeCN; (iii) 10% HCl solution; (iv) C_6F_5OH, DCC, 1,4-dioxane, 10 h, ambient temperature.



Scheme 2 Synthesis of $(Cys\text{-}His\text{-}OMe)_2$ pyrrole derivative **14**. *Reagents and conditions*: (i) C_6F_5OH, DCC, 1,4-dioxane, 10 h, ambient temperature; (ii) L-histidine methyl ester dihydrochloride, Et_3N, THF, 12 h at ambient temperature and 2 h at 50 °C; (iii) TFA; (iv) Et_3N, pentafluorophenyl 3-(pyrrol-1-yl)propanoate, THF, 12 h at ambient temperature.

in functionalised films bearing redox active centres it was found desirable to introduce ionic groups, either indirectly by co-polymerisation with alkylammonium derived pyrroles[1] or directly by co-functionalisation.[16] For example, cholamide-cysteinyl functionalised polymers bind anionic ferredoxin-type centres *via* thiolate ligation, with charge balance during redox cycling of the cluster maintained by the import or export of an anionic counter ion from the cationic polymer framework.[16] To extend this approach, we have sought routes to other cationic poly(pyrroles). The pseudo-betaine *N*,*N*′-{*N*,*N*′-bis[3-(pyrrol-1-yl)propanoyl]-L-cystinylbis(aminoethyl)}-*N*,*N*′-bis(carboxy-



Scheme 3 Synthesis of pyrrolyl-cystinyl pseudo-betaine **16** monomer and polymer. *Reagents and conditions*: (i) ICH_2COONa, CH_2Cl_2–MeOH (1 : 1); (ii) electropolymerisation in 0.2 M NBu_4BF_4–MeCN in presence of HBF_4; (iii) Et_3N–MeCN; (iv) ICH_2COOH, Et_3N, CH_3CN.

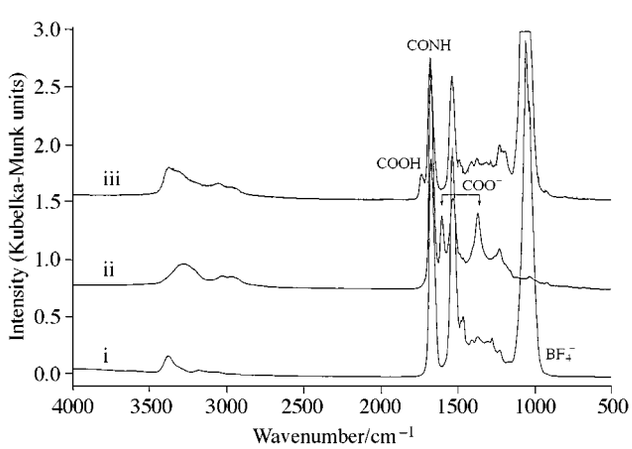


Fig. 3 Reflectance FT-IR spectra of (i) poly(**15**–HBF_4); (ii) same as (i) but after reaction with iodoacetic acid–Et_3N; (iii) same as (ii) but after reaction with HBF_4, $2Et_2O$.

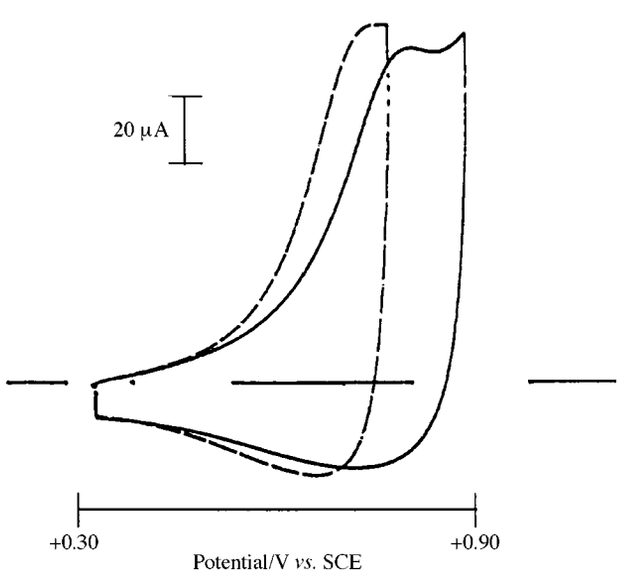


Fig. 4 Cyclic voltammetric response of poly(**15**–HBF_4) *before* (dashed line) and *after* (solid line) reaction of the film with iodoacetic acid–Et_3N; scan-rate, 50 mV s^{-1}. The film was grown on a Pt disk electrode (area = 0.325 cm^2) in 0.2 M $[NBu_4][BF_4]$–MeCN containing 7 mM of the protonated monomer **15**, washed (MeCN) and transferred to a fresh monomer-free electrolyte.

methyl)-*N*,*N*′-dimethyldiammonium diiodide, disodium salt **16** was synthesised as outlined in Scheme 3. Nucleophilic addition of sodium iodoacetate to *N*,*N*′-bis[*N*-3-(pyrrol-1-yl)propanoyl]-L-cystinylbis-*N*″,*N*″-dimethylaminoethylamide[16] (**15**) gave the quaternary amine **16**. However, the pseudo-betaine **16** could not be electropolymerised presumably because the nucleophilic iodide counter anion inhibited polymer growth. Ion-exchange using $TlPF_6$ failed to give an electropolymerisable product.

It is however possible to form poly(**16**) from poly(**15**), Scheme 3. This has advantages in that separation of the solid-phase (polymer film) from excess reactants and co-products is facile, as is the exchange of the counter anion. The modification reactions were followed by reflectance FT-IR spectroscopy. Spectra obtained before and after reaction of poly(**15**) with iodoacetic acid in presence of Et_3N show the appearance of $\nu(CO_2^-)$ (antisymmetric and symmetric stretches) at 1605 and 1370 cm^{-1}. When the film is then soaked in acidic MeCN solution these bands are replaced by new bands at 1737 cm^{-1} and 1050 cm^{-1} corresponding to ν(CO) of the COOH acid form and ν(BF) of the counter ion, respectively, Fig. 3.

The electrochemical behaviour of the poly(pyrrole) backbone *before* and *after* covalent modification with iodoacetic acid is shown in Fig. 4. The magnitude of the peak current for

the oxidation of the two polymers are very similar. This shows that modification has not (i) led to the loss of film from the surface, (ii) produced insulated domains *within* the film, (iii) significantly changed the adhesion–electrical contact at the metal–polymer interface. The similar shapes of the voltammograms for the two polymers shows modification does not have a detrimental effect on the dynamics of interconversion of their conducting and insulating forms. This compares favourably with earlier observations on active ester electropolymers[10] which also retain their intrinsic redox activity upon derivatisation. However, as we have noted elsewhere,[7] chemical or photochemical deprotection of Fmoc or Nvoc protected amino electropolymers can lead to some degradation of the electrochemical response.

Conclusion

We have described the synthesis and characterisation of new pyrrole derivatives which allow the assembly of amino acid and peptide functionalised electropolymers directly or *via* post-polymerisational reactions. Whilst the focus has been on the synthesis of certain amino acid and peptide groups, post-polymerisation chemistry offers a wide scope for functionalisation of electropolymers.

Experimental

All chemical compounds were purchased from Aldrich apart from the amino acid derivatives (from Sigma) and the L-cystine bisallyl ester bis(toluene-4-sulfonate) (from Fluka). Reagents used in the synthesis were used as supplied. All solvents were freshly distilled under dinitrogen from appropriate drying agents. NMR spectra were recorded on a JEOL 400 MHz spectrometer. Monomers were characterised by ^{1}H, ^{13}C, ^{19}F NMR and ^{1}H–^{1}H COSY spectroscopy. *J* values are given in Hz. FT-IR spectra of monomers and polymers were recorded on a Bio-Rad FTS-7 single-beam spectrometer. For polymer spectra, the instrument was operated in the diffuse reflectance mode with the Kubelka–Munk algorithm used to resolve multiple internal reflections and spectra were ratioed against uncoated polished electrode. Electrochemical measurements were made using a Hi-Tek potentiostat type DT2101/waveform generator type PPR1. Output was recorded on a Philips PM8043 X-Y recorder. Electropolymerisation of the monomers was carried out in MeCN–0.2 M NBu_4BF_4 under dinitrogen in a two-compartment cell at ambient temperature. The polymers were grown on platinum disc electrodes (area = 0.64 cm^2) that were previously polished using diamond paste and Al_2O_3 and then washed successively with water and MeCN before use.

3-(Pyrrol-1-yl)propionic acid,[12] 2-(pyrrol-3-yl)acetic acid,[13] pentafluorophenyl 3-(pyrrol-1-yl)propanoate,[12] *N*,*N*′-bis(Boc)-L-cystinyl-bis-*N*″,*N*″-dimethylaminoethylamide[16] and *N*,*N*′-bis[*N*-3-(pyrrol-1-yl)propanoyl]-L-cystinyl-bis-*N*″,*N*″-dimethylaminoethylamide[16] were prepared according to literature methods.

3-(Pyrrol-1-yl)propylamine 1

In a 500 cm^3 three neck round bottom flask fitted with a condenser and a dropping funnel, $LiAlH_4$ (9.5 g, 0.25 mol) was added to dry vigorously stirred Et_2O (150 cm^3). 3-(Pyrrol-1-yl)propionitrile (15 g, 0.125 mol) was added dropwise and the mixture was left stirring for *ca.* 4 hours. To destroy the excess of $LiAlH_4$, distilled water was added slowly until no further H_2 evolution was observed. After filtration, the water phase was isolated and the product was extracted 3 times with Et_2O. All the etherated phases were combined and dried over Na_2SO_4. After filtration and evaporation of the solvent, **1** was obtained (8.7 g, 56%) as a yellow–orange oil (Found: C, 66.87; H, 9.70; N, 22.59. $C_7H_{12}N_2$ requires C, 67.70; H, 9.74; N, 22.56%); ν_{max}(Nujol)/cm^{-1} 3365–3001 (NH), 728 (CH pyrrole); δ_H(400 MHz, $CDCl_3$) 1.02 (2H, s, NH_2), 1.90 (2H, quintet, *J* 6.7, $C_4H_4NCH_2CH_2CH_2$), 2.70 (2H, t, *J* 6.7, CH_2NH_2), 3.97 (2H, t, *J* 6.7, $C_4H_4NCH_2CH_2$), 6.15 (2H, t, *J* 2.1, C(β)H pyrrole), 6.65 (2H, t, *J* 2.1, C(α)H pyrrole).

tert-Butyl *N*-[3-(pyrrol-1-yl)propyl]carbamate 2

3-(Pyrrol-1-yl)propylamine **1** (1.24 g, 10.0 mmol) was dissolved in a 1,4-dioxane–H_2O solution (20 cm^3 : 10 cm^3). Di-*tert*-butyl dicarbonate (2.40 g, 11.0 mmol) was then added along with Et_3N (1.44 cm^3, 10.0 mmol) and the reaction mixture was left stirring for 4 hours at ambient temperature. The pH was adjusted to 3 using $KHSO_4$ and the product extracted in Et_2O (3 × 15 cm^3). The organic phase was then dried over Na_2SO_4. After filtration and evaporation of the filtrate, a white solid was obtained which was recrystallised from Et_2O–hexane to give **2** (1.90 g, 85%); mp 61–62 °C (Found: C, 64.18; H, 8.92; N, 12.51. $C_{12}H_{26}N_2O_2$ requires C, 64.26; H, 8.99; N, 12.49%); ν_{max}(Nujol)/cm^{-1} 3366 (NH), 1694 (CO), 724 (pyrrole); δ_H(400 MHz, $CDCl_3$) 1.42 (9H, s, 3 × CH_3), 1.95 (2H, quintet, *J* 6.7, $C_4H_4NCH_2CH_2CH_2$), 3.10 (2H, m, $C_4H_4NCH_2CH_2CH_2$), 3.95 (2H, t, *J* 6.7, $C_4H_4NCH_2CH_2CH_2$), 4.52 (1H, br, NH), 6.15 (2H, t, *J* 2.1, C(β)H pyrrole), 6.65 (2H, t, *J* 2.1, C(α)H pyrrole).

Fluoren-9-ylmethyl *N*-[3-(pyrrol-1-yl)propyl]carbamate 3

3-(Pyrrol-1-yl)propylamine **1** (1.24 g, 10.0 mmol) was dissolved in a 1,4-dioxane–H_2O solution (20 cm^3 : 10 cm^3). Fluoren-9-ylmethoxycarbonyl chloride (2.58 g, 10.00 mmol) was then added along with 0.5 M K_2CO_3 solution (20 cm^3) and the reaction mixture was left stirring for 4 hours at ambient temperature. The product was extracted in ethyl acetate (3 × 15 cm^3), the organic phase was then dried over Na_2SO_4. After filtration and evaporation of the filtrate, a white solid was obtained which was recrystallised from ethyl acetate–diethyl ether to give **3** (2.42 g, 70%); mp 116–117 °C (Found: C, 76.19; H, 6.46; N, 8.12. $C_{22}H_{22}N_2O_2$ requires C, 76.28; H, 6.40; N, 8.09%); ν_{max}(Nujol)/cm^{-1} 3339 (NH), 1681 (CO), 721 (CH pyrrole); δ_H(400 MHz, $CDCl_3$) 1.98 (2H, quintet, *J* 6.7, $C_4H_4NCH_2CH_2CH_2$), 3.20 (2H, m, $C_4H_4NCH_2CH_2CH_2$), 3.92 (2H, t, *J* 6.7, $C_4H_4NCH_2CH_2CH_2NH$), 4.21 (1H, t, *J* 7.0, C(9)H fluorene), 4.41 (2H, d, *J* 7.0, $COOCH_2$), 4.59 (1H, br, NH), 6.17 (2H, t, *J* 2.1, C(β)H pyrrole), 6.65 (2H, t, *J* 2.1, C(α)H pyrrole), 7.35 (2H, t, *J* 8.5 and 8.3, C(3,6)H fluorene), 7.41 (2H, t, *J* 8.5 and 8.4, C(2,7)H fluorene), 7.60 (2H, d, *J* 8.3, C(4,5)H fluorene), 7.79 (2H, d, *J* 8.4, C(1,8)H fluorene).

4,5-Dimethoxy-2-nitrobenzyl *N*-[3-(pyrrol-1-yl)propyl]-carbamate 4

3-(Pyrrol-1-yl)propylamine **1** (1.24 g, 10.0 mmol) was dissolved in a 1,4-dioxane–H_2O solution (20 cm^3 : 10 cm^3). 6-Nitroveratryloxycarbonyl chloride (2.62 g, 10.0 mmol) was then added along with 0.5 M K_2CO_3 solution (20 cm^3) and the reaction mixture was left stirring for 4 hours at ambient temperature. The product was extracted in CH_2Cl_2. The organic phase was then dried over Na_2SO_4. After filtration and evaporation of the filtrate, a white–yellow powder was obtained which was recrystallised from ethyl acetate–hexane to give **4** (2.01 g, 60%) as a yellow solid; mp 104–105 °C (Found: C, 56.5; H, 5.9; N, 11.1. $C_{17}H_{21}N_3O_6$ requires C, 56.19; H, 5.82; N, 11.56%); ν_{max}(Nujol)/cm^{-1} 3424 (NH), 1730 (CO), 723 (pyrrole); δ_H(400 MHz, $CDCl_3$) 2.00 (2H, quintet, *J* 6.8 and 6.7, $C_4H_4NCH_2CH_2CH_2$), 3.22 (2H, m, $C_4H_4NCH_2CH_2CH_2$), 3.75 (6H, s, 2 × OCH_3), 3.96 (2H, t, *J* 6.8, $C_4H_4NCH_2CH_2CH_2$), 4.63 (1H, br, NH), 5.50 (2H, s, $COOCH_2$), 6.17 (2H, t, *J* 2.1, C(β)H pyrrole), 6.65 (2H, t, *J* 2.1, C(α)H pyrrole), 6.97 (1H, C(6)H phenyl), 7.70 (1H, s, C(3)H phenyl).

4-Methoxybenzyl 3-(pyrrol-1-yl)propanoate 5

In a 250 cm^3 Schlenk flask a solution of 3-(pyrrol-1-yl)-propanoic acid (5 g, 35.9 mmol), 4-dimethylaminopyridine (0.46 g, 3.6 mmol) and 4-methoxybenzyl alcohol (4.73 g, 34.2 mmol) in 150 cm^3 of dry CH_2Cl_2 was cooled with stirring in an ice bath. 7.50 g (39.16 mmol) of 1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide hydrochloride were added and the reaction mixture was stirred at 0 °C for two hours and at room temperature for 10 hours. The solution was then concentrated to dryness under vacuum. The residue was taken up in ethyl acetate (250 cm^3) and water (150 cm^3). The organic layer was separated, washed with $NaHCO_3$ (2 × 50 cm^3) and water (2 × 50 cm^3) and dried over Na_2SO_4 overnight. After filtration, the filtrate was evaporated under vacuum and **5** was obtained as a white–yellow solid which crystallised with chilling (7.88 g, 89%); mp 32–34 °C (Found: C, 69.64; H, 6.65; N, 5.54. $C_{15}H_{17}NO_3$ requires C, 69.56; H, 6.66; N, 5.41%); ν_{max}(Nujol)/cm^{-1} 1732 (CO ester), 1248 (CO), 818 (CH phenyl), 724 (CH pyrrole); δ_H(400 MHz, CD_2Cl_2) 2.76 (2H, t, *J* 6.8, $C_4H_4NCH_2CH_2$), 3.79 (3H, s, OCH_3), 4.18 (2H, t, *J* 6.8, $C_4H_4NCH_2CH_2$), 5.03 (1H, s, $COOCH_2$), 6.06 (2H, t, *J* 2.2, C(β)H pyrrole), 6.63 (2H, t, *J* 2.2, C(α)H pyrrole), 6.88 (2H, m, C(3,5)H phenyl), 7.25 (2H, m, C(2,6)H phenyl); *m*/*z* (EI) 259 $[M]^{+\bullet}$, 121 $[CH_2–C_6H_5–OMe]^-$.

N-[3-(Pyrrol-1-yl)propanoyl]-L-histidine methyl ester 6

To a stirred solution of 3-(pyrrol-1-yl)propanoic acid (1.39 g, 10 mmol) in THF (10 cm^3), 1,1′-carbonyldiimidazole (1.62 g, 10 mmol) was added portionwise and the mixture was left stirring at 25 °C until CO_2 evolution stopped. L-Histidine methyl ester dihydrochloride (2.42 g, 10 mmol) was then added along with Et_3N (1.45 cm^3). The reaction mixture was stirred overnight at room temperature and at reflux for 10 min. The hot solution was filtered off and the filtrate evaporated under vacuum. The solid residue was washed with CH_2Cl_2, dried in air and recrystallised from cold MeOH–Et_2O to give **6** (0.70 g, 24%) as a colourless solid; mp 137 °C (Found: C, 59.17; H, 5.78; N, 19.86. $C_{14}H_{18}N_4O_3$ requires C, 57.92; H, 6.25; N, 19.29%); ν_{max}(Nujol)/cm^{-1} 3216 (NH), 1730 (CO ester), 1644 (CO amide), 1578 (NH amide), 729 (CH pyrrole); δ_H(270 MHz, CD_3CN) 2.57 (2H, t, *J* 6.7, CH_2CH_2CO), 2.92 (2H, d, *J* 6.2, $CHCH_2[C_3H_3N_2]$), 3.61 (3H, s, OCH_3), 4.11 (2H, t, *J* 6.7, $C_4H_4NCH_2CH_2$), 4.57 (1H, dt, *J* 5.9 and 6.2, $NHCH(CO_2Me)CH_2$), 5.98 (2H, t, *J* 2.0, C(β)H pyrrole), 6.62 (2H, *J* 2.0, C(α)H pyrrole), 6.75 (1H, s, C(4)H imidazole), 7.20 (1H, m, NH), 7.48 (1H, s, C(2)H imidazole); *m*/*z* (FAB) 291 (MH^+, 100), 231 (10), 80 (16%).

N-[3-(Pyrrol-1-yl)propanoyl]-L-methionine methyl ester 7

To a stirred solution of 3-(pyrrol-1-yl)propanoic acid (0.70 g, 5 mmol) in THF (5 cm^3), CDI (0.81 g, 5 mmol) was added portionwise and the mixture was left stirring at 25 °C until CO_2 evolution stopped. L-Methionine methyl ester hydrochloride (1.00 g, 5 mmol) was then added along with Et_3N (0.7 cm^3). The reaction mixture was stirred overnight at room temperature. The solution was then evaporated under vacuum. The oily residue was dissolved in CH_2Cl_2 (20 cm^3) and washed with 1 M HCl (20 cm^3), Na_2CO_3 solution (15 cm^3) and H_2O (15 cm^3). The organic phase was dried over $MgSO_4$. After filtration, the filtrate was taken to dryness to form an oil which crystallised at −20 °C and was recrystallised from ethyl acetate–hexane to give **7** (0.30 g, 21%) as colourless needles; mp 39 °C (Found: C, 55.34; H, 6.98; N, 9.96. $C_{13}H_{20}N_2O_3S$ requires C, 54.93; H, 7.04; N, 9.86%); ν_{max}(KBr)/cm^{-1} 3308 (NH), 1745 (CO ester), 1648 (CO amide), 1534 (NH amide), 1224, 709 (CH pyrrole); δ_H(270 MHz, CD_3CN) 1.98 (2H, m, $C(H)CH_2CH_2SCH_3$), 2.00 (3H, s, SCH_3), 2.34 (2H, m, $CH_2CH_2SCH_3$), 2.55 (2H, t, *J* 6.2, $C_4H_4NCH_2CH_2CO$), 3.61 (3H, s, OCH_3), 4.11 (2H, t, *J* 6.2, $C_4H_4NCH_2CH_2$), 4.45 (1H, m, $NHC(H)(CO_2CH_3)CH_2$), 5.96 (2H, t, *J* 2.0, C(β)H pyrrole), 6.61 (2H, t, *J* 2.0, C(α)H pyrrole); *m*/*z* (EI) 284 (M^+, 65), 94 ($C_7H_{10}N^+$, 100), 80 ($C_5H_6N^+$, 96%).

Pyrrol-3-ylacetyl-L-histidine methyl ester 8

1,1′-Carbonyldiimidazole (0.324 g, 2 mmol) was added to a stirred solution of 2-(pyrrol-3-yl)acetic acid (0.25 g, 2 mmol) in THF (20 cm^3). After an hour of stirring at room temperature, L-histidine methyl ester dihydrochloride (0.484 g, 2 mmol) and Et_3N (1.10 cm^3, 8 mmol) in THF (20 cm^3) were added and the reaction mixture was left stirring overnight at room temperature then at reflux for 3 hours. After filtration, the filtrate was evaporated under vacuum and the residue washed with Et_2O to afford **8** (0.27 g, 49%) as a yellow oil; ν_{max}(Nujol)/cm^{-1} 3200, 1743 (CO ester), 1650 (CO amide), 839 (CH imidazole), 754 (CH pyrrole); δ_H(270 MHz, $CDCl_3$) 3.05 (2H, s, $CH_2[C_3H_3N_2]$), 3.35 (2H, s, $C_4H_4NCH_2CO$), 3.60 (3H, m, $COOCH_3$), 3.80 (1H, s, CONH), 4.66 (1H, m, C(H)COOMe), 5.96 (1H, m, C(4)H pyrrole), 6.68 (1H, m, C(2)H pyrrole), 6.79 (1H, m, C(5)H pyrrole), 7.10 (1H, m, CH imidazole), 7.59 (1H, m, CONH), 7.75 (1H, m, CH imidazole); *m*/*z* (FAB) 277 (MH^+, 67), 170 (67), 68 (100%).

N,*N*′-Bis[3-(pyrrol-1-yl)propanoyl]-L-cystine diallyl ester 9

1,1′-Carbonyldiimidazole (3.0 g, 18 mmol) was added to a solution of 3-(pyrrol-1-yl)propionic acid (2.66 g, 18 mmol) in dry THF (40 cm^3) and the reaction mixture was stirred for 1 hour at 25 °C. L-Cystine bisallyl ester bis(toluene-4-sulfonate) (6 g, 8.2 mmol) was dissolved in THF (60 cm^3) by adding Et_3N and this was added to the above solution. The reaction mixture was left stirring for 48 hours at room temperature then for 6 hours at 50 °C. The solvent was then evaporated under vacuum and the oily residue was dissolved in warm CH_2Cl_2. After filtration, Et_2O (10 cm^3) was added to the filtrate which was then left at 4 °C overnight. After filtration, the residue was washed with MeOH to afford **9** (3.0 g, 79%) as a white solid; mp 164–165 °C (Found: C, 55.50; H, 6.19; N, 9.82. $C_{26}H_{34}N_4O_6S_2$ requires C, 55.50; H, 6.09; N, 9.96%); ν_{max}(Nujol)/cm^{-1} 3315 (NH), 1733 (CO ester), 1640 (CO amide), 1537 (NH amide), 731 (CH pyrrole); δ_H(400 MHz, $CDCl_3$, 45 °C) 2.63 (4H, t, *J* 6.7, 2 × $C_4H_4NCH_2CH_2CO$), 2.99 (4H, m, 2 × CH_2S), 4.17 (4H, m, 2 × $C_4H_4NCH_2CH_2CO$), 4.61 (4H, t, *J* 3.0, 2 × OCH_2CHCH_2), 4.80 (2H, m, 2 × $C(H)CH_2S$), 5.28 (4H, m, 2 × $OCH_2CH{=}CH_2$), 5.83 (2H, m, 2 × $OCH_2CH{=}CH_2$), 6.08 (4H, t, *J* 2.0, 2 × C(β)H pyrrole), 6.31 (2H, d, *J* 7.3, 2 × NH), 6.62 (4H, t, *J* 2.0, 2 × C(α)H pyrrole).

N,*N*′-Bis[3-(pyrrol-1-yl)propanoyl]-L-cystine 10

PPh_3 (49.7 mg, 0.19 mmol) and $Pd(PPh_3)_4$ (0.112 g, 0.09 mmol) were added to a stirred suspension of **9** (0.89 g, 1.58 mmol) in MeCN (20 cm^3). Addition of pyrrolidine (0.56 cm^3, 6.7 mmol) resulted in precipitation of a fluffy solid which was isolated by filtration, washed with MeCN, dried under vacuum and was then dissolved in thoroughly degassed distilled water. After filtration, the filtrate was acidified to pH 2 with 10% HCl solution. A white solid precipitated and was isolated by filtration and recrystallised from MeCN to give **10** (0.59 g, 77%) as a white solid; mp 147–148 °C (Found: C, 49.59; H, 5.54; N, 11.80. $C_{20}H_{26}N_4O_6S_2$ requires C, 49.77; H, 5.44; N, 11.62%); ν_{max}(Nujol)/cm^{-1} 3350 (NH), 1710 (CO acid), 1617 (CO amide), 1558 (NH amide), 732 (CH pyrrole); δ_H(400 MHz, CD_3CN, 70 °C) 2.64 (4H, t, *J* 7.0, 2 × $C_4H_4NCH_2CH_2CO$), 2.99 (4H, m, 2 × CH_2S), 4.14 (4H, t, *J* 7.0, 2 × $C_4H_4NCH_2CH_2CO$), 4.64 (2H, m, 2 × $C(H)CH_2S$), 6.01 (4H, t, *J* 2.0, 2 × C(β)H pyrrole), 6.66 (4H, t, *J* 2.0, 2 × C(α)H pyrrole), 6.82 (2H, d, *J* 7.0, 2 × NH); *m*/*z* (FAB) 483 (MH^+, 89), 241 (M/2, 61), 154 (100%).

N,*N*′-Bis[3-(pyrrol-1-yl)propanoyl]-L-cystine bis(pentafluorophenyl) ester 11

Pyrrolylcystine **10** (0.50 g, 1 mmol) was dissolved in 1,4-dioxane (30 cm^3) and pentafluorophenol (0.385 g, 2 mmol) was then added along with DCC (0.430 g, 2 mmol). The reaction mixture was left stirring overnight and after filtration and evaporation of the filtrate solution, a golden oil was obtained which was washed with hexane. The residue was dissolved in MeCN and after filtration, the solvent was removed under vacuum to yield a pale yellow solid which was thoroughly washed with Et_2O and hexane to give **11** (0.390 g, 47%) as a white powder (Found: C, 47.48; H, 3.09; N, 7.20. $C_{32}H_{24}N_4O_6S_2F_{10}$ requires C, 47.18; H, 2.97; N, 6.87%); ν_{max}(Nujol)/cm^{-1} 3302 (NH), 1779 (CO ester), 1647 (CO amide), 997 (CF), 725 (CH pyrrole); δ_H(400 MHz, $CDCl_3$) set A: 2.75 (4H, m, 2 × $C_4H_4NCH_2CH_2CO$), 3.18 (4H, m, 2 × C(H)CH_2S), 4.26 (4H, m, 2 × $C_4H_4NCH_2CH_2CO$), 5.15 (2H, m, 2 × C(*H*)CH_2S), 6.10 (4H, t, *J* 2.0, 2 × C(β)Hpyrrole), 6.42 (2H, d, *J* 7.1, 2 × NH), 6.69 (4H, t, *J* 2.0, 2 × C(α)Hpyrrole); set B: 2.68–2.87 (4H, m, 2 × $C_4H_4NCH_2CH_2CO$), 3.20 (4H, m, 2 × C(H)CH_2S), 4.19–4.36 (4H, m, 2 × $C_4H_4NCH_2$-CH_2CO), 5.10 (2H, dt, *J* 7.8 and 6.4, 2 × C(*H*)CH_2S), 6.10 (4H, t, *J* 2.0, 2 × C(β)Hpyrrole), 6.40 (2H, d, *J* 7.8, 2 × NH), 6.69 (4H, t, *J* 2.0, 2 × C(α)Hpyrrole); δ_F(376 MHz, $CDCl_3$): set A: −152.3 (4F, d, *J* 18.4, 2 × *ortho*-F), −156.7 (2F, t, *J* 22.0, 2 × *para*-F), −161.7 (4F, dd, *J* 22.0 and 18.4, 2 × *meta*-F), set B: −152.1 (4F, d, *J* 18.4, 2 × *ortho*-F), −156.9 (2F, t, *J* 22.0, 2 × *para*-F), −161.8 (4F, dd, *J* 22.0 and 18.4, 2 × *meta*-F).

N,*N*′-Bis(*tert*-butoxycarbonyl)-L-cystine bis(pentafluorophenyl) ester 12

Pentafluorophenol (2.51 g, 13.62 mmol) along with DCC (2.81 g, 13.62 mmol) was added to a stirred and cooled solution of *N*,*N*′-bis(Boc)-L-cystine (3 g, 6.81 mmol) in 1,4-dioxane (60 cm^3). The reaction mixture was left stirring overnight at room temperature. After filtration of the DCU, the solvent was evaporated under vacuum and the residue washed with hexane to afford **12** as a white solid (4.67 g, 89%); mp 157–158 °C; ν_{max}(Nujol)/cm^{-1} 3347 (NH), 1780 (CO ester), 1680 (CONH), 1522, 1004 (CF); δ_H(400 MHz, $CDCl_3$) 1.58 (18H, s, 2 × $(CH_3)_3$), 3.37 (4H, m, 2 × CH_2S), 4.98 (2H, m, 2 × C(*H*)CH_2S), 5.52 (2H, m, 2 × NH); δ_F(376 MHz, $CDCl_3$) −152.08 (4F, m, 2 × *ortho*-F), −157.22 (2F, m, 2 × *para*-F), −162.08 (2F, m, 2 × *meta*-F); δ_C(100 MHz, $CDCl_3$) 28.19 ($(CH_3)_3$), 40.50 (CH_2), 53.00 (CH), 81.11 (COO*C*Me_3), 136.08 (*meta*-C_6F_5), 138.20 (*para*-C_6F_5), 142.82 (*ortho*-C_6F_5), 154.85 (O*C*ONH), 167.22 (*C*OOC_6F_5).

[*N*,*N*′-Bis(*tert*-butoxycarbonyl)-L-cystinyl]-di-L-histidine dimethyl ester 13

L-Histidine methyl ester dihydrochloride (0.9 g, 3.72 mmol) and Et_3N (0.6 cm^3, 4.3 mmol) were left reacting for 1 hour at room temperature in dry CH_3CN (50 cm^3). A solution of **12** (1 g, 1.29 mmol) in CH_3CN (30 cm^3) was then added slowly to the above solution and the reaction mixture was left stirring overnight at room temperature and then for 2 hours at 50 °C. On cooling, a white–brown precipitate was formed which was isolated by filtration and thoroughly washed with Et_2O to afford **13** (0.645 g, 67%) as a white solid; mp 126–127 °C; ν_{max}(Nujol)/cm^{-1} 3318 (NH), 1737 (CO ester), 1692 (CO urethane), 1658 (CO amide), 860 (CH imidazole); δ_H(400 MHz, DMSO) 1.36 (18H, s, 2 × $(CH_3)_3$), 2.78 (4H, m, 2 × C(H)CH_2S), 2.93 (4H, m, 2 × CHCH_2[$C_3H_3N_2$]), 3.67 (6H, s, 2 × COOCH_3), 4.19 (2H, m, 2 × C(*H*)CH_2S), 4.48 (2H, q, *J* 4.5, 2 × C(*H*)COOMe), 6.88 (2H, s, 2 × C(4)*H* imidazole), 7.12 (2H, d, *J* 9.0, 2 × NH), 7.64 (2H, s, 2 × C(2)*H* imidazole), 8.39 (2H, d, *J* 4.5, 2 × NH); *m*/*z* (FAB) 743 (MH^+, 61), 239 (69), 102 (100%).

[*N*,*N*′-Bis[3-(pyrrol-1-yl)propanoyl]-L-cystinyl]-di-L-histidine dimethyl ester 14

Trifluoroacetic acid (TFA) (10 cm^3) was added dropwise to **13** (1 g, 1.35 mmol) at −10 °C and the solution was left stirring for 1 hour at −10 °C and for 3 hours at 0 °C. TFA was then removed under vacuum and the oily residue was washed with Et_2O and then dissolved in dry THF (50 cm^3) and Et_3N was added until *ca.* pH 10 was reached. Pentafluorophenyl 3-(pyrrol-1-yl)propanoate (0.74 g, 2.42 mmol) was then added and the mixture was left stirring at room temperature overnight. After filtration, the filtrate solution was evaporated under vacuum to form an orange oil which was washed with hexane. The oil crystallised in CH_3CN at −14 °C to give **14** (0.56 g, 53%) as a yellow solid (Found: C, 51.92; H, 5.48; N, 17.70. $C_{34}H_{44}N_{10}O_8S_2$ requires C, 52.03; H, 5.65; N, 17.84%); ν_{max}(Nujol)/cm^{-1} 3320 (NH), 1736 (CO ester), 1675 (CO amide), 828 (CH imidazole), 726 (CH pyrrole); δ_H(400 MHz, DMSO) 2.59 (4H, t, *J* 7.3, 2 × C_4H_4-NCH_2CH_2CO), 2.78 (2H, dd, *J* 13.5 and 9.6, 2 × C*H*(H)S), 2.93 (4H, m, 2 × CH_2[$C_3H_3N_2$]), 3.05 (2H, dd, *J* 13.5 and 4.8, 2 × C*H*(H)S), 3.56 (6H, s, 2 × COOCH_3), 4.08 (4H, t, *J* 7.3, 2 × CH_2CH_2CO), 4.46 (2H, m, 2 × C*H*COOMe), 4.61 (2H, m, 2 × C(*H*)CH_2S), 5.93 (4H, t, *J* 2.1, 2 × C(β)H pyrrole), 6.70 (4H, t, *J* 2.1, 2 × C(α)H pyrrole), 6.85 (2H, s, 2 × C(4)*H* imidazole), 7.61 (2H, s, 2 × C(2)*H* imidazole), 8.38 (2H, d, *J* 8.3, 2 × N*H*C(H)CH_2S), 8.50 (2H, d, *J* 7.3, 2 × N*H*C(H)COOMe); δ_C(100 MHz, DMSO) 28.56 (CH*C*H_2imidazole), 40.46 (*C*H_2S), 37.37 ($C_4H_4NCH_2CH_2CO$), 44.75 ($C_4H_4NCH_2CH_2CO$), 51.6 (NH*C*(H)CH_2S), 51.8 (O*C*H_3), 52.5 (NH*C*(H)CO_2Me), 107.5 (C(β)pyrrole), 113.4 (C(4)imidazole), 120.4 (C(β)pyrrole), 134.9 (C(2)imidazole), 138.9 (C(5)imidazole), 169.9 (CO), 170.1 (CO), 171.5 (CO); *m*/*z* (FAB), 785 (MH^+).

N,*N*′-{*N*,*N*′-Bis[3-(pyrrol-1-yl)propanoyl]-L-cystinylbis(aminoethyl)}-*N*,*N*′-bis(carboxymethyl)-*N*,*N*′-dimethyldiammonium diiodide disodium salt 16

Sodium iodoacetate (0.2 g, 0.96 mmol) was dissolved in dry MeOH (10 cm^3) and was added dropwise to a solution of *N*,*N*′-bis[*N*-3-(pyrrol-1-yl)propanoyl]-L-cystinyl-bis-*N*″,*N*″-dimethylaminoethylamide (0.30 g, 0.48 mmol) in dry CH_2Cl_2 (10 cm^3). The reaction mixture was stirred overnight at room temperature. The solution was then concentrated to dryness and the residue washed with ethyl acetate to give **16** (0.37 g, 72%) as a white solid (Found: C, 36.92; H, 4.98; N, 10.97. $C_{32}H_{50}N_8$-$S_2Na_2I_2$ requires C, 37.00; H, 4.85; N, 10.78%); ν_{max}(Nujol)/cm^{-1} 3243, 3448, 1649 (CO amide), 1526 (CO), 1397 (CO), 734 (CH pyrrole); δ_H(400 MHz, $CDCl_3$) 2.72 (4H, t, *J* 6.7, C_4H_4-NCH_2CH_2CO), 2.87 (2H, dd, *J* 13.9 and 8.8, 2 × C*H*(H)S), 3.15 (2H, dd, *J* 13.9 and 5.6, 2 × C*H*(H)S), 3.26 (12H, s, 2 × $(CH_3)_2$), 3.63 (4H, t, *J* 6.3, 2 × NHC$H_2CH_2N^+$), 3.77 (4H, t, *J* 6.3, 2 × NHC$H_2CH_2N^+$), 3.93 (4H, s, 2 × CH_2COO), 4.20 (4H, t, *J* 6.7, 2 × $C_4H_4NCH_2CH_2CO$), 4.60 (2H, dd, *J* 8.8, 5.6, 2 × C(*H*)CH_2S), 6.03 (4H, t, *J* 2.2, 2 × C(β)H pyrrole), 6.68 (4H, t, *J* 2.2, 2 × C(α)H pyrrole).

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