Formation of oligopeptides in high yield under simple programmable conditions

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Many high-yielding reactions for forming peptide bonds have been developed but these are complex, requiring activated amino-acid precursors and heterogeneous supports. Herein we demonstrate the programmable one-pot dehydration–hydration condensation of amino acids forming oligopeptide chains in around 50% yield. A digital recursive reactor system was developed to investigate this process, performing these reactions with control over parameters such as temperature, number of cycles, cycle duration, initial monomer concentration and initial pH. Glycine oligopeptides up to 20 amino acids long were formed with very high monomer-to-oligomer conversion, and the majority of these products comprised three amino acid residues or more. Having established the formation of glycine homo-oligopeptides, we then demonstrated the co-condensation of glycine with eight other amino acids (Ala, Asp, Glu, His, Lys, Pro, Thr and Val), incorporating a range of side-chain functionality.
The peptide bonds that link together amino acids into short oligomers and proteins are vital for biology. Because of this biological importance, many high-yielding reactions for forming peptide bonds have been developed, but these typically require activated amino-acid precursors and heterogeneous supports. The formation of peptides from unactivated amino acids is hindered by thermodynamic constraints, thermal decomposition if heated and requires a catalyst if yields higher than ca. 1% are to be achieved. In addition, the formation of peptide bonds between amino acid monomers and the emergence of sequence bias is crucial to understanding the emergence of life.

Although peptide bond formation has been widely established, obtaining oligopeptides in high yields requires catalysis, to overcome kinetic limitations, and activation of the amino acid monomers, to overcome thermodynamic limitations. Without these, studies have explored peptide synthesis on clays, minerals, at air–water interfaces, on metal oxide surfaces, and under hydrothermal conditions, resulting in very low yields (typically <1%) of oligomeric products (where n > 3). The difficulty arises as the condensation of amino acid monomers to form peptide bonds in aqueous solution (Fig. 1) is hampered by both unfavourable kinetics and thermodynamics, that is, the formation of peptide bonds is slow, and in aqueous solution the reagents are thermodynamically more stable than the peptide products.

In this work, we demonstrate an uncatalysed, amino acid oligomerization reaction producing unprecedentedly high yields of long oligomers using a very simple approach with a programmable reactor system allowing the exploration of many experimental parameters. (see Supplementary Figs 1–6).

**Results**

**The abiotic peptide synthesizer system.** In this work, we set out to explore the formation of peptide oligomers under the simplest possible ‘one-pot’ reaction conditions. To do this, aqueous solutions of amino acid monomers were added to a hot empty glass vial and the water was removed by continuous heating. For subsequent dehydration–hydration cycles, further amounts of water were added to the reaction vials and were again allowed to completely evaporate. By taking this approach, we aimed to explore the formation of peptide bonds with minimal chemical inputs, see Fig. 2. Our investigations showed that even the simplest process parameters (that is, just a single addition–dehydration step) give high conversion of amino acid monomers to peptide oligomers. As we wished to investigate many different combinations of conditions (temperature, concentration of starting materials, pH and number of dehydration–hydration cycles), we designed the ‘abiotic peptide synthesizer’ (APS), a computer-controlled reaction system that allowed us to run several reactions in parallel (see Fig. 2b), and automatically vary both the input and process variables.

A typical reaction run involved injection (10 ml min⁻¹) of an aqueous solution of glycine (4 ml, 0.0875 M) containing NaCl (0.25 M), pH adjusted with NaOH (to 9.8), into a pre-heated vial (T = 90 °C–130 °C), which was then maintained at that temperature for ~15 h, evaporating the solution to dryness (the ‘dehydration step’). Subsequent cycles began with rehydration of the sample with 4 ml of water (the ‘hydration step’) and proceeded similarly; after the final cycle, the vial was allowed to cool to room temperature. To prepare a solution for analysis, 8 ml of water was then added; typically, some insoluble precipitate is also observed, which was analysed separately. After only one dehydration–hydration cycle we can already observe oligomers in solution (up to Gly₁₂) in up to around 50% yield by ion-pairing high performance liquid chromatography (IP-HPLC, see Methods section and Supplementary Figs 7–22) along with some cyclic glycine dimer (diketopiperazine DKP, not included in yields). Although our reaction conditions incorporate some NaCl (to maintain ionic strength at a similar order of magnitude in the absence of strong base to adjust pH), these conditions are very different to many previous studies (where often [NaCl] >> [Gly]). Furthermore, our observations suggest that NaCl can be omitted, without significant loss of yield.

**Analysis of the products.** Size exclusion chromatography–mass spectrometry (SEC-MS) was used to further confirm the identity of the oligomeric products and the presence of peptide bonds, revealing a range of oligomers that yielded tandem mass spectrometry (MS/MS) fragmentation patterns consistent with a peptide structure, see Fig. 3a,b (see Supplementary Figs 23–41). This was further corroborated by infrared analysis of precipitate (consistent with oligomer standards, see Supplementary Figs 42 and 43, and Fig. 3c,d), proton nuclear magnetic resonance spectroscopy (¹H–NMR, see Supplementary Figs 44 and 45) and Biuret assay (a test for peptide oligomers, see Supplementary Figs 46–48).

**Exploring the parameter space.** One important aspect of this work was the development of a robotic protocol to explore the parameter space for peptide bond formation. To do this, we constructed a robotic system to automatically search the parameter space. This is because we have previously found that automation and feedback can allow even simple systems to exhibit interesting outcomes. To establish a feasible range of dehydration times for glycine oligomer formation, APS reactions were carried with dehydration times between 1 and 24 h. IP-HPLC analyses of the resulting soluble products showed that longer reaction times led to progressively longer oligomer products; products up to Gly₁₂ could be observed after a single dehydration–hydration cycle (Fig. 4). Furthermore, significant quantities of insoluble products were observed in some of these reactions. To produce a solution amenable to IP-HPLC analysis, these precipitates were washed with an aqueous solution of 0.1% v/v trifluoroacetic acid; although not dissolving all the material, it was possible to observe larger oligomeric glycine species in the fraction which was dissolved, and this comprised mostly of higher oligomers (n > 5, see Fig. 4b). Although not a quantitative technique, matrix-assisted laser desorption/ionization analysis of these insoluble fractions yielded evidence of oligomers > 20-mer (see Supplementary Figs 40 and 41).

Having demonstrated unactivated glycine oligomerization, we used the APS to systematically investigate the influence of other variables such as temperature, pH, number of cycles and cycle duration on the distribution of the oligopeptides formed (see Fig. 5). On raising the temperature of reaction from 90 °C to 130 °C, we observed a general increase in yield (from <1% after 1 h at 90 °C to ca. 50% after 15 h at 130 °C; see Fig. 5a). However, later in reactions at higher temperatures, we also observed the appearance of a brown colour (from a colourless solution; see Supplementary Fig. 11) and it is noteworthy that this coincides with an apparent drop in solution yields. This may be due to both precipitation of longer oligomer products or decomposition.

![Figure 1](https://example.com/f1.png) **Figure 1 | Peptide bond formation.** Scheme showing equilibrium and ΔG° for peptide bond formation in aqueous solution. The reaction is represented as follows:

\[\text{R-NH_3} + \text{O-R-NH_3} \rightleftharpoons \text{R-NH-CO-NH-R} + \text{H_2O}\]

\[\Delta G° = -8.16 \text{ kJ mol}^{-1} (R = \text{H; Glycine} = 15.2 \text{ kJ mol}^{-1})\]
Both are possible, but we note that no significant new peaks are resolved in IP-HPLC for decomposition products. Setting the pH of the amino acid input solutions was found to influence the reaction (see Fig. 5b); we observed a \(0.1\%\) yield at pH 6.1, rising to \(45\%\) yield at pH 9.75 in more basic conditions, and to \(20\%\) in more acidic conditions.

We also found that the formation of oligopeptides is possible over a monomer concentration range of \(10^{-4}\) to \(10^{-1}\) M.
As the number of cycles increases the distribution of oligomer chain lengths observed in solution shifts. The yield of the lower oligomers decreases, whereas that of the longer oligomers in solution remains fixed and the amount of solid material precipitated increases. The yields achieved by the process described above are considerably in excess of those previously reported to result from similar reactions; this is probably the result of exploring the effects of several parameters at once, without the constraint of hypotheses on the nature of optimum conditions. Although the system under consideration is more complex than might previously have been imagined (and mechanistic explanation of all the variance in reactivity observed is beyond the scope of this communication), we note that the starting pH is of particular importance (Fig. 5b and Supplementary Figs 12 and 13), with unprecedented yields observed from acidic and basic reaction mixtures. This is readily rationalized mechanistically: it has previously been shown that glycine dimerization proceeds most readily at high pH (ref. 18) where unprotonated amine groups are more nucleophilic, and hence more readily attack partner carbonyls, whereas at neutral pH glycine monomers are zwitterionic and interactions between the charged amino group and a charged carboxyl group reduce reactivity. The oligomerization of glycine under acidic conditions has not attracted particular attention because of the poor nucleophilicity of protonated amines; however, we note that acid catalysis should not be unexpected, as the OH group of the carboxylate becomes a better leaving group (H₂O) on protonation and equilibria supplying a small amount of deprotonated amines should always be operative.

Making and breaking peptide bonds. In addition to the oligomerization of glycine, we found that reaction of both glycinamide and DKP produce reasonable yields (> 10%) at 130 °C, giving oligomers up to 10-mer (see Supplementary Figs 16 and 17). The role of DKP has been subject to debate: either seen as a ‘dead end’/thermodynamic ‘sink’ or as able to react (often with caveats such as the presence of ‘free’ amines). Observation of

(see Supplementary Fig. 15 and Supplementary Table 4). As the number of cycles increases the distribution of oligomer chain lengths observed in solution shifts. The yield of the lower oligomers decreases, whereas that of the longer oligomers in solution remains fixed and the amount of solid material precipitated increases (see Supplementary Fig. 14 and Supplementary Table 3). The yields achieved by the process described above are considerably in excess of those previously reported to result from similar reactions; this is probably the result of exploring the effects of several parameters at once, without the constraint of hypotheses on the nature of optimum conditions. Although the system under consideration is more complex than might previously have been imagined (and mechanistic explanation of all the variance in reactivity observed is beyond the scope of this communication), we note that the starting pH is of particular importance (Fig. 5b and Supplementary Figs 12 and 13), with unprecedented yields observed from acidic and basic reaction mixtures. This is readily rationalized mechanistically: it has previously been shown that glycine dimerization proceeds most readily at high pH (ref. 18) where unprotonated amine groups are more nucleophilic, and hence more readily attack partner carbonyls, whereas at neutral pH glycine monomers are zwitterionic and interactions between the charged amino group and a charged carboxyl group reduce reactivity. The oligomerization of glycine under acidic conditions has not attracted particular attention because of the poor nucleophilicity of protonated amines; however, we note that acid catalysis should not be unexpected, as the OH group of the carboxylate becomes a better leaving group (H₂O) on protonation and equilibria supplying a small amount of deprotonated amines should always be operative.

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condensation of these amides and of possible traces of glycine monomer in DKP reactions lead us to pose an important question: are peptide bonds being concurrently made and broken during this process? To test this, we studied the reaction of linear Gly₂ dimers under the same conditions. Along with the series of event-numbered Glyₓ oligomers expected if only bond formation was occurring, we observed the formation of an odd-numbered series (x = 3, 5, 7, etc.; see Supplementary Figs 19 and 20). This provides clear evidence that peptide bonds are both being formed and being broken concurrently, raising the possibility of dynamic combinatorial processes.

Heteropolymers and expansion to other amino acids. Having established the formation of glycine homo-oligopeptides, we made some exploration of the co-condensation of glycine with several other amino acids (Ala, Asp, Glu, His, Lys, Pro, Thr and Val). In all of these cases, reverse-phase (RP)-HPLC-MS analysis established the formation of glycine homo-oligopeptides, we combinational processes. and being broken concurrently, raising the possibility of dynamic combinatorial processes.

Methods

Apparatus. The synthesis took place in a Bespoke automated apparatus comprising a set of programmable syringe pumps (C3000 Tricontinent), which were employed to flow the solutions to the heated reaction vessels. The pumps were controlled employing in-house developed LabView applications. Standard PEEK fittings were used to connect the tubing (180 mm OD, 0.3 mm ID) and the reaction vessels. Custom three-dimensional printed caps/fittings were manufactured for the reaction vessels. Two different contact hotplates (RCT basic, IKA) fitted with DrySyn heat-transfer blocks were used in parallel, to perform an array of experiments under different temperature conditions (see Supplementary Figs 1 and 2).

Operation and programme. The unit operations of each cycle are controlled by LabView. We designed a programme capable of controlling the flow rate of addition, volume and cycle time of each individual experiment within a continuous experiment (see Supplementary Figs 3–6 and Supplementary Methods). Each one of these values can be easily modified between experiments, as well as the total number of cycles. Before starting the experiment, the desired values were entered in the programme and the experiments were left running autonomously over a specific period of time (depending on the number of cycles).

A typical peptide synthesis experiment involved the following: (a) the preparation of a dilute solution of starting material was performed by taking an aliquot of 350 µl from a 1 M solution of glycine, to which we subsequently added 1 ml of a 1 M NaCl solution and 2.5 ml of (HPLC) water, and finally the pH was adjusted to 9.8 by adding 100 µl of 1 M NaOH. (b) Glass reaction vessels were placed in the corresponding DrySyn hotplate inserts. Custom-made three-dimensional printed polypropylene lids with integrated holes were placed on each vial to connect them to the pumps, which facilitated the evaporation during the drying step. Water solutions were connected to each individual pump to deliver a given volume in each re-hydrating step. (c) Then, the prepared solution was injected in a pre-heated vial (T = 130°C). (d) The process inputs (volume, flow rate, dehydration time and number of cycles) were entered for each pump or set of pumps. The pumps were initialized and tested before starting the experiment, to ensure their correct functioning. Finally, the array of experiments was started by pressing the START button. (e) After initializing the programme, the vials were kept at 130°C for a given time, to evaporate the solution to complete dryness. Once a cycle was finished, the process was restarted by rehydrating the sample with 4 ml of HPLC water. (f) Once finished, products were collected for analysis by adding 8 ml of a 0.1% trifluoroacetic acid aqueous solution. Then, 500 µl of the extracted sample were taken for HPLC analysis.

Although the reactions shown here were performed in glass vials, we note that the same series of oligomeric products were also observed if the reactions were run in Teflon reactors (see Supplementary Fig. 18). Although NaCl is present in these reactions, omission of NaCl in otherwise identical reactions resulted in no significant drop in yield (see Supplementary Information, Supplementary Fig. 21). Furthermore, although NaOH was used to adjust pH, reactions using LiOH instead show that Na⁺ is not crucial (see Supplementary Figs 22 and 23).

Determination of soluble oligomer yields. The concentration of the smaller soluble oligomer products (1-mer to 6-mer; also DKP) was established by integration of absorbance values (195 nm) and calibration with commercially available standards. The calibration constants for larger oligomers were estimated based on the mean absorbance per glycine unit in the larger standards, which was observed to become approximately constant > 3-mer (see Supplementary Figs 7 and 8). The yield was then calculated as a proportion of glycine (or glycine oligomer) starting material input. The data are averaged over three repetitions and error bars show the s.d.

IP-HPLC analysis. IP-HPLC analysis was performed using an Agilent 1100 HPLC system fitted with a reversed-phase C18 column (Phenomenex Luna, 300 x 7.8 mm). Samples were injected in 5 µl aliquots and eluted isocratically at 0.3 ml min⁻¹ with a mobile phase consisting of 50 mM KH₂PO₄ and 7.2 mM C₆H₁₃SO₃Na solution, adjusted to pH 2.5 using H₃PO₄. The oligomeric products were detected at 195 nm and the retention times confirmed by comparison with premade standards containing glycine monomer, glycine anhydride, as well as glycine peptide oligomers (n = 2–6). The instrument was controlled and the resulting data analysed using Agilent Technologies OpenLAB Software.
**SEC-MS analysis.** SEC-MS analyses were performed (also with an Agilent 1100 system fitted with a Polysacrylyl-GPC-P-1,100 column (Phenomenex, 300 × 7.8 mm) and Polysacrylyl-GPC-P-5 column (Phenomenex, 200 × 2.7 mm) by using a Thermo Scientific LTQ Orbitrap XL apparatus. Sample was attempted by solvent-free MALDI, initially with CHCA (μ-Cyano-4-hydroxycinnamic acid) matrix typically used for peptide samples. However, no polymeric species and only matrix ions were observed. When the analysis was repeated with DHB (2,5-dihydroxycinnamic acid) matrix, four oligomeric series were observed in addition to matrix ions. The four ions all show the expected repeat unit mass of 57 Da and correspond to [M + H]⁺, [M + Na]⁺, [M + K]⁺ and the MALDI artefact [M − H + 2Na]⁺ (see Supplementary Figs 40 and 41).

**Transmission infrared spectroscopy.** Transmission infrared spectroscopy was performed on samples in the solid phase using a Thermo Scientific Nicolet iS5 instrument with Specac Golden Gate attachment and processed with OMNIC software (see Supplementary Figs 42 and 43 and Supplementary Table 5).

**3H-NMR spectrometry.** 3H-NMR spectra were recorded on a Bruker Avance III (500.2 MHz) using the deuterated solvent as the lock and the residual solvent as the reference. All spectra were run in D2O (see Supplementary Figs 44 and 45).

**Qualitative chemical testing for peptide bonds.** Qualitative chemical testing for peptide bonds was performed using the Biuret test. One millilitre of Biuret reagent (hydrated copper (II) sulfate, sodium hydroxide (NaOH) and potassium sodium tartrate) was added to a solution of ~5 mg amino acid/polyamino acid in 1 ml of fresh 0.1 M sodium hydroxide solution. A positive test for peptide bonds is shown by a colour change from pale blue to violet. Further quantitative analysis was performed (see Supplementary Table 6 and Supplementary Methods).

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Author contributions

L.C. conceived the idea, designed the project and coordinated the efforts of the research team with A.S. and G.C., M.R.G. and A.S. contributed equally. M.R.G. developed the synthetic system, the protocols with designs and guidance from L.C., and A.S. the analytical protocols. A.S. and M.R.G. did most of the analysis together with advice from L.C., G.C. and I.S.M. helped with other analytical experiments. Z.H. together with M.P.L. wrote the software for the control of the system. L.C. co-wrote the paper with input from all the authors.

Additional information

Supplementary Information accompanies this paper at http://www.nature.com/naturecommunications

Competing financial interests: A patent application is being filed based on the work reported in the manuscript.

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