**Enhancing temperature cycle-induced deracemization via combined cooling and antisolvent crystallization: a proof of concept study**

**Supporting information**

**Method validation by reproducing data from the literature**

Cameli and co-workers proposed applying microwave heating enhanced deracemization to enhance the process. They demonstrated remarkable improvement in the deracemization rate when compared to conventional heating (Cameli et al., 2018). Since the temperature cycles of these conventional heating experiments, as depicted in Figure 1 of the paper, could easily be reproduced by our system, it was decided to use these experiments as a reference. The recipe extracted from the paper and scaled up to the volume of our reactor is listed in Table A1.

Table A1. The recipe of the TCID experiments. These experiments reproduce the data from the literature (Cameli et al., 2018).

|  |  |  |
| --- | --- | --- |
|  | Exp. #160 % initial EE | Exp. #222 % initial EE |
| Amount of *L*-**Glu** weighted in (g) | 8.93 | 6.82 |
| Amount of *D*-**Glu** weighted in (g) | 2.25 | 4.36 |
| Salicylaldehyde (mL) | 2.5 |
| AA (g) | 225.75 | 225.75 |
| Water (g) | 0\* | 0\* |
| $T\_{lo}$ / $T\_{hi}$ (°C)  | 60 / 80 |
| Dissolvable\*\* *L*-**Glu** at $T\_{lo}$/ $T\_{hi}$°C (g) | 0.152 / 0.315 |
| Dissolvable\*\* *DL*-**Glu** at $T\_{lo}$/ $T\_{hi}$°C (g) | 0.350 / 0.723 |

\* no water was weighted in, but the *DL*-**Glu** monohydrate contained a small amount of it

\*\* the salicylaldehyde slightly increases the solubility, which effect was neglected

According to Figure A1, our measurements followed the trends from the literature well. The deviations are attributed to the differences in initial crystal size distribution as well as different mixing. Furthermore, the different EE measurement methods may also have contributed. Beyond the trends of Figure 3, the weight of recovered crystals was also measured. In the two experiments (60 % and 22 % initial EE), we recovered 5.15 and 2.44 g products. These amounts are lower than the overall weight of Glu (11.18 g based on Table A1). A part of the losses is explained with the intermediate sampling: nearly 5 mL sample was taken each time, which is not negligible. A part of the Glu remained in the supernatant, which is the loss of the crystallization process. Furthermore, at long reaction times with high-temperature exposure, the side reaction (Scheme 3) may have consumed a part of Glu, as reported (Cameli et al., 2018).



Figure A1. Temperature cycling induced deracemization of glutamic acid at 22 and 60 % initial EE from pure AA solvent. Literature: (Cameli et al., 2018). The continuous lines are only guides to the eye.

**Solubility measurements and unit conversions**

The solubilities were determined using the gravimetric method. The average of three measurements is represented in Table A1. The eventual outliers were excluded from the calculations.

The solubilities were measured in mg/g solvent for practical convenience. However, the solubility models use weight fractions; thus, unit conversions were executed. First, the measured solubilities expressed in mg/g solvent were divided by 1000 to obtain the solubility in g dissolved material in g solvent ($C\_{s,i}$). Then, for the *L*-**Glu** solubilities, the weight fraction ($w\_{s,i}$) was expressed as:

|  |  |
| --- | --- |
| $$w\_{s,i}=\frac{C\_{s,i}}{1+C\_{s,i}}$$ | (A1) |

The assumption that the concentrations of enantiomers equaled each other when the racemic mixture's solubility was measured is used. Then, the measured apparent solubility ($C\_{s}$) can be used to express the solubility of *L*-**Glu** as $C\_{s,i}=C\_{s}/2$. With this, the solubility of *L*-**Glu** can be expressed in weight fraction as:

|  |  |
| --- | --- |
| $$w\_{s,i}=\frac{C\_{s,i}}{1+C\_{s}}$$ | (A2) |

Table A1. The solubility of **Glu** in mixtures of water and AA.

|  |  |  |  |
| --- | --- | --- | --- |
| EE for **Glu** | Temperature (°C) | Antisolvent content (weight fraction) | Measured solubility ± st. dev. (mg/g solvent) |
| 100 | 20 | 0.00 | 6.80 ± 0.063 |
| 100 | 30 | 0.00 | 10.22 ± 0.090 |
| 100 | 40 | 0.00 | 15.08 ± 0.077 |
| 100 | 50 | 0.00 | 21.40 ± 0.152 |
| 100 | 70 | 0.00 | 39.39 ± 0.551 |
| 100 | 80 | 0.00 |  55.65 ± 0.791 |
| 100 | 30 | 0.25 | 11.39 ± 0.643 |
| 100 | 40 | 0.25 | 15.69 ± 0.184 |
| 100 | 50 | 0.25 | 20.10 ± 0.265 |
| 100 | 60 | 0.25 | 26.15 ± 0.226 |
| 100 | 20 | 0.50 | 6.27 ± 0.387 |
| 100 | 30 | 0.50 | 8.25 ± 0.864 |
| 100 | 40 | 0.50 | 10.83 ± 0.126 |
| 100 | 50 | 0.50 | 14.10 ± 0.204 |
| 100 | 80 | 0.50 | 36.03 ± 0.408 |
| 100 | 30 | 0.75 | 4.98 ± 1.234 |
| 100 | 40 | 0.75 | 5.92 ± 1.761 |
| 100 | 50 | 0.75 | 7.30 ± 0.798 |
| 100 | 60 | 0.75 | 9.20 ± 1.579 |
| 100 | 40 | 1.00 | 0.27 ± 0.150 |
| 100 | 60 | 1.00 | 0.40 ± 0.100 |
| 100 | 70 | 1.00 | 0.50 ± 0.050 |
| 100 | 80 | 1.00 | 0.99 ± 0.018 |
| 0 | 30 | 0.00 |  22.64 ± 1.548  |
| 0 | 30 | 1.00 | 2.27 ± 0.281 |
| 0 | 80 | 0.00 | 139.10 ± 3.210 |
| 0 | 80 | 1.00 | 8.17 ± 0.289 |
| 0 | 55 | 0.50 | 40.26 ± 8.528 |

**References**

Cameli, F., Xiouras, C., Stefanidis, G.D., 2018. Intensified deracemization via rapid microwave-assisted temperature cycling. CrystEngComm 20, 2897–2901. https://doi.org/10.1039/C8CE00575C