Pasteur Made Simple - Mechanochemical Transformation of Racemic Amino Acid Crystals into Racemic Conglomerate Crystals

In Memoriam Margarita Salas (1938-2019), an outstanding scientist

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Table of Contents

S.1 Materials and methods

S.2 Synthetic procedures

S.2.1 Procedure for valine racemic conglomerate formation *via* ball-milling

S.2.2 Procedure for leucine racemic conglomerate formation *via* ball-milling

S.2.3 Procedure for isoleucine racemic conglomerate formation *via* ball-milling

S.2.4 Procedure for racemic conglomerate formation *via* neat ball-milling

S.2.5 Procedure for racemic conglomerate formation *via* stirred slurry

S.3 Powder X-ray diffractograms of neat milling products

S.4 Solvent screening on milling product powder X-ray diffractograms

S.5 *Ex-situ* time-monitored powder x-ray diffractogram of racemic conglomerate formation *via* slurry method

S.6 Thermogravimetric analysis/differential scanning calorimetry (TGA/DSC)

S.7 ^{13}C solid-state NMR of racemic conglomerate formation *via* mechanochemical milling

S.8 X-ray photoelectron spectroscopy (XPS)

S.9 Zinc and amino acid separation

S10 References

S.1 Materials and methods

All materials were used without further purification unless otherwise specified. Amino acids (DL-valine, L-valine, DL-leucine, D-leucine, L-leucine, DL-isoleucine and L-isoleucine) were obtained from Alfa Aesar.

S.1.1 Powder x-ray diffraction (PXRD)

Powder XRD of milled reactions were obtained in 2θ range from 5° to 40° on a Bruker D2 PHASER X-Ray Diffractometer equipped with a Cu-K_a ($\lambda = 1.54$Å) source, LinxEye detector and a Ni filter. Powder XRD for slurry-based results were obtained on a Bruker ADVANCE D8 X-Ray Diffractometer with a Cu-K_a ($\lambda = 1.54$Å) source, LinxEye detector and a Ni filter.

S.1.2 Thermal analysis

Simultaneous thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) was conducted on a TGA/DSC 1 thermal balance (Mettler-Toledo), with sample size ranging from 4 mg to 8 mg in an open 70 μL alumina crucible. All measurements were done with a dynamic atmosphere of air (gas flow of 25 mL/min), with heating up to 800 °C at a constant rate of 10 °C/min.

S.1.3 Solid-state NMR spectroscopy

^{13}C CPMAS spectra were acquired on a Varian VNMRS (now Agilent, Santa Clara, CA, USA) spectrometer operating at 399.8 MHz for 1H and 100.5 MHz for ^{13}C using a 4 mm double-resonance Varian Chemagnetics T3 probe. The samples were spun at 13 kHz and acquired in 64 or 128 scans, using a recycle delay of 5 s with a contact time of 2 ms at a ^{13}C rf field of approximately 60 kHz. SPINAL-64 decoupling at a rf field of 90 kHz was applied during acquisition. Spectra were referenced using the carbonyl carbon signal in glycine at 176.4 ppm with respect to TMS.

S.1.4 X-ray photoelectron spectroscopy (XPS)

Analysis was performed on a Fisher Scientific Kα spectrometer using a spot size of 200 μm, running 3 survey scans at 200 mV for 50 ms residence times and 10 scans for specific elements

(similarly at residence times of 50 ms). Deconvolution and peak position were determined using Avantage software.

S.2 Synthetic Procedures

Mechanochemical experiments were carried out in a Teflon or Zirconia milling jar, as indicated below, of 15 mL volume along with a one 7 mm diameter (3.25 g) zirconia ball in either a Retsch MM400 or Retsch 200 operated at 30 Hz or 25 Hz, respectively, as indicated below. All material was used without further treatment.

S.2.1 Procedure for valine racemic conglomerate formation *via* ball-milling

A solid mixture of DL-valine (200 mg, 1.7 mmol) and ZnO (100 mg, 1.22 mmol, 50% wt/wt) was placed in a 15 mL Teflon jar along with 100 μL and milled at 25 Hz for 30 minutes. Product was analysed by PXRD in order to verify conversion from the racemic phase to the conglomerate phase.

S.2.2 Procedure for leucine racemic conglomerate formation *via* ball-milling

A solid mixture of DL-leucine (200mg, 1.53mmol) and ZnO (100 mg, 1.22 mmol, 50% wt/wt) was placed in a 15 mL Teflon jar along with 100 μL and milled at 25 Hz for 30 minutes. Product was analysed by PXRD in order to verify conversion from the racemic phase to the conglomerate phase.

S.2.3 Procedure for isoleucine racemic conglomerate formation *via* ball-milling

A solid mixture of DL-isoleucine (200 mg, 1.53 mmol) and ZnO (100 mg, 1.22 mmol, 50% wt/wt) was placed in a 15 mL Teflon jar along with 100 μL of methanol and milled at 25 Hz for 30 minutes. Product was analysed by PXRD in order to verify conversion from the racemic phase to the conglomerate phase.

S.2.4 Procedure for racemic conglomerate formation *via* neat ball-milling

A solid mixture of DL-valine (200 mg, 1.7 mmol), DL-leucine (200 mg, 1.7 mmol) or DL-isoleucine (200 mg, 1.53 mmol) and ZnO (100 mg, 1.22 mmol, 50% wt/wt) was placed in a 15 mL Zirconia jar and milled at 30 Hz for 60 minutes. Product was analysed by PXRD in order to verify conversion from the racemic phase to the conglomerate phase.

S.2.5 Procedure for conglomerate formation *via* stirred slurry

DL-leucine (400 mg, 3.05 mmol), DL-isoleucine (400 mg, 3.05 mmol) or DL-valine (400 mg, 3.41 mmol), was suspended in 6 mL of ethanol in the presence of 400 mg of zinc powder (30 μm) along with 8 g of 3 mm diameter glass balls and allowed to stir at 600 RPM for 24 to 48 hours. Conglomerate formation was monitored *via* PXRD.

S.3 Powder X-ray diffractograms of neat milling products

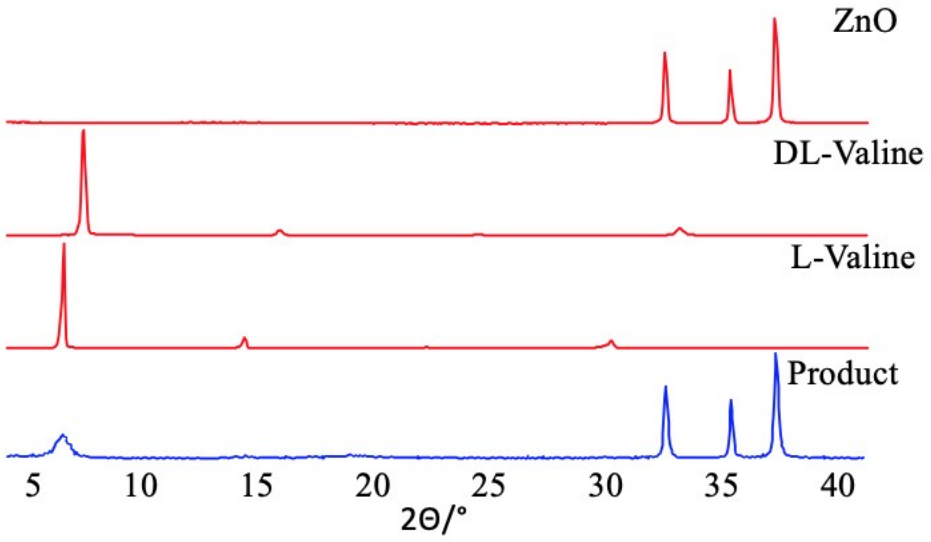

Figure S.3.1 Diffractograms of the mechanochemical ball milling conversion of racemic valine crystals into their respective racemic conglomerate crystals, monitored *via* PXRD. Milling conditions: 50% wt/wt (ZnO : amino acids) – 200 mg of amino acid, 100 mg of ZnO; 15 mL Teflon jar with a 10 mm zirconium ball; milled at 30 Hz for 60 minutes. The L-valine pattern is used as a reference, yet the resulting product is a racemic conglomerate of valine.

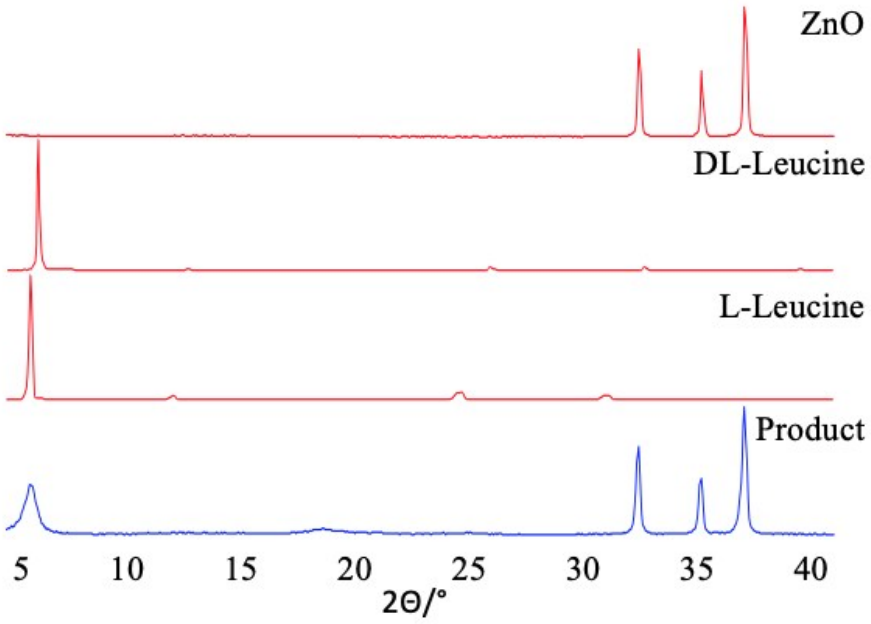

Figure S.3.2 Diffractogram of the mechanochemical ball milling conversion of racemic leucine crystals into their respective racemic conglomerate crystals, monitored *via* PXRD. Milling conditions: 50% wt/wt (ZnO:amino acids) – 200 mg of amino acid, 100 mg of ZnO; 15 mL Teflon jar with a 10 mm zirconium ball; milled at 30 Hz for 60 minutes. The L-leucine pattern is used as a reference, yet the resulting product is a racemic conglomerate of leucine.

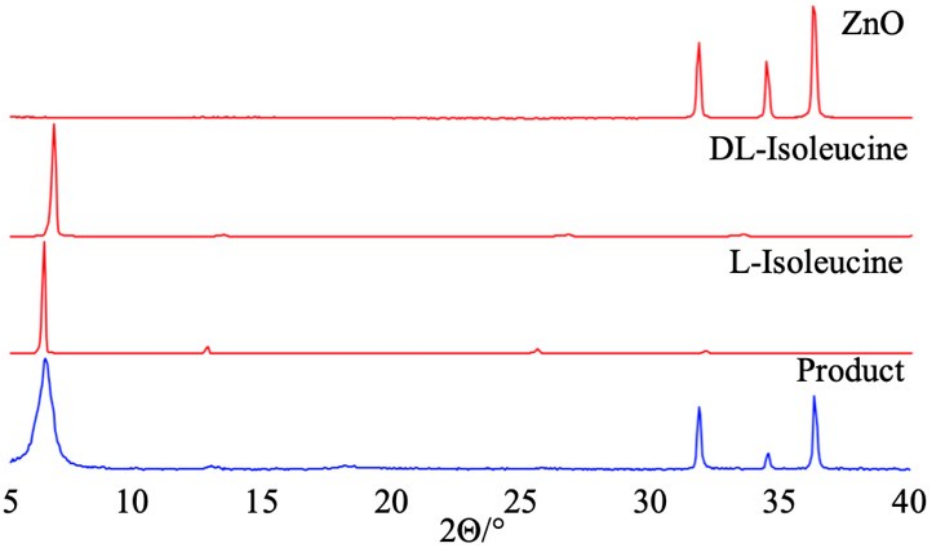

Figure S.3.3 Diffractogram of the mechanochemical ball milling conversion of racemic isoleucine crystals into their respective racemic conglomerate crystals, monitored *via* PXRD. Milling conditions: 50% wt/wt (ZnO:amino acids) – 200 mg of amino acid, 100 mg of ZnO; 15 mL Teflon jar with a 10 mm zirconium ball; milled at 30 Hz for 60 minutes. The L-isoleucine pattern is used as a reference, yet the resulting product is a racemic conglomerate of isoleucine.

S.4 Solvent screening powder x-ray diffractograms

Leucine is used as a model system

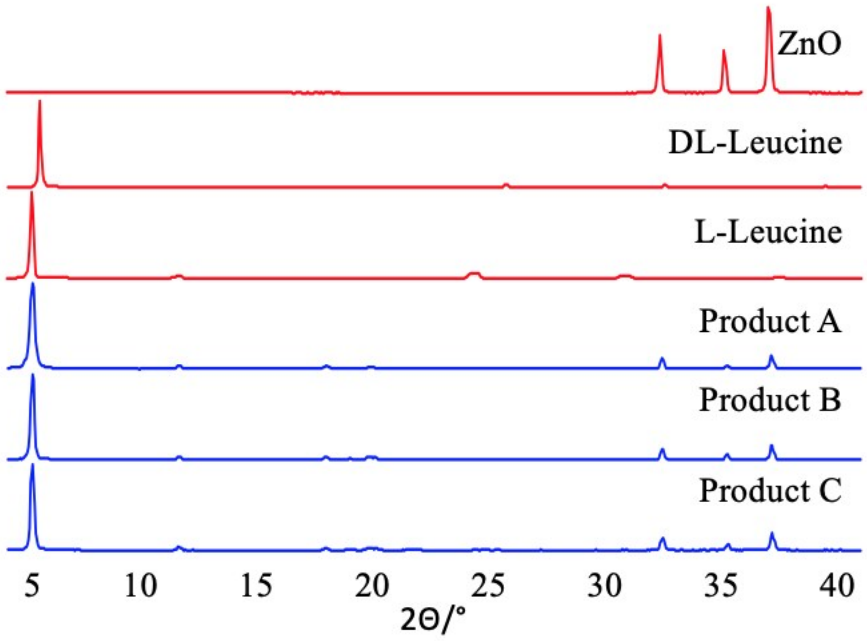

Figure S.4.1 Diffractogram of the mechanochemical ball milling conversion of racemic leucine crystals into their respective racemic conglomerate crystals with various solvents, monitored *via* PXRD. Milling conditions: 50% wt/wt (ZnO:amino acids) – 200 mg of amino acid, 100 mg of ZnO; 15 mL Teflon jar with a 10 mm zirconium ball; milled at 30 Hz for 60 minutes and 100 μL of toluene (product A), acetonitrile (product B) and water (product C). The L-leucine pattern is used as a reference, yet the resulting product is a racemic conglomerate of leucine.

S.5 *Ex-situ* time-monitored powder x-ray diffractograms of racemic conglomerate formation *via* slurry method

Valine is used as a model system

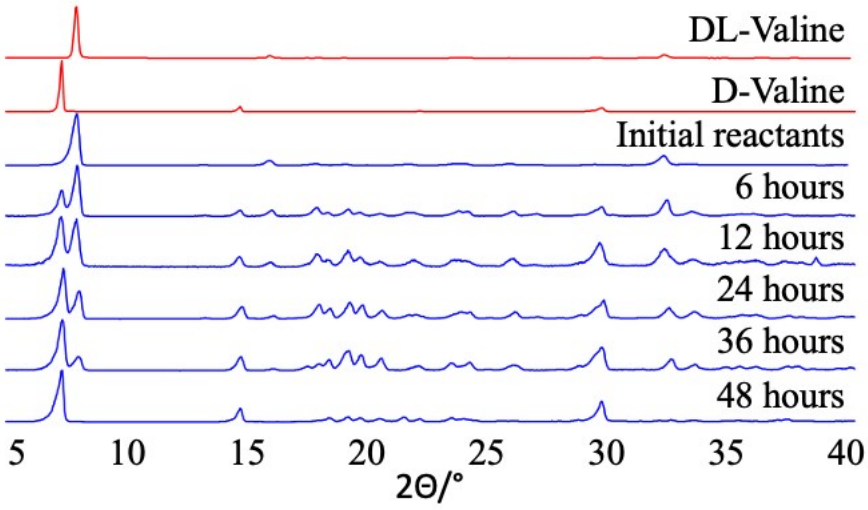

Figure S.5.1 Diffractogram of the slurry stirring conversion of racemic valine crystals into their respective racemic conglomerate crystals monitored ex-situ *via* powder XRD. Experimental conditions: 400 mg of amino acid, 400 mg of Zn powder (30-μm); 8 g of 3 mm diameter glass balls and allowed to stir at 600 RPM for 48 hours. The D-valine pattern is used as a reference, yet the resulting product is a racemic conglomerate of valine.

S.6 Thermogravimetric analysis / differential scanning calorimetry (TGA/DSC)

Leucine is used as a model system

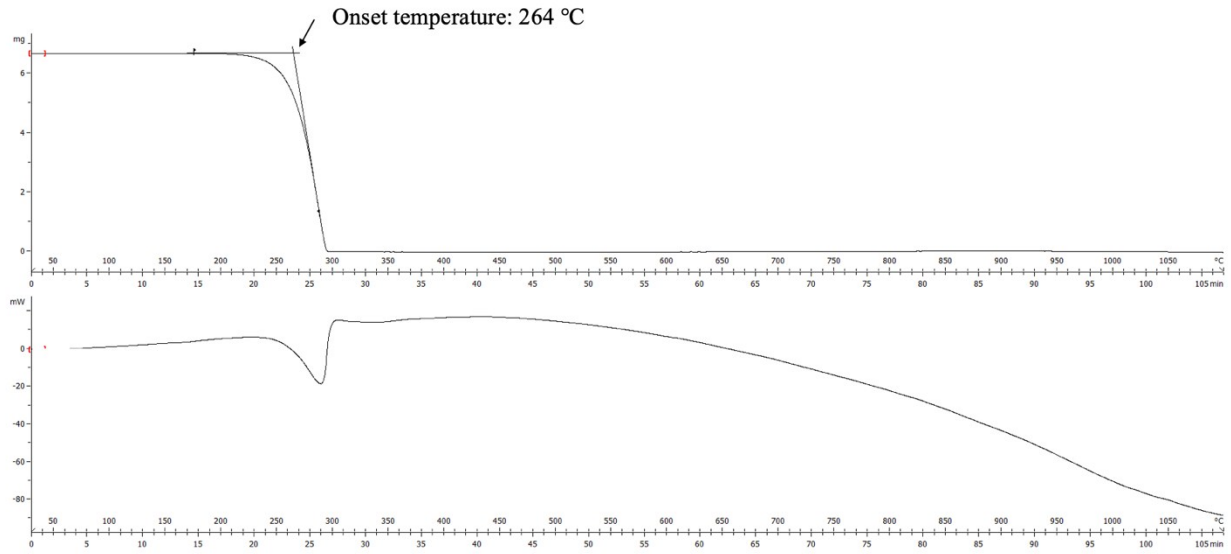

Figure S.6.1 TGA (top) showing thermal response of L-leucine conglomerate. Decomposition onset temperature is 264 °C. DSC (bottom) shows heat flow response.

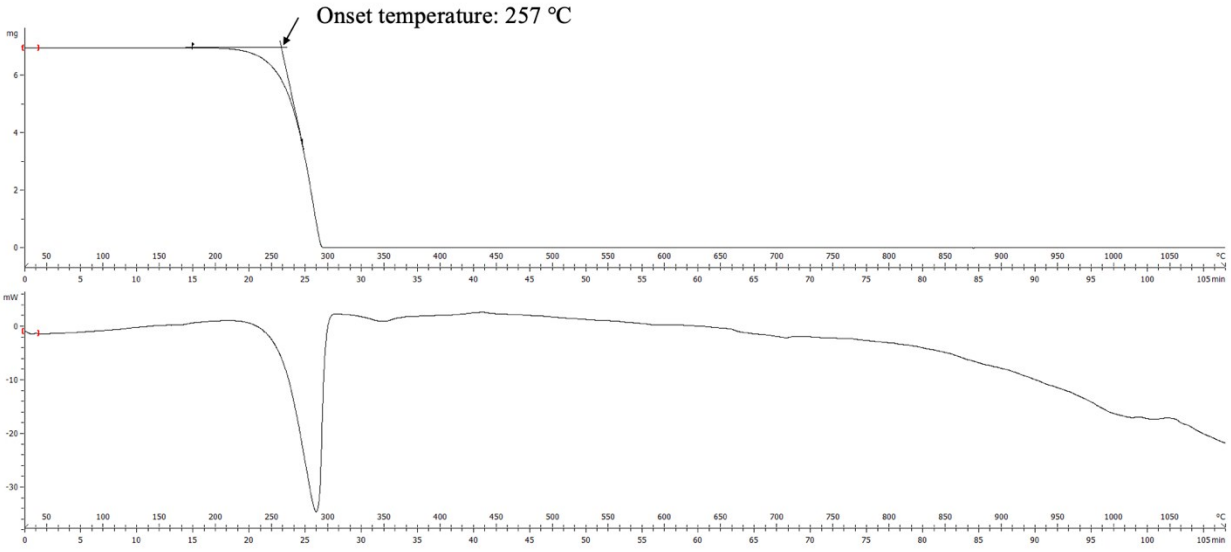

Figure S.6.2 TGA (top) showing thermal response of DL-leucine. Decomposition onset temperature is 257 °C. DSC (bottom) shows heat flow response.

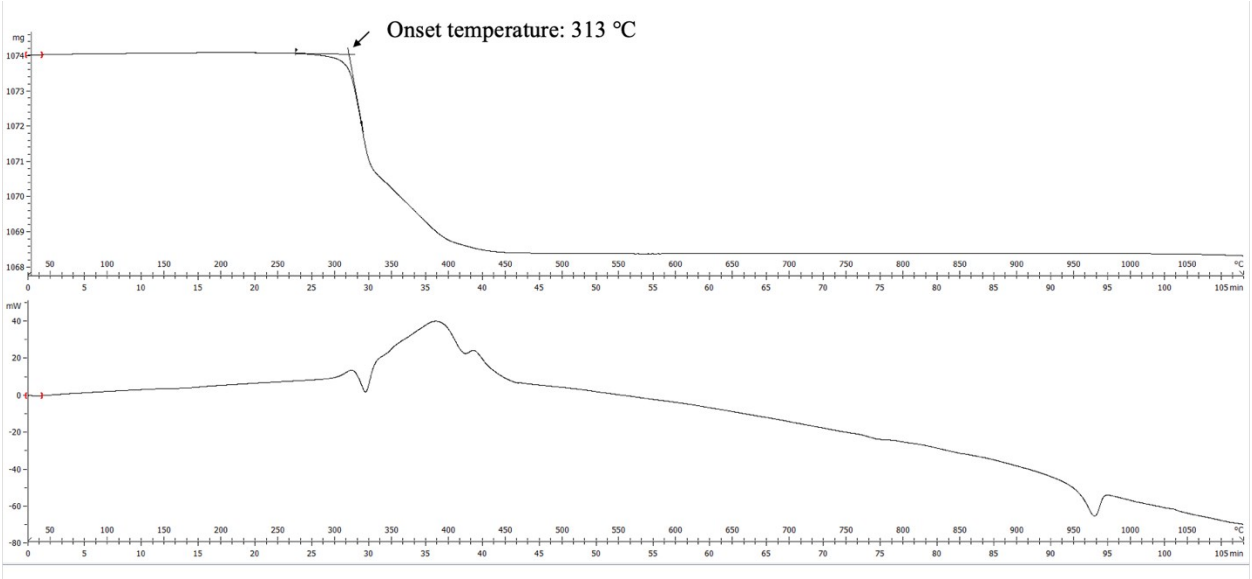

Figure S.6.3 TGA (top) showing thermal response of the conglomerate product resulting from milling DL-leucine with ZnO in the presence of methanol. Decomposition onset temperature is 313 °C. DSC (bottom) shows heat flow response.

S.7 ^{13}C solid-state NMR of racemic conglomerate formation *via* mechanochemical milling

Leucine is used as a model system

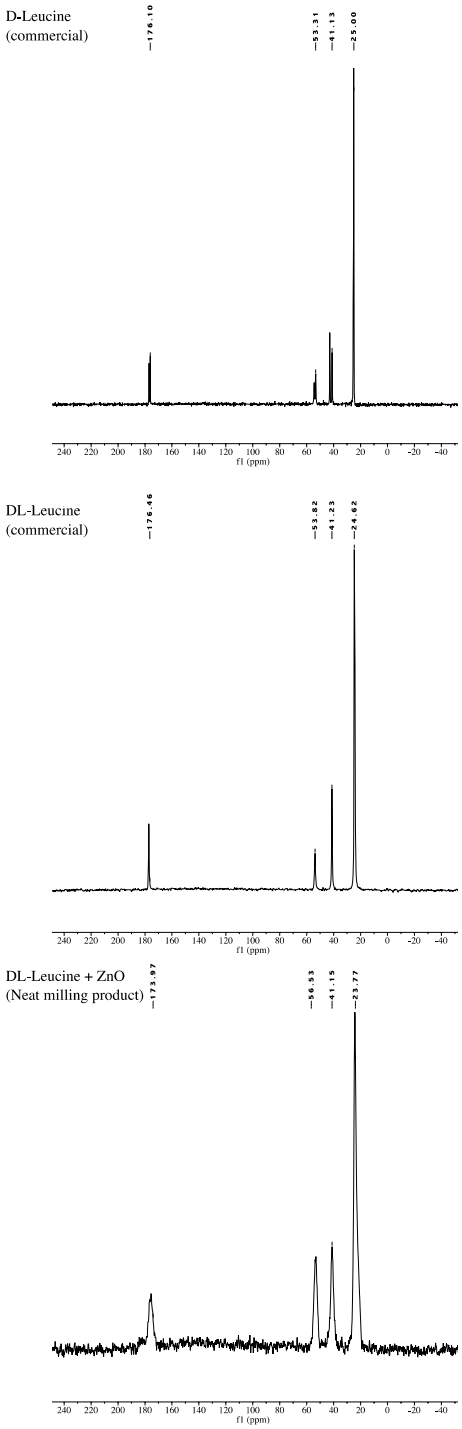

Figure S.7.1 ^{13}C solid-state NMR spectrum of commercial D-leucine (*top*), commercial DL-leucine (*middle*) and neat milling product of DL-leucine and ZnO (*bottom*) (prepared as in *S.3.2*).

S.8 XPS of racemic conglomerate formation *via* mechanochemical milling

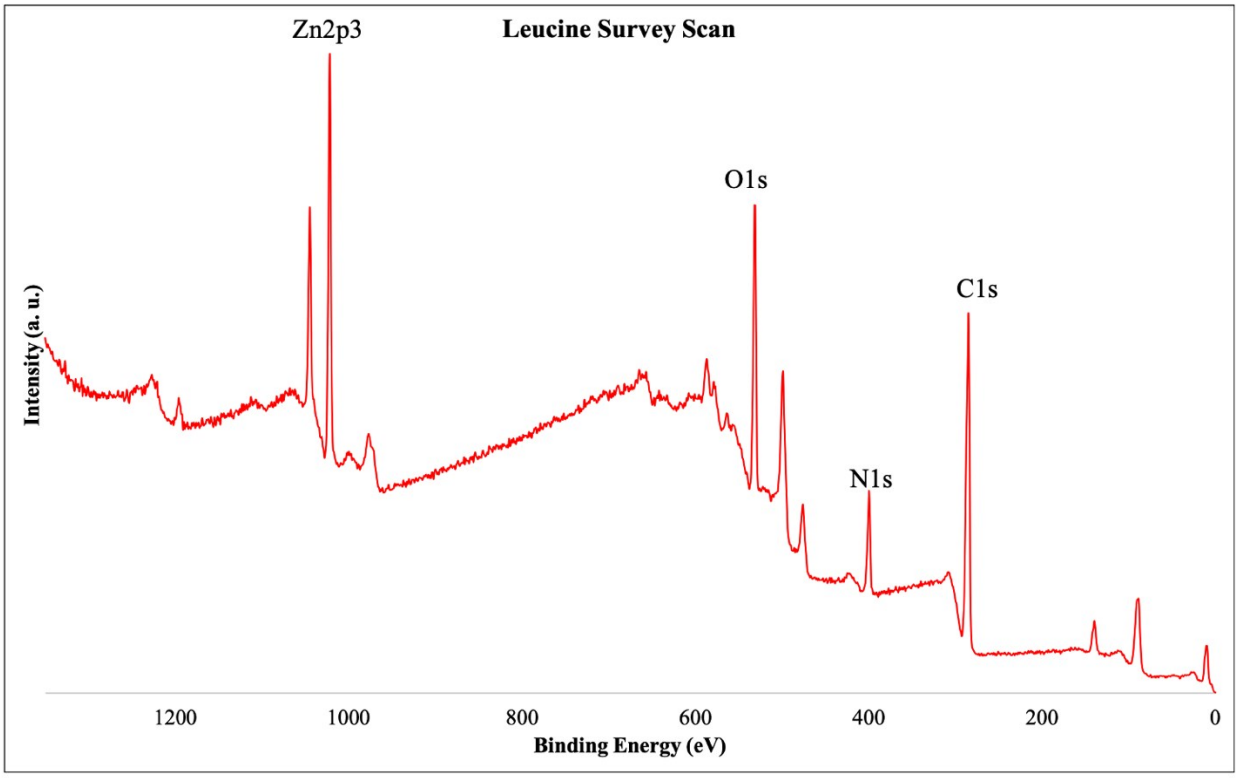

Figure S.8.1 XPS survey spectrum of leucine conglomerate prepared as in *S.2.1* with characteristic binding energies of components labelled.

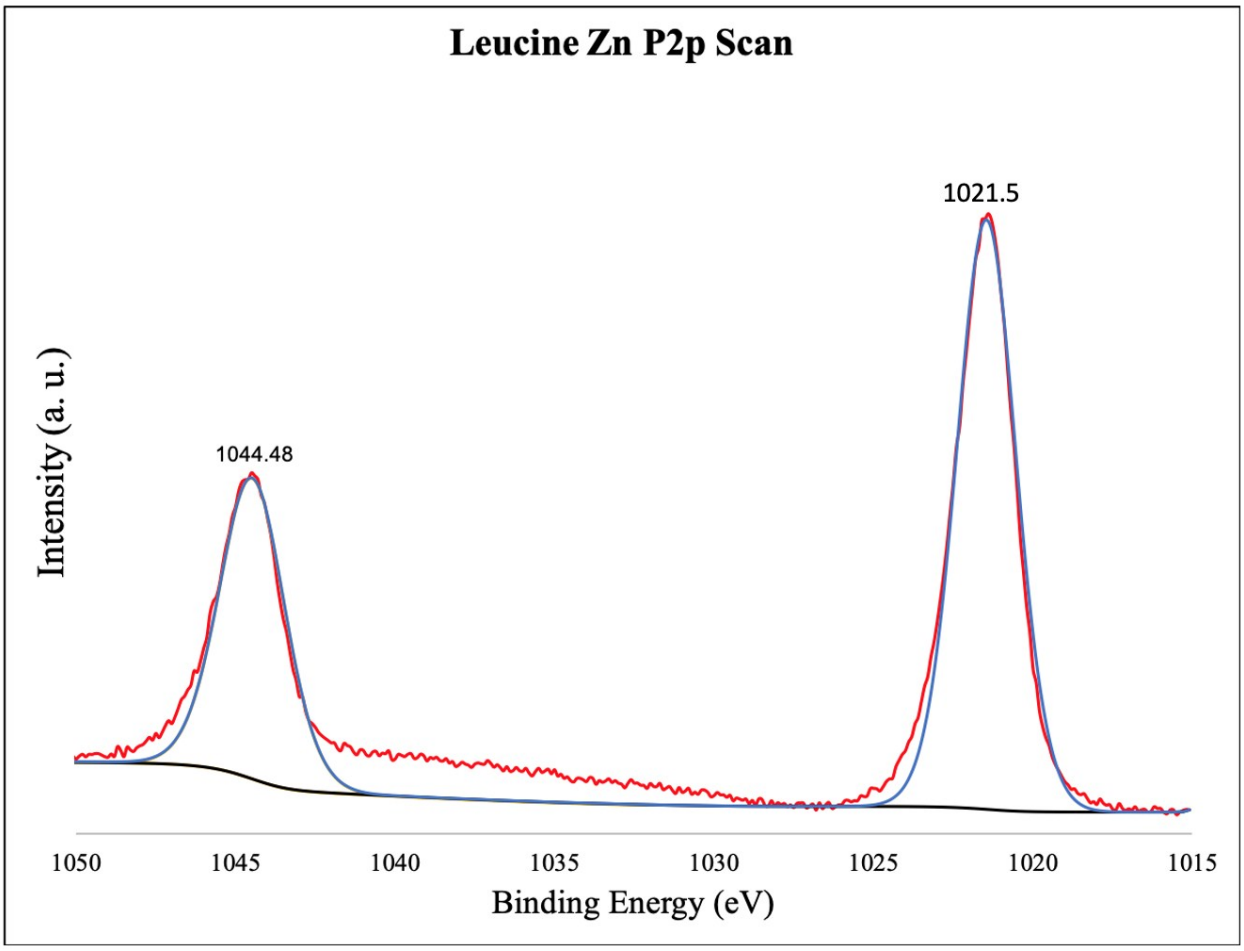

Figure S.8.2 Zn2p XPS spectrum of leucine conglomerate prepared as in *S.2.1* with characteristic binding energies of 1044.48 eV and 1021.5 eV corresponding to $Zn2p_{3/2}$ and $Zn2p_{1/2}$, respectively.[1]

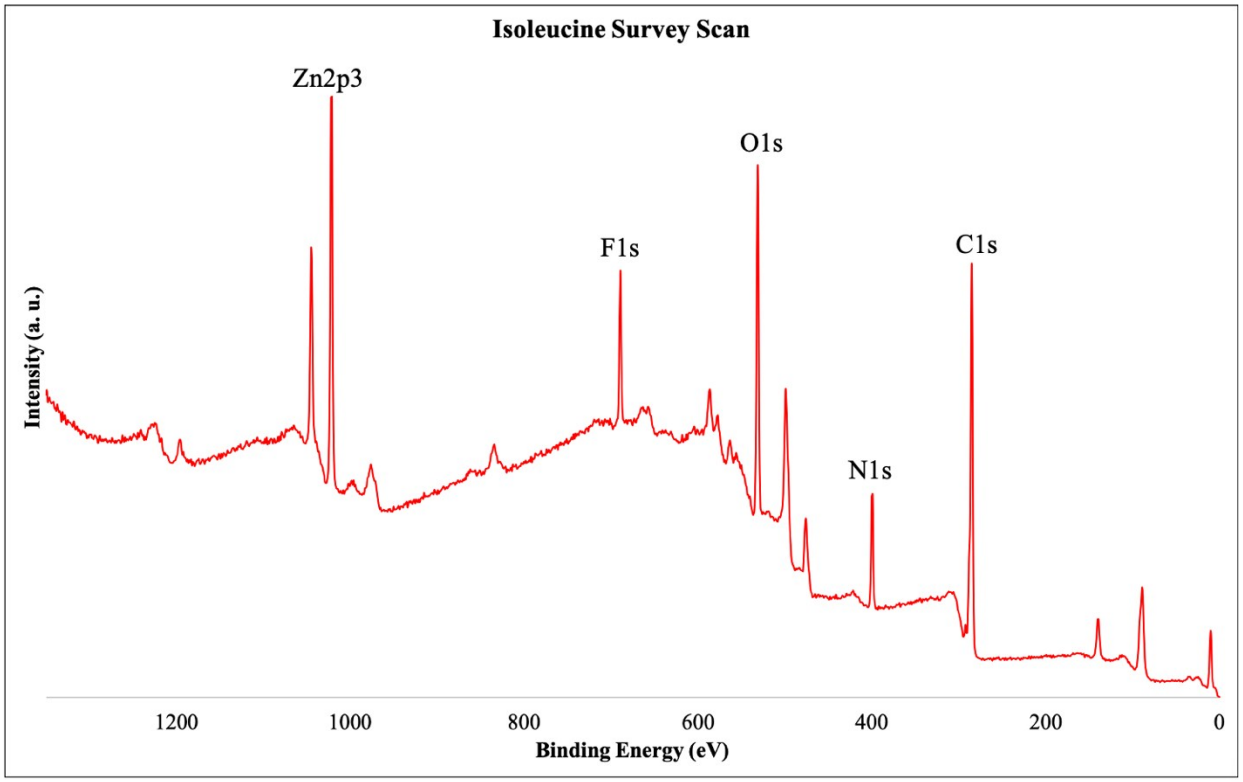

Figure S.8.3 XPS survey spectrum of isoleucine conglomerate prepared as in *S.2.2* with characteristic binding energies of components labelled. *Note: Fluorine is present as a contaminant as a result of using Teflon milling vessels to prepare sample. This was an isolated case and not representative of other milling reactions carried out in Teflon, as is evidenced by the other XPS spectra.*

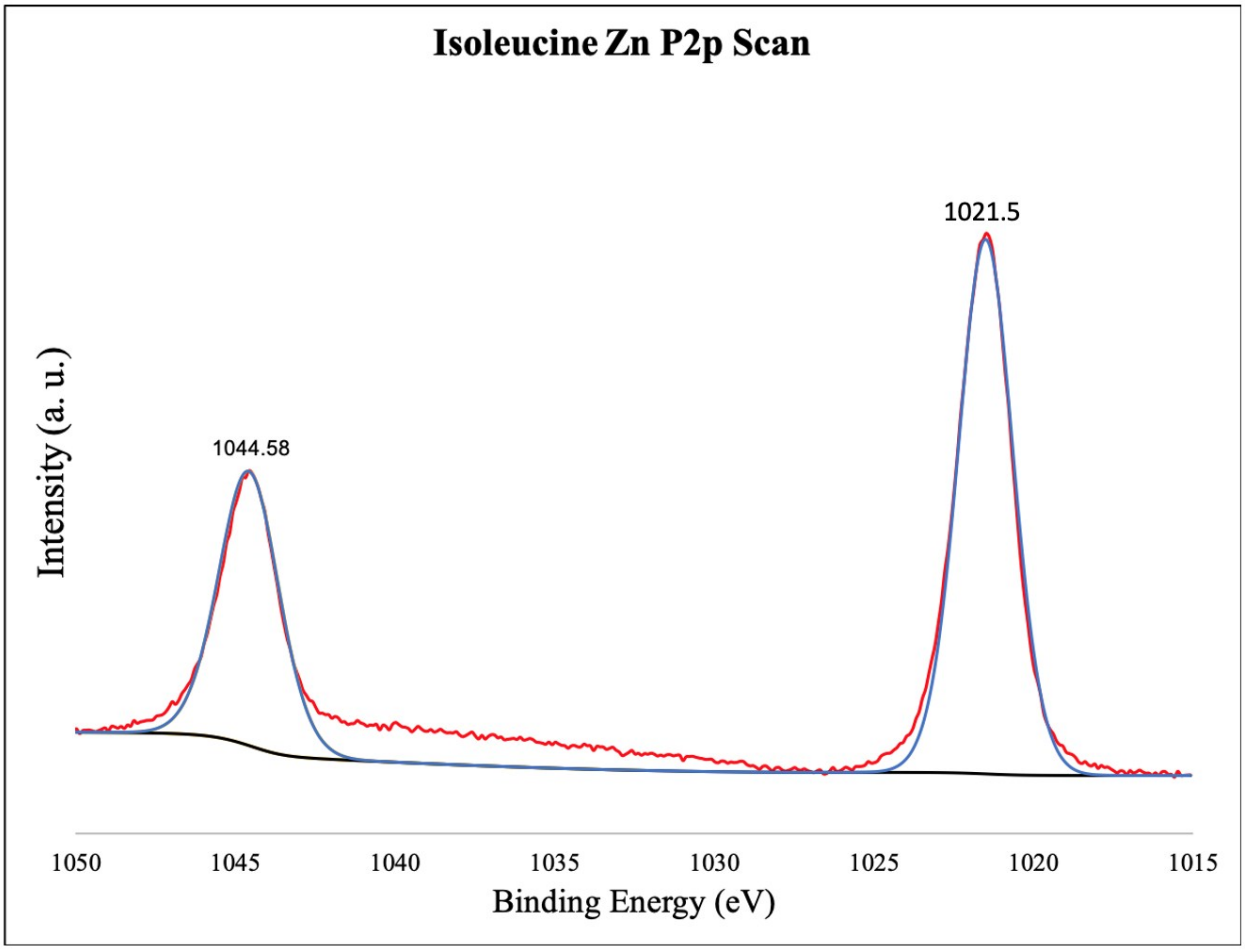

Figure S.8.4 Zn2p XPS spectrum of isoleucine conglomerate prepared as in *S.2.2* with characteristic binding energies of 1044.58 eV and 1021.5 eV corresponding to $Zn2p_{3/2}$ and $Zn2p_{1/2}$, respectively.[1]

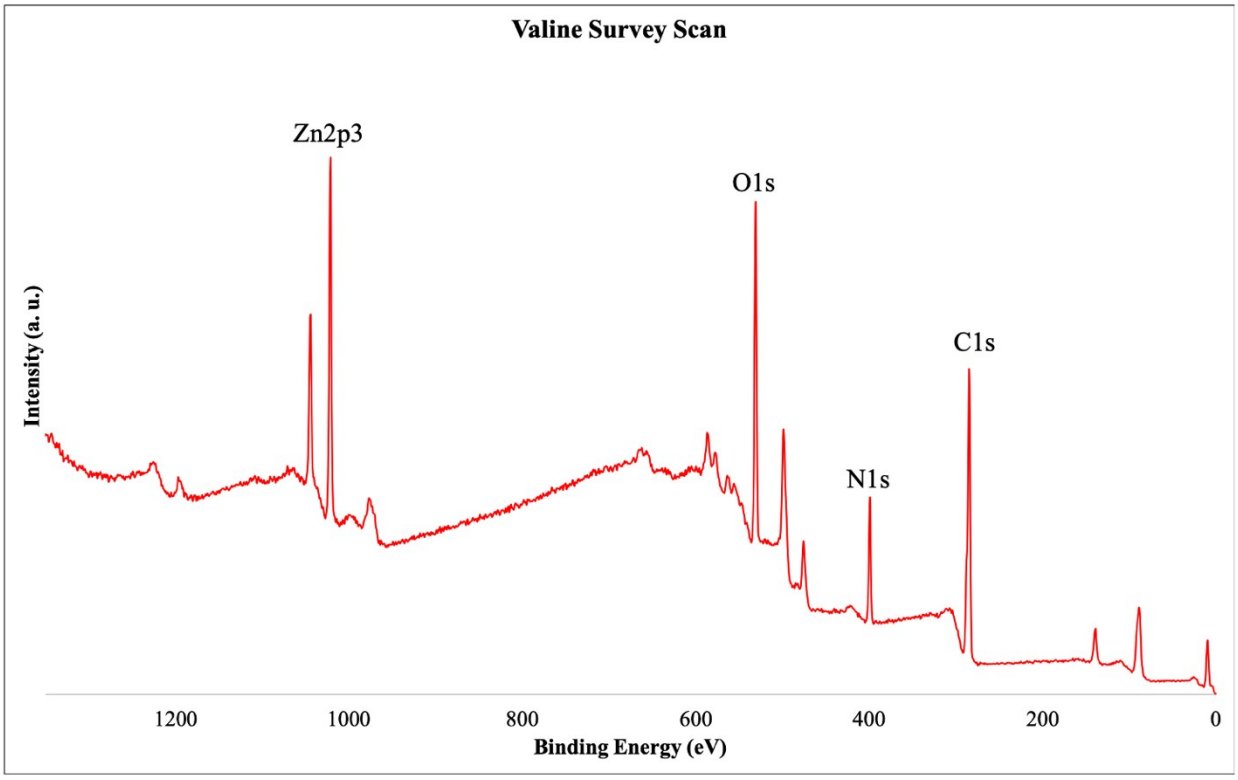

Figure S.8.5 XPS survey spectrum of valine conglomerate prepared as in *S.2.3* with characteristic binding energies of components labelled.

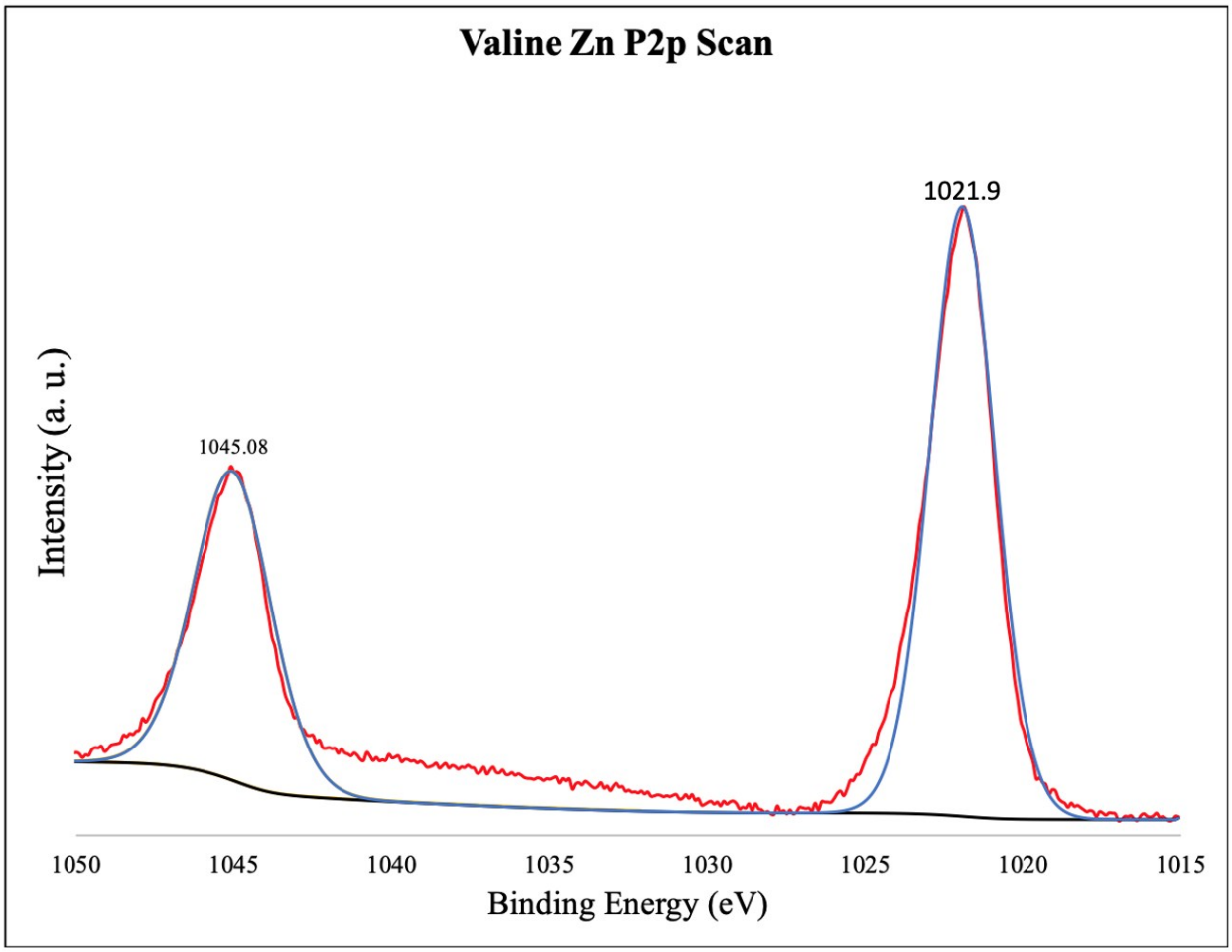

Figure S.8.3 Zn2p XPS spectrum of valine conglomerate prepared as in *S.2.3* with characteristic binding energies of 1045.08 eV and 1021.9 eV corresponding to $Zn2p_{3/2}$ and $Zn2p_{1/2}$, respectively.[1]

Figure S9 After conversion to conglomerate the denser zinc powder was separated from amino acid by centrifugation.

S10 References

(1) B. Strohmeier and D Hercules. *J. Catal.* 1984, ***86*** (2), 266–279.