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Synthesis and evaluation of fully (5-amidoisophthalic acid)-functionalised polyacrylamides as selective inhibitors of the beta crystal polymorph of L-glutamic acid

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ABSTRACT

Poly-*N*-5-acrylamidoisophthalic acid (**4**), poly-*N*-(5-(*N*′-(3,5-dicarboxyphenyl)carbamoyl)pentyl)acrylamide (**10a**) and poly-*N*-(11-(*N*′-(3,5-dicarboxyphenyl)carbamoyl)undecyl)acrylamide (**10b**) were prepared and assessed as polymorph-selective crystallization inhibitors of the stable β form of L-glutamic acid. Polymerization was carried out as the final step in the preparation of **10a** and **10b** to ensure the preparation of fully functionalized polymers. Polymers **4**, **10a** and **10b** were effective as complete inhibitors of the stable β form of L-glutamic acid in quantities of 0.5% w/w or greater, whereas the corresponding 'monomeric' additives **2** and **11** required quantities of 3% or greater to completely inhibit the β form, demonstrating a cooperative binding effect by the polymeric additives. Within the series of polymers **4**, **10a** and **10b**, polymer **10a**, which features a short tethering chain, was the most effective.

1. Introduction

Crystal polymorphism of organic compounds has become an area of considerable current interest,[1] in particular because of the significance of polymorphism for pharmaceuticals.[2] This has driven much new research in crystallisation methods and polymorph discovery. Examples of new crystallisation technologies include co-crystallization,[3] supercritical fluid crystallization,[4] sonocrystallization,[5] laser-induced crystal nucleation[6] and capillary-space crystallization.[7] New approaches to polymorph discovery have been developed utilising high-throughput screening technologies.[8] Recent research has also attempted to examine the molecular level events occurring prior to crystal nucleation, using techniques such as small-angle neutron scattering[9] and NMR spectroscopy.[10]

It is widely appreciated that molecular species other than the crystallizing solute or the crystallization solvent can have a significant impact on the outcome of crystallizations. Process impurities can affect crystal morphology[11] and form.[12] Impurities can be deliberately added to influence process outcomes. Polymeric additives have been used as crystal heteronuclei in polymorph screening.[13] Structurally similar materials have been added as pseudoseeds.[14] Some recent research on co-crystallization has resulted in novel or unexpected crystal forms being obtained as a consequence of putative co-crystallizing compounds acting as crystallization additives.[15] Rationally designed additives, known as 'tailor-made' additives, have been used to control crystal morphology and polymorphism.[16] Usually, such additives will be structurally analogous to molecules of the crystallizing substance, as analogues are likely to have sufficient structural similarity to the crystallizing compound to allow incorporation into pre-critical crystal nuclei, after which any structural dissimilarity can impede addition of further molecules of crystallising substance.[17] That portion of the analogue structure, which permits selective interaction with pre-critical nuclei has been referred to as the 'binder', while that portion which impedes further addition has been referred to as the 'perturber'.[18]

Davey et al. have shown that certain conformationally restricted diacids can act as selective binder groups for the stable β crystal polymorph of L-glutamic acid, inhibiting crystallisation of that form.[19] This effect is based upon mimicry of the L-glutamic acid conformation found in the β form. The conformations of L-glutamic acid found in the stable β form and the metastable α form are illustrated in Figure 1. The β form can be seen to have a more open or extended conformation, with the carboxyl groups further apart; while the α form possesses a more closed or folded conformation with the carboxyl groups closer together. Addition of conformationally restricted mimics of the β form conformation, such as trimesic acid, to L-glutamic acid crystallisations was found to result in crystallisation of the metastable α form under conditions, which would normally produce the more stable β form.[19] This effect is attributed to selective addition of molecules of trimesic acid to crystal nuclei of the β form and inhibition of their growth into

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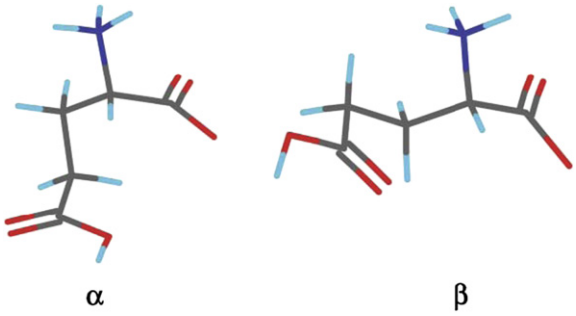
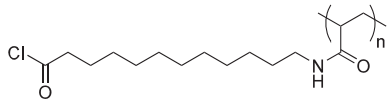


Figure 1. Conformations of L-glutamic acid found in the α and β crystal polymorphs.

mature crystals, whereas crystal nuclei of the metastable α form are not similarly affected.

We have previously shown that the efficiency of these inhibitors can be improved through the use of a cooperative binding effect.[20] This effect involves the use of polymeric additives, rather than their monomeric counterparts. Whereas each molecule of a monomer-like additive, such as trimesic acid, binds independently to crystal nuclei, once one residue of a polymeric additive binds to a crystal nucleus, binding of further residues is assisted. Hence, while 10% w/w of trimesic acid is required to fully inhibit crystallization of the β polymorph of L-glutamic acid, a corresponding polyacrylamide-borne analogue was found to fully inhibit β form crystallization at 1% w/w quantities.[21] The preparation of this polymeric analogue involved treatment of an acid chloride functionalized polyacrylamide (compound **1**[20]) with 5-aminoisophthalic acid. This direct polymer functionalization process resulted in a material in which only approximately 50% (as determined by ^{1}H NMR) of the polymer residues were functionalized with 5-aminoisophthalic acid residues. Any attempts to improve on the efficiency of these tailor-made crystallization additives would need to address the additive preparation so as to, preferably, provide polymeric material, which is completely functionalized. In this paper we described the preparation of fully functionalized polymeric additives and their efficacy as inhibitors of the β crystal form of L-glutamic acid.



1

2. Results and discussion

Our previously reported additive was based on the use of 5-aminoisophthalic acid (**2**), rather than trimesic acid, as the 'binder' group.[21] 5-Aminoisophthalic acid and its derivatives are usable in this way as only two of the three carboxylic acid groups of trimesic acid are necessary for its mimicry of the conformation found in the β crystal form of L-glutamic acid, and its selective binding to crystal nuclei of this form. This is illustrated in Figure 2. The amino group of 5-aminoisophthalic acid is hence free to be used as a point of attachment by an amide formation.

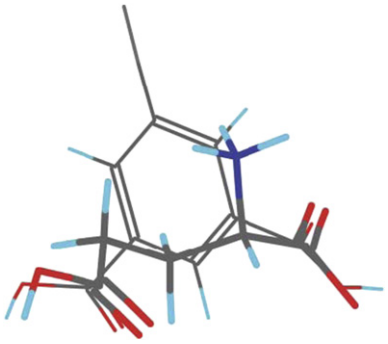
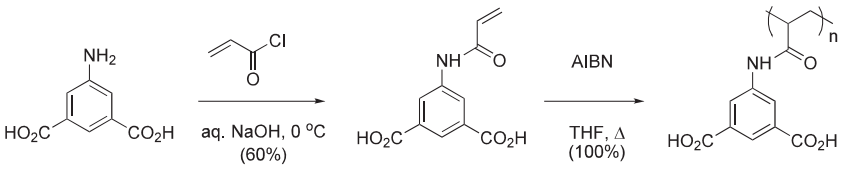


Figure 2. Mimicry of the conformation found in the β crystal polymorph of L-glutamic acid by benzene-1,3-dicarboxylic acid units.

The simplest completely functionalised polymer, which could be prepared would hence be just the polyacrylamide formed from 5-acrylamidoisophthalic acid. This was prepared from 5-aminoisophthalic acid (**2**) by a reaction with acryloyl chloride, followed by free radical polymerisation to give compound **4** (Scheme 1).



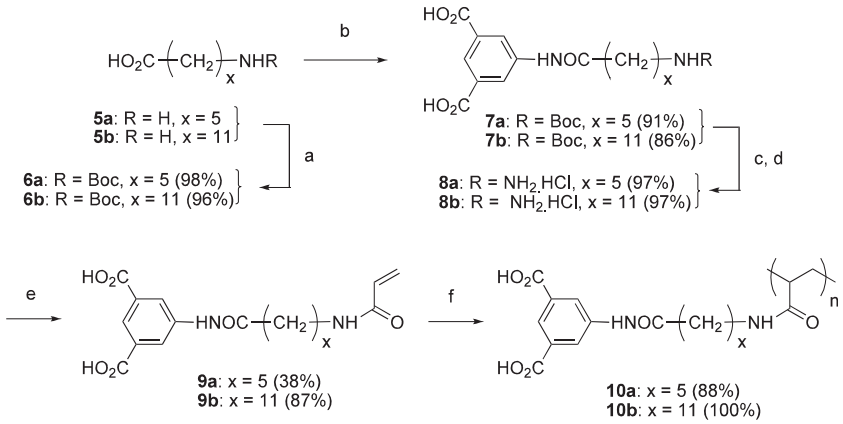
2 **3** **4**

Scheme 1. Preparation of compound **4**.

The details of the molecular level events, which precede the appearance of crystal nuclei are still very uncertain and are a subject of current interest.[9] For this reason, it is often beneficial to allow compounds intended to interact with crystal nuclei to have a degree of conformational flexibility, so as to allow the binder groups to achieve a 'best fit' with the crystal nucleus. The 12-carbon chain in the polyacrylamide precursor **1** is intended to provide such flexibility. While the polyacrylamide **4** is fully functionalized with 5-amidoisophthalic acid groups, it lacks the conformational flexibility provided by such a tethering carbon chain. Hence, the preparation of analogues of polyacrylamide **4** with inserted six and 12-carbon chains (compounds **10a** and **10b**) was also carried out.

Fully functionalised tethered polyacrylamides **10a** and **10b** were prepared as outlined in Scheme 2. The corresponding six and 12-carbon terminal amino acids (**5a** and **5b**) were first N-protected with Boc groups, after which the 4-amidoisophathalic acid group was introduced by DCC/HOBt coupling to give compounds **7a** and **7b**. The Boc *N*-protection was removed by treatment with trifluoroacetic acid, after which it was found to be preferable to isolate the deprotected amines as the hydrochloride salts (**8a** and **8b**). These were converted to the corresponding acrylamides (**9a** and **9b**), which were polymerised in the final step to give the required polyacrylamides.

Compounds **4**, **10a** and **10b** were assessed for their effects on the crystallisation of L-glutamic acid from water. The crystal form of samples of L-glutamic acid can be initially assigned on the basis of crystal morphology. Typically, crystals of the α form of L-glutamic acid have the prismatic morphology shown in Figure 3(left), whereas those of the β form have the needle-like morphology



Scheme 2. Reagents and conditions: (a) Boc_2O, dioxane, aq $NaHCO_3$; (b) 5-aminoisophthalic acid, DCC, HOBt, DIPEA, DMF; (c) TFA, DCM; (d) HCl, EtOH; (e) acryloyl chloride, aq NaOH; (f) AIBN, DMF, 80 °C.

shown in Figure 3(right). However, more rigorous assignment can be achieved using powder X-ray diffraction (PXRD). Theoretical PXRD patterns, shown in Figure 4, were generated from crystal structural data obtained from the Cambridge Structural Database. The PXRD patterns of the two forms are clearly different, allowing unambiguous assignment of crystal form. For example, Figure 5 shows typical PXRD patterns of actual samples of the α and β crystal forms obtained in this study. It can be seen that these corresponded very well with their theoretical counterparts.

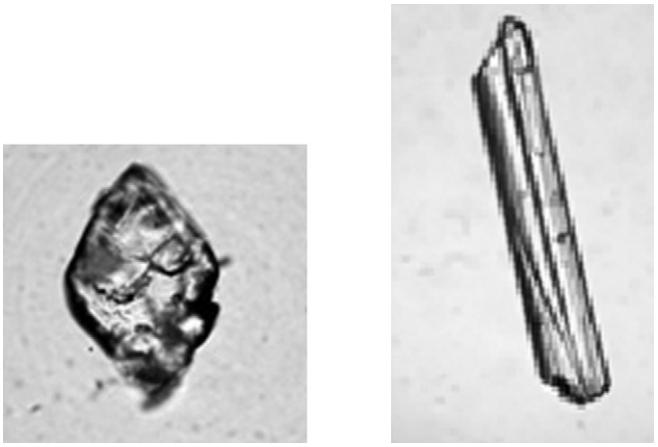
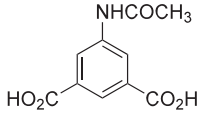


Figure 3. Typical prismatic morphology of the α crystal form of L-glutamic acid (left); typical needle-like morphology of the β crystal form of L-glutamic acid (right).

Table 1 summarises the outcomes of crystallizations of L-glutamic acid is the absence and presence of quantities of compounds **4**, **10a** and **10b**. For comparison, data on the use of the 'monomeric' analogues 5-aminoisophthalic acid **2** and its acetamido derivative **11** are also presented.



11

Crystallization of L-glutamic acid from water reliably gives the β form when carried out at 38 °C using 35 g of solute per litre of solvent, and gives the α form when carried out at 18 °C using 20 g of solute per litre of solvent, as described in the literature[24]; likewise, crystallization from a solution containing 45 g per litre of solvent at 45 °C gives a mixture of α and β forms (Table 1).

Addition of sufficient quantities of 5-aminoisophthalic acid derivatives generally inhibits formation of the more stable β form, and promotes crystallization of the metastable α form. However, the quantity of additive necessary to completely suppress β form crystallization varies considerably with structure. Addition of 10% w/w of 5-aminoisophthalic acid (**2**) is required to fully inhibit formation of the β form. Addition of 5% w/w of **2** results in crystallization of a mixture of polymorphs, while compound **2** has no inhibitory effect when added in 2 or 1% w/w quantity (Table 1). The acetamido derivative **11** shows somewhat greater inhibitory activity, with 3% w/w completely suppressing the appearance of the β form. Addition of 1% w/w of **11** has no effect on the polymorphic outcome.

Addition of poly(5-acylamidoisophthalic acid) **4** in quantities of 0.5% w/w or greater resulted in a complete inhibition of the β form. This effect was lost upon reduction of the added quantity to 0.1% w/w (Table 1). The fact that polymer **4** is an order of magnitude more active than, for example, 5-aminoisophthalic acid **2**, is a demonstration of the cooperative binding effect mentioned above.

Polymers **10a** and **10b** additionally have tethering chains, consisting of five or eleven carbons plus an amide group, inserted between the 5-aminoisophthalic acid groups and the polyacrylamide backbone found in polymer **4**. These tethering chains should provide the isophthalic acid groups with the flexibility to achieve a 'best fit' when binding to crystal nuclei. In fact, polymer **10a**, which contains the shorter tethering chain, gives complete inhibition of the β form at 0.2% w/w or greater. This clearly shows a cooperative binding effect, which is superior to that shown by the simple polyacrylamide **4**. However, the β form reappears upon reduction of the amount of **10a** added to 0.1% w/w. Polymer **10b**, which contains the longer tethering group, is only equally active to the simple polyacrylamide **4**, with complete inhibition of the β form observed at 0.5% w/w quantities, but not at lesser quantities.

In general, the polymeric additives **4**, **10a** and **10b** were found to fully inhibit the β form in quantities of approximately an order of magnitude less than those required by the 'monomeric' additives **2** and **11**, demonstrating the effectiveness of cooperative binding. While inclusion of the tethering group in polymer **10a** gives an improvement over the simple polyacrylamide **4**, possibility through increased ability to achieve a 'best fit' with crystal nuclei, that improvement was effectively lost on moving to the longer tethering group in polymer **10b**. As these crystallizations are from water, the hydrophility/hydrophobicity of the polymeric additive becomes a possible issue. The polyacrylamide backbone is itself reasonably hydrophilic, allowing polymers **4** and **10a** to act effectively in water. However, the 11-carbon tethering group in polymer **10b** may be too hydrophobic for efficient solvation in water, reducing the efficacy of polymer **10b** compared to that of polymers **4** and **10a**.

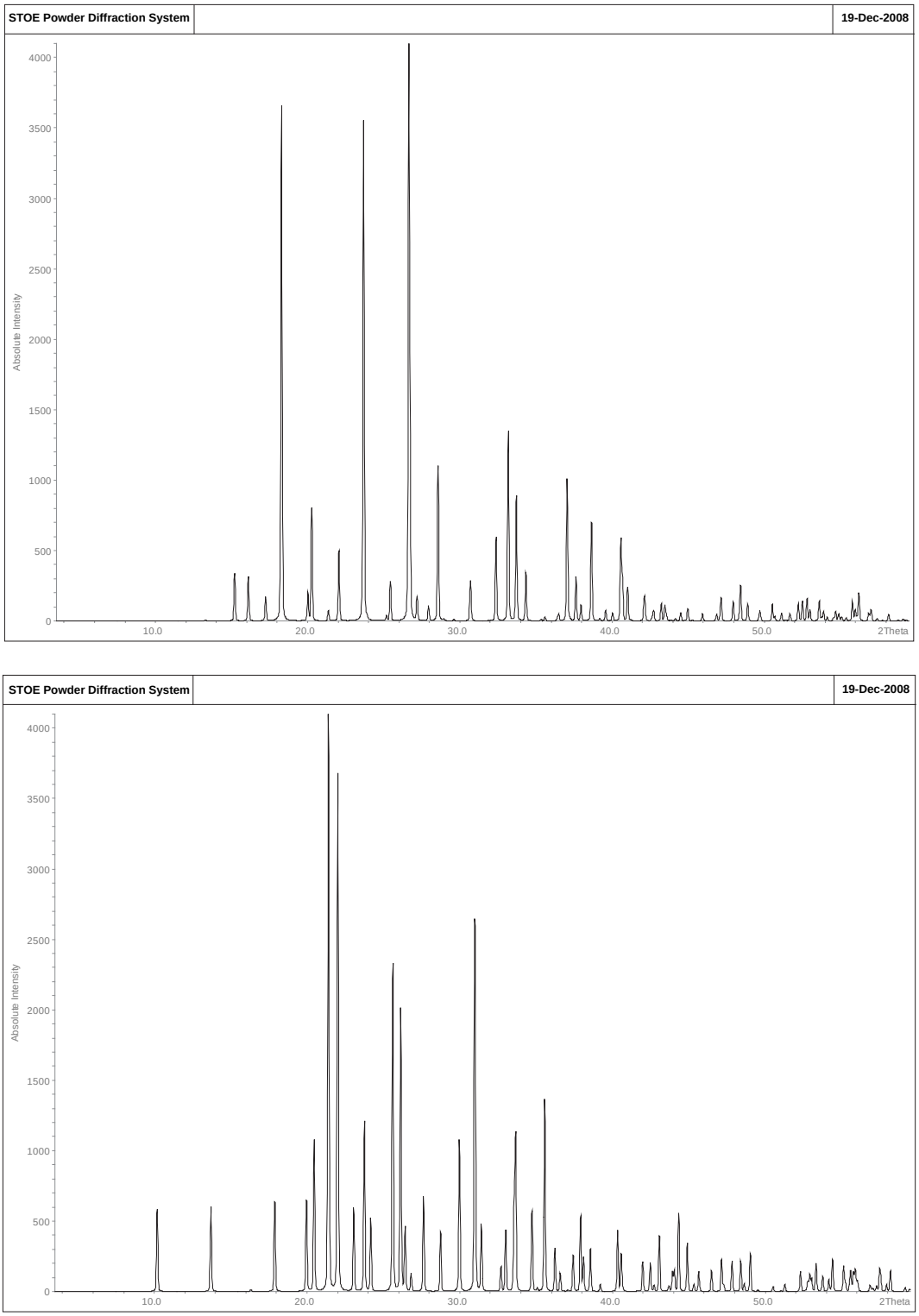


Figure 4. Theoretical PXRD pattern of α form of L-glutamic acid (CSD Ref. LCLUAC02[22]) (top); theoretical PXRD pattern of β-form of L-glutamic acid (CSD Ref. LGLUAC[23]) (bottom).

Our previously reported additives were prepared by the direct functionalization of polymer **1**.[21] These suffered from the drawback that the extent of functionalization was variable, typically around 50%. This presented an uncertainty when comparing the performance of these polymers with their 'monomeric' counterparts. However, the polymeric additives described in this paper do not suffer from this drawback, as polymerization is kept until the final step, hence ensuring 100% functionalization. The direct comparison of these polymers with their 'monomeric' analogues as crystallization additives is therefore placed on a sounder footing.

3. Conclusions

The 5-amidoisophthalic acid functionalized polymers **4**, **10a** and **10b** demonstrated a cooperative binding effect compared to their 'monomeric' analogues **2** and **11**, in that approximately one order of

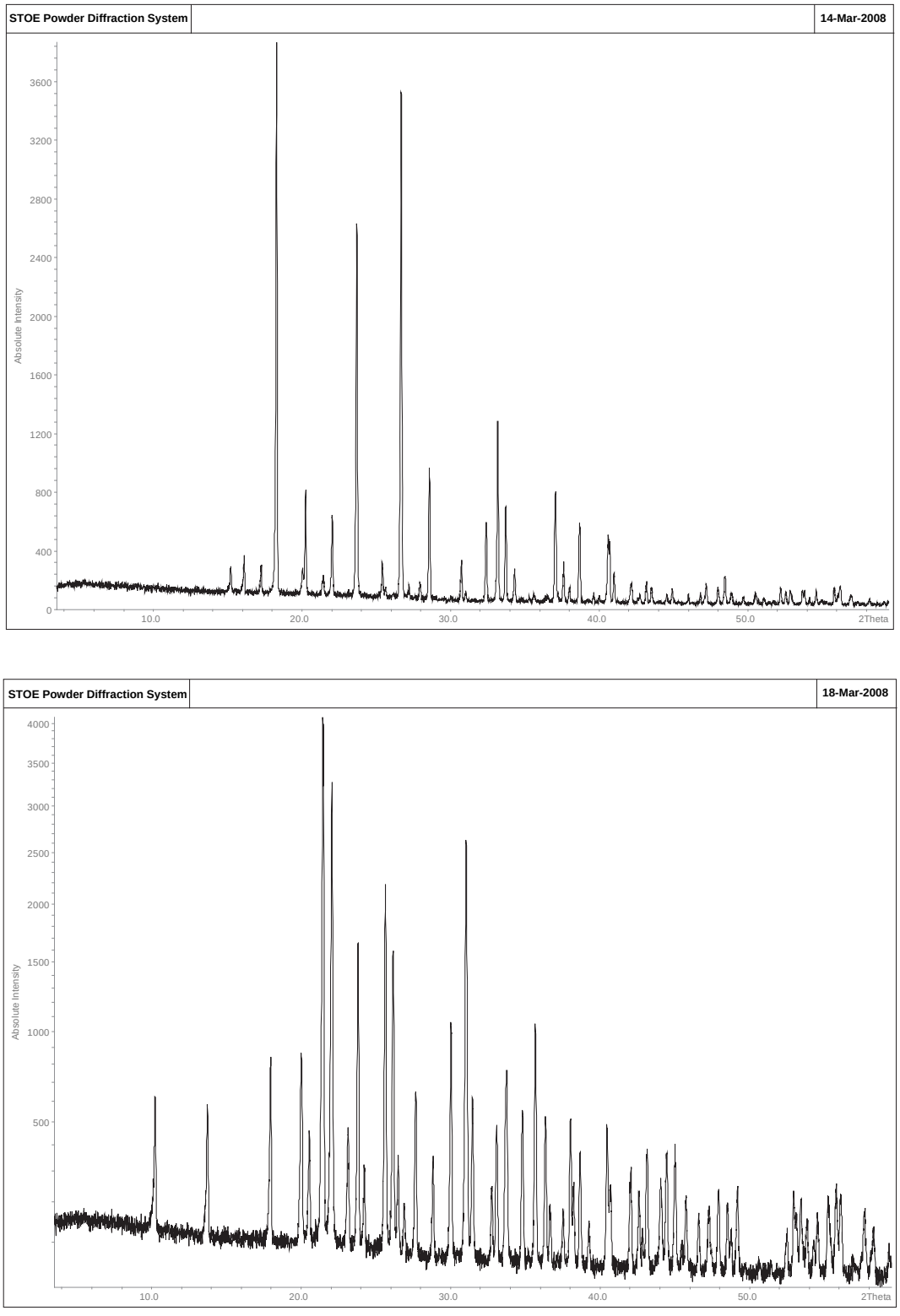


Figure 5. PXRD pattern of a sample of the α form of L-glutamic acid (top); PXRD pattern of a sample of the β-form of L-glutamic acid (bottom).

magnitude less than the polymeric compounds was sufficient to fully inhibit the appearance of the more stable β crystal form of L-glutamic acid. Polymerization was kept until the final step in the preparations of **4**, **10a** and **10b**, ensuring that the resulting polymers were 100% functionalized with 5-aminoisophthalic acid group, hence removing any doubt that incomplete functionalization might be a factor affecting efficacy. Our findings suggest that the effectiveness of the polymers lies in a balance between the efficient solvation, and the ability to achieve a 'best fit' with pre-critical crystal nuclei.

Crystallization additives, which reliably control polymeric outcome in quantities in the order of 0.1% w/w or less are approaching a level of efficacy, which may be acceptable for many industrial applications, for example, in the manufacturing of metastable

Table 1
Outcome of crystallisations of L-glutamic acid from water in the presence of additives **2**, **4**, **10a**, **10b** and **11**

Entry no.	Concn[a] (g L^{-1})	Additive no.	% w/w[b]	Form
1	35	None	—	β
2	20	None	—	α[c]
3	45	None	—	α and β[d]
4	35	**2**	10	α
5	35	**2**	5	α and β
6	35	**2**	2	β
7	35	**2**	1	β
8	35	**11**	3	α
9	35	**11**	1	β
10	35	**4**	2.2	α
11	35	**4**	1	α
12	35	**4**	0.8	α
13	35	**4**	0.5	α
14	35	**4**	0.1	β
15	35	**10a**	0.3	α
16	35	**10a**	0.2	α
17	35	**10a**	0.1	α and β
18	35	**10b**	0.5	α
19	35	**10b**	0.4	β

[a] Crystallizations were carried out at 35 g L^{-1} at 38 °C as described in Ref. 24.
[b] % w/w of additive.
[c] Crystallizations of entry no. 2 were carried out at 20 g L^{-1} at 18 °C as described by Ref. 24.
[d] Crystallizations of entry no. 3 were carried out at 45 g L^{-1} at 45 °C as described by Ref. 24.

crystal forms of high-value fine chemicals such as pigments, high-energy compounds, organic magnets or organic conducting compounds. Further improvement in the design of the additives described here, which may make them effective in quantities of 0.1% w/w or less includes improved solvation of the tethering sidechains, or alternative structured scaffolds such as dendrimers.

The additives also demonstrate that relatively minor quantities of impurities can have a significant impact of the outcome of crystallization. This is an especially relevant issue for the manufacture of highly regulated compounds such as pharmaceuticals.

4. Experimental

4.1. General

Materials used were purchased from Sigma–Aldrich. IR spectra were recorded on a Perkin–Elmer 1000 spectrometer in the range of 4000–500 cm^{-1}. All melting points were recorded on a Vickers Microscope model M14/2 and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer at 300 and 75 MHz, respectively. The NMR spectra were recorded in either deuteriochloroform ($CDCl_3$) or deuterated dimethylsulphoxide (DMSO-d_6) and tetramethylsilane (TMS) was used as an internal standard. Chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS. Coupling constants (J) are quoted in hertz (Hz) and splitting patterns are indicated as s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets) and m (multiplet). For ^{13}C NMR spectra, assignments are made from ^{13}C DEPT spectra run in DEPT-90 and DEPT-135 modes. Liquid chromatography mass spectra (MS) were obtained using an LCT Premier Time of Flight instrument and a Quattro Micro triple quadrupole instrument. Elemental analysis for carbon, hydrogen and nitrogen was recorded on a CE440 elemental analyser. Thermal analysis was recorded on a DSC Q1000 instrument. Polymer molecular weights were determined by Intertek MSG, Redcar, UK, by Gel Permeation Chromatography using a Viscotek GPC Max TDA302 instrument and a 2×30 cm Plgel Omnisec GPC column with dimethylacetamide as eluent, flow rate of 0.8 ml min^{-1}, temperature of 50 °C and detection by ELSD@95C. The system was calibrated against a series of linear polystyrene standards covering a range from aprroximately 160 to 6,000,000 Da. Data is presented as weight average molecular weight (M_w) and polydispersity index (M_w/M_n) where M_n is the number average molecular weight.

*4.1.1. 5-Acryloylaminoisophthalic acid (**3**)*[25]. 5-aminoisophthalic acid **2** (1 g, 5.52 mmol) and sodium hydroxide (0.66 g, 16.56 mmol) were added to water (11 ml) and the mixture was cooled to 0 °C in an ice bath. The excess sodium hydroxide served to maintain the pH above 12. Acryloyl chloride (0.62 ml, 6.10 mmol) was added in 0.1 ml portions every 2 min over a 12 min period to the rapidly stirred aqueous suspension. After an additional 2 min the reaction mixture was acidified to pH 2.6, using a pH metre, by the drop-wise addition of concd HCl at 0 °C with stirring. The precipitate was collected by filtration, washed with a little ice cold water and dried in a desiccator to afford **3** (0.76 g, 60%) as a light pink solid: mp 267–272 °C; IR (KBr) ν 3345, 2965, 1716, 1605, 1559, 1201; ^1H NMR (DMSO-d_6) δ 5.81 (1H, dd J=1.5, 10.5 Hz), 6.30 (1H, dd J=1.5, 16.5 Hz), 6.49 (1H, dd J=10.5, 16.5 Hz), 8.17 (1H, s), 8.54 (2H, s), 10.69 (1H, s). MS m/z (%) 236 (M^+, 14), 146 (15), 116 (4), 115 (56), 105 (100), 74 (38), 64 (16). Calcd for $C_{11}H_{10}NO_5$: M, 236.0559. Found: m/z 236.0548.

*4.1.2. Poly-N-5-acrylamidoisophthalic acid (**4**)*[20]. 5-Acryloylaminoisophthalic acid **3** (0.53 g, 2.72 mmol) was refluxed in 5 ml THF at 70 °C for 72 h in the presence of AIBN (30 mg, 0.18 mmol). The solvent was removed using a rotary evaporator to afford **3** (0.53 g, 100% recovery) as a yellow solid, degree of grafting (determined from the relative integration of the aryl*H* and $-CH_2CH_2(CO)-$ resonances) 100%: mp 250–251 °C (decomp.); IR (KBr) ν 3000–3500, 1711, 1603, 1559, 1203; ^1H NMR (DMSO-d_6) δ 1.20–1.80 (br m), 8.17 (1H, s), 8.54 (2H, s), 10.71 (1H, s); M_w 21,600 Da, M_w/M_n 9.0.

4.2. General procedure for the N-protection of amino acids[26]

A suspension of amino acid (20 mmol) and di-*tert*-butyldicarbonate (33.6 mmol) in dioxane (30 ml) and saturated aq sodium bicarbonate solution (40 ml, freshly prepared) was stirred at room temperature for 5 days. The bulk of the dioxane was removed under reduced pressure. Ethyl acetate (30 ml) was added and the mixture was acidified to pH 3–4 by addition of concd HCl. The mixture was extracted with ethyl acetate (3×20 ml). The organic layers were combined, washed with water (2×25 ml), dried over $MgSO_4$ and the solvent evaporated to afford a white waxy solid.

*4.2.1. N-tert-Butoxycarbonyl-6-aminohexanoic acid (**6a**)*[27]. Obtained by the N-protection of 6-aminohexanoic acid to afford 4.54 g (98%): mp 34–36 °C (lit.[27] 38–39 °C); IR (thin film) 3336, 2977, 1710, 1169; ^1H NMR ($CDCl_3$) δ 1.26–1.45 (2H, m), 1.44 (9H, s), 1.62–1.69 (4H, m), 2.35 (2H, t, J=7.5 Hz), 3.10–3.14 (2H, q, J=9 Hz), 4.60 (1H, br s), 5.79 (1H, br s).

*4.2.2. N-tert-Butoxycarbonyl-12-aminododecanoic acid (**6b**)*[27]. Obtained by the N-protection of 12-aminododecanoic acid to afford 7.65 g (96%): mp 83–85 °C (lit.[27] 83.5–84.5 °C); IR (thin film) ν 3369, 2985, 1724, 1687, 1523, 1172; ^1H NMR ($CDCl_3$) δ 1.27 (14H, m), 1.53 (9H, s), 1.50–1.53 (2H, m) 1.58–1.65 (2H, m), 2.34 (2H, t, J=7.5 Hz), 3.07–3.13 (2H, q, J=12 Hz), 4.51 (1H, br s), 5.62 (1H, br s).

4.3. General procedure for the DCC coupling of *N*-protected amino acids 6a and 6b[5]

To a solution of *N*-protected amino acid (20 mmol) in dry DMF (200 ml) was carefully added DCC (4.12 g, 22 mmol) at 0 °C followed by HOBt (2.97 g, 22 mmol) and DIPEA (10.45 ml, 60 mmol). After continuous stirring for 10 min at 0 °C, a solution of 5-aminoisophthalic acid **2** (3.99 g, 22 mmol) in dry DMF (10 ml) was added

dropwise to the reaction mixture at 0 °C. Stirring was continued for 1 h at 0 °C and then overnight at room temperature. The reaction mixture was then cooled to below 4 °C for 30 min to promote the precipitation of the white crystalline side product, DCU. This was then filtered from the reaction mixture and the filtrate was collected and evaporated using a rotary evaporator to remove the bulk of the DMF. The remaining solution was poured onto ice with stirring and left overnight to remove residual DMF and HOBt. The product was collected by suction filtration to afford a white solid.

*4.3.1. 5-(6-(tert-Butoxycarbonylamino)hexanamido)isophthalic acid (**7a**).* Obtained using DCC coupling of *N*-protected amino acid **6a** to afford 7.19 g (91%): mp 179–182 °C; IR (KBr) ν 3361, 3315, 1683, 1605, 1538, 1282, 1167; ^{1}H NMR (DMSO-d_6) δ 1.23–1.40 (2H, m), 1.35 (9H, s), 1.56–1.61 (4H, m), 2.32 (2H, t, J=7.5 Hz), 2.90 (2H, q, J=9 Hz), 6.79 (1H, t, J=6 Hz), 8.14 (1H, s), 8.43 (2H, s), 10.24 (1H, br s), 12.72 (2H, br s); ^{13}C NMR (DMSO-d_6) δ 24.70, 25.89, 28.21, 29.27, 33.30, 36.33, 77.26, 123.35, 124.31, 131.60, 139.81, 155.55, 166.60, 171.68. Anal. Calcd for $C_{19}H_{26}N_2O_7$: C, 57.86; H, 6.64; N, 7.10. Found: C, 57.86; H, 7.16; N, 7.62.

*4.3.2. 5-(6-(tert-Butoxycarbonylamino)dodecanamido)isophthalic acid (**7b**).* Obtained using DCC coupling of *N*-protected amino acid **6b** to afford 8.20 g (86%): mp 182–184 °C; IR (KBr) ν 3352, 1687 (CO), 1607, 1541, 1280, 1169; ^{1}H NMR (DMSO-d_6) δ 1.27 (14H, br s), 1.44 (9H, s), 1.42–1.44 (2H, m) 1.61–1.65 (2H, m), 2.34 (2H, t, J=7.5 Hz), 2.91–2.96 (2H, q, J=12 Hz), 6.71 (1H, br s), 8.14 (1H, s), 8.28 (2H, s), 10.21 (1H, br s), 12.72 (2H, br s); ^{13}C NMR (DMSO-d_6) δ 26.2, 28.2, 28.6, 28.8, 28.9, 28.9, 28.9, 29.4, 36.4, 40.3, 77.2, 123.3, 124.3, 131.8, 139.8, 155.5, 166.5, 171.8. Anal. Calcd for $C_{25}H_{38}N_2O_7$: C, 62.74; H, 8.00; N, 5.85. Found: C, 63.22; H, 8.28; N, 6.40.

4.4. General procedure for the trifluoroacetic acid cleavage of the functionalised *tert*-butyl cpds 7a and 7b and the subsequent formation of their hydrochloride salts[6]

To a solution of the functionalised *tert*-butyl compound (2 mmol) in DCM (10 ml) was added trifluoroacetic acid (10 ml) in one portion at room temperature. The reaction mixture was stirred for 1 h and then evaporated under vacuum to remove the solvent and pumped dry using a high vacuum pump. This afforded the crude trifluoroacetate salt as a light pink solid. This was then dissolved in ethanol (2 ml) containing 1 ml of concd HCl. The mixture was evaporated under vacuum to afford the hydrochloride salt as a yellow solid.

*4.4.1. 5-(3,5-Dicarboxyphenylcarbamoyl)pentylammonium chloride (**8a**).* Obtained by trifluoroacetic acid cleavage of **7b** to afford 0.64 g (97%): mp 300–301 °C (decomp.); IR (KBr) ν 2931, 1699, 1654, 1609, 1565, 1219; ^{1}H NMR (DMSO-d_6) δ 1.20–1.41 (2H, m), 1.43–1.73 (4H, m), 2.32 (2H, t, J=7.5 Hz), 2.70–2.81 (2H, m), 7.89 (2H, br s), 8.11 (1H, s), 8.45 (2H, s), 10.41 (1H, br s); ^{13}C NMR (DMSO-d_6) δ 24.4, 25.4, 26.7, 33.3, 36.0, 123.4, 124.3, 131.6, 139.9, 166.5, 171.6. MS m/z (%) 295 (M^+, 100), 225 (2), 191 (6), 177 (10), 136 (16), 130 (42), 105 (4). Calcd for $C_{14}H_{19}N_2O_5$: M, 295.1294. Found: m/z 295.1284.

*4.4.2. 11-(3,5-Dicarboxyphenylcarbamoyl)undecylammonium chloride (**8b**).* Obtained by the trifluoroacetic acid cleavage of **7b** to afford 0.78 g (97%): mp 300 °C (decomp.); IR (KBr) ν 3490, 2922, 1710, 1606, 1562, 1204; ^{1}H NMR (DMSO-d_6) δ 1.19 (14H, m), 1.38–1.42 (2H, m) 1.47–1.52 (2H, m), 2.26 (2H, t, J=7.5 Hz), 2.66–2.82 (2H, q, J=12 Hz), 7.67 (3H, br s), 8.07 (1H, s), 8.38 (2H, s), 10.25 (1H, br s), 12.72 (2H, br s); ^{13}C NMR (DMSO-d_6) δ 25.0, 25.8, 26.9, 28.5, 28.7, 28.8, 40.0, 123.4, 131.8, 139.8, 166.5, 171.8. MS m/z (%) 379 (M^+, 100), 285 (4), 244 (5), 216 (16), 130 (4), 115 (34), 74 (25). Calcd for $C_{20}H_{31}N_2O_5$: M, 379.2233. Found: m/z 379.2223.

4.5. General procedure for acrylating 8a and 8b[25]

The functionalised hydrochloride salt (7.35 mmol) and sodium hydroxide (1.03 g, 25.73 mol) were added to water (14.5 ml) and the mixture was cooled to 0 °C. The excess sodium hydroxide served to keep the pH above 12. Acryloyl chloride (0.67 ml, 8.3 mmol) was added in 0.1 ml portions every 2 min over a 12 min period to the rapidly stirred aqueous suspension. After an additional 2 min stirring, the reaction mixture was acidified to pH 2.6 by the drop-wise addition of concd HCl while maintaining the temperature at 0 °C. The product precipitated out of solution and was collected by filtration and washed with ice cold water to afford a light pink solid.

*4.5.1. 5-(6-Acylamidohexanamido)isophthalic acid (**9a**).* Obtained by reaction of acryloyl chloride with **4c** to afford 0.97 g (38%): mp 138–142 °C; IR (KBr) ν 3372, 3215, 1702, 1656, 1564, 1260; ^{1}H NMR (DMSO-d_6) δ 1.09–1.32 (2H, m), 1.33–1.69 (4H, m), 2.27 (2H, t, J=7.5 Hz), 3.11–3.15 (2H, m), 5.48 (1H, dd, J=3, 9 Hz), 5.98 (1H, dd, J=3, 18 Hz), 6.15 (1H, dd J=10.5, 16.5 Hz), 7.80 (1H, s), 7.89 (2H, br s), 8.11 (1H, s), 8.45 (2H, s), 10.21 (1H, br s); ^{13}C NMR (DMSO-d_6) δ 25.4, 26.1, 26.7, 28.8, 33.3, 40.3, 123.0, 124.6, 131.9, 133.3, 139.4, 164.4, 167.3, 171.6. MS m/z (%) 349 (M^+, 30), 278 (16), 266 (25), 264 (18), 225 (60), 190 (10), 136 (10), 130 (19), 115 (100), 74 (60), 64 (18). Calcd for $C_{17}H_{21}N_2O_6$: M, 349.1400. Found: m/z 349.1389.

*4.5.2. 5-(12-Acylamidododecanamido)isophthalic acid (**9b**).* Obtained by reaction of acryloyl chloride with **5c** to afford 2.77 g (87%): mp 140–143 °C; IR (KBr) ν 3283, 3115, 1702, 1657, 1622, 1552, 1229; ^{1}H NMR (DMSO-d_6) δ 1.39 (14H, br s), 1.42–1.45 (2H, m), 1.47–1.50 (2H, m), 2.24 (2H, t, J=7.5 Hz), 2.99–3.06 (2H, q, J=12 Hz), 5.48 (1H, dd, J=3, 9 Hz), 5.98 (1H, dd J=3, 15 Hz), 6.14 (1H, dd J=9.6, 17.2 Hz), 8.02 (1H, s), 8.30 (2H, s), 10.11 (1H, br s), 12.72 (2H, br s); ^{13}C NMR (DMSO-d_6) δ 25.8, 26.4, 27.1, 28.3, 28.4, 28.5, 28.7, 28.9, 36.4, 38.5, 122.9, 124.6, 131.9, 133.2, 139.4, 164.4, 167.1, 167.4, 171.6. MS m/z (%) 433 (M^+, 50), 381 (2), 380 (18), 379 (100), 339 (6), 270 (12), 244 (6), 192 (4), 116 (4), 115 (74), 75 (5), 74 (78). Calcd for $C_{23}H_{33}N_2O_6$: M, 433.2339. Found: m/z 433.2331.

4.6. General procedure for the preparation of the functionalised polymers (10a) and (10b) with 100% functionality[3]

The acryloyl compound (1.2 g, 3.45 mmol) was polymerized in DMF (10 ml) at 80 °C for 72 h with AIBN (30 mg, 0.18 mmol). The bulk of the DMF was removed using rotary evaporation and the resulting polymer was precipitated from water and filtered to give a yellow solid.

*4.6.1. Poly-N-(5-(N′-(3,5-dicarboxyphenyl)carbamoyl)pentyl)acrylamide (**10a**).* Compound **10a** (1.05 g, 88% recovery): mp above 250 °C (decomp.); IR (KBr) ν 3338, 3115, 1708, 1651, 1556, 1219; ^{1}H NMR (DMSO-d_6) δ 1.09–1.32 (2H, br m), 1.33–1.69 (4H, m), 2.24–2.27 (2H, m), 3.10–3.15 (2H, m), 7.89 (2H, br s), 8.11 (1H, s), 8.45 (2H, s), 8.82 (1H, s), 10.21 (1H, br s); M_w 84,000 Da; M_w/M_n 17.5.

*4.6.2. Poly-N-(11-(N′-(3, 5-dicarboxyphenyl)carbamoyl)undecyl)acrylamide (**10b**).* Compound **10b** (1.49 g, 100% recovery): mp above 250 °C (decomp.); IR (KBr) ν (KBr) 3337, 3114, 1705, 1652, 1555, 1218; ^{1}H NMR (DMSO-d_6) δ 01.01–1.42 (14H, br s), 1.42–1.45 (2H, m), 1.43–1.56 (2H, m), 2.34 (2H, t, J=7.5 Hz), 2.70–3.74 (2H, q, J=12 Hz), 8.10 (1H, s), 8.43 (2H, s), 10.23 (1H, br s), 12.72 (2H, br s); M_w 68,000 Da, M_w/M_n 26.2.

*4.6.3. 5-Acetamidoisophthalic acid (**11**)[21].* To a stirred solution of 5-aminoisophthalic acid **2** (3.62 g, 20 mmol) in DMF (30 ml), acetic anhydride (2.83 ml, 30 mmol) and acetic acid (0.6 ml, 10 mmol)

were added. The reaction mixture was stirred at room temperature for 4 h. Water (20 ml) was then added and the reaction mixture was allowed to stir for a further 30 min at 0 °C. The precipitate, which formed was isolated by filtration and recrystallised from ethanol to afford **2** (4.21 g, 94%) as a white solid: mp 313–315 °C (decomp.); IR (KBr) ν 3546, 3450, 1722, 1671, 1616, 1573, 1205; ^{1}H NMR (DMSO-d_6) δ 2.16 (3H, s), 8.22 (1H, s), 8.49 (2H, s), 10.39 (1H, br s).

4.7. Crystallizations

All recrystallisations were carried out in 100 ml round bottom flasks. Solutions of L-glutamic acid were prepared in deionised water at the following concentrations: 20 g L^{-1}, 35 g L^{-1}, 45 g L^{-1}, maintained at 18 °C, 38 °C and 45 °C, respectively. The solutions were heated to dissolve the acid and additives. In some cases filtration was necessary prior to recrystallisation. Samples of the α-form of L-glutamic acid were prepared by the method of Garti and Zour[7] as follows: Monosodium-L-glutamate, (5 g, 29.5 mmol), was dissolved in water (50 ml). Concd HCl (2 ml) was added dropwise and the solution was stirred for 10 min at room temperature. A further 1 ml concd HCl was then added dropwise and the resulting precipitate was collected by filtration to yield rhombic crystals (1.99 g, 13.5 mmol, 45.7%), mp 199–204 °C.

4.7.1. Crystal habit. Crystal habits were observed using a Nikon ECLIPSE 50i POL Polarizing Microscope. Crystal pictures were obtained using a Nikon COOLPIX 8400 digital camera with 8.0 effective megapixels.

4.7.2. Powder X-ray diffraction (PXRD). Powder X-ray diffraction was performed at ambient temperature using a Stoe Stadi MP PXRD operating in transmission mode with a linear PSD detector with an anode current of 40 mA, an accelerating voltage of 40 kV and Cu $K\alpha_1$ X-radiation (l=1.5406 Å) over a scan range of 3.5° to 60° 2θ, scanning in steps of 2° for 90 s per step. Samples were held between acetate foils and were not ground. Calculated patterns were generated from crystallographic information files downloaded from the Cambridge Structural Database, using the THEO function on the Stoe WinX^{POW} software with a pseudo-Voigt profile-shape function and a Gauss component of 0.8.

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