Real-time monitoring of crystallization from solution by using an interdigitated array electrode sensor

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Supplementary Information

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Other Supplementary Material for this manuscript includes the following: Movie S1

S1. Interdigitated array electrode

Interdigitated electrodes were made with photolithography using chromium and gold. The large width (1600 μ m) and short separation (60 μ m) are selected to obtain high sensitivity of the electro-chemical sensor for this study. Further improvement may be achieved by decreasing the separation length even down to hundreds of nanometers.



Fig. S1 Optical microscope image of the interdigitated electrode.

S2. In-situ monitoring of crystallization from solution

S2.1 In-situ measurements without Faraday cage

Initially, we performed crystallization experiments without Faraday cage so that the crystallization could be directly inspected by optical microscopy. Even though the measurements are noisy, the overall trend is clear, and in particular, a clear difference between glycine solution and water is observed in the current measured by the IES.

Note that the optical microscope is not exactly perpendicular to the device, so it is not possible to add an accurate scale bar in the optical images. To get an idea of the droplet size, the size of the interdigitated electrodes appearing at the bottom can be taken as a reference.

In this section, we show two additional experiments performed in order to ensure reproducibility of the results. As shown in Fig. S2A, at around 574-575 s, crystals appear, starting from the edge of the droplet, and then spread towards the center, finally covering the whole surface. The IES measurement shows a characteristic increase in the current as soon as crystals appear. Fig. S2B shows that similar results are obtained in a second experiment, where the increase of current is seen at 529-532 s in correspondence of the crystals becoming visible under the optical microscope. The small difference in time between the three experiments (see also Fig. 2) is due to the intrinsic nature of crystallization, which strongly depends on

parameters such as temperature and relative humidity. Small variations in these parameters will affect the time at which the crystals appear.



Fig. S2 (**A**) and (**B**) Additional experiments of *in-situ* monitoring of crystallization of 1 M glycine from solution. The top panels in (A) and (B) are images of the droplet over the time taken from video recording covering the whole process. The red arrow shows the spreading direction of the crystals as observed from the videos. The bottom panels show the corresponding recorded current curves over the time at a fixed voltage of 0.7 V; the red line, obtained by applying fast Fourier Transform (FFT) filtering of the curve, is a guide for the eyes. The blue dashed arrows show the increase of the current observed at 574 s and 529 s in the two experiments, respectively.



Fig. S3 The recorded current curve over the time at a fixed voltage of 0.7 V for water. The red full line, obtained by applying fast Fourier Transform (FFT) filtering of the curve, is a guide for the eyes. The red dotted line indicates the time at which the off state is reached.

S2.2 In-situ measurements with the Faraday cage - control experiment

A droplet of water was first tested as control experiment. Measurements were performed with a Faraday cage to minimize the noise. Figure S4 shows that the current decreases over time as a result of the droplet size reduction, which corresponds to the active area of the device. However, at the very end of the process a sharp peak in the current is observed (Inset, Fig. S4), as also observed in Figure S3. Apart from this spike, no other large oscillation or strong change in the current is observed. Note that the time of which the off state is reached (Fig. S6) is 1278 s, which is larger than 920 s from the experiment shown in Fig. S3, indicating a slightly slower evaporation rate of the droplet due to the presence of the closed environment due to the use of the Faraday cage.



Fig. S4 The recorded current over time from the evaporation of a droplet of water at a fixed voltage of 0.7 V. The inset show that a sharp increase in the current is observed at the very end of the evaporative process.

S2.3 In-situ measurements with the Faraday cage

The use of the cage does not allow the crystals to be seen optically and also slightly changes the crystallization conditions (see also section S2.2), so the induction times are not expected to be the same of the experiments performed without the Faraday cage. However, in this work we are focusing on the dynamics of the process, not on the absolute values, which strongly depend on the specific experimental conditions.

Figure S5 shows that in the initial stage of solvent evaporation the current follows a similar trend for different concentrations of glycine solution and water only. In particular, the current decreases exponentially, without showing any discontinuity, indicating formation of a stable EDL formed at the interface of the electrode. This similar trend also indicates roughly the same evaporation rate for glycine droplets with different concentrations, which is commonly observed when the conditions, i.e. temperature and relative humidity, are comparable during the crystallization experiments.¹



Fig. S5 The recorded current over time from the evaporation of water and glycine solution with concentrations of 2.5 M, 2 M, 1.5 M, 1 M, 0.7 M, and 0.4 M at the first stage of solvent evaporation.

The accurate determination of the induction time is important in crystallization, as it provides pathway to get information on nucleation kinetics. For example, the nucleation rate is often reconstructed by measuring induction times.² Here, we show that the induction time for droplets of organic molecules such as glycine, L-Alanine and D-Mannitol at different concentrations can be accurately determined. Because supersaturation of individual droplets and critical supersaturation ratio of solution are directly related to nucleation events, they can also be obtained from these experiments.

Figures S6-S8 show the curves recorded by IES in the second stage of crystallization, characterized by strong fluctuations in the current. In the droplet measurements, the variation of the current is large enough to be assigned to crystallization events and not to simple noise, confirming the high sensitivity of the IES for the detection of the dynamics in large molecular ensemble via changes in the EDL. By using the time at which the current fluctuations start as the induction time, the supersaturation ratio for different concentrations of glycine solution can also be obtained (see main text). The results are summarized in Tables S1-S3 for glycine, L-Alanine and D-Mannitol, respectively.



Fig. S6 The recorded curves over time from the evaporation of glycine droplets with concentrations of (A) 0.4 M, (B) 0.7 M, (C) 1 M, (D) 1.5 M, (E) 2 M and (F) 2.5 M.

Glycine	Number of	Induction time: Mean ±	Supersaturation ratio:	
concentration / M	devices	Standard Deviation / s	Mean \pm Standard Deviation	
2.5	4	369 ± 91	1.09 ± 0.11	
2	4	551 ± 30	1.11 ± 0.05	
1.5	4	699 ± 63	1.09 ± 0.15	
1	4	909 ± 27	1.24 ± 0.12	
0.7	4	991 ± 32	1.21 ± 0.20	
0.4	4	1092 ± 65	1.74 ± 1.01	
water	3	1203 ± 53	N/A	

Table S1 Statistic of the induction time of glycine droplets with different concentrations (see also Figure S6).



Fig. S7 The recorded curves over time with the evaporation of L-Alanine droplets with concentrations of (A) 0.2 M, (B) 0.4 M, (C) 0.8 M, (D) 1.2 M, and (F) 1.6 M.

Table S2	Statistic	of the	induction	time	of L-Alanine	e droplets	with	different	concentra	ations
(see also I	Figure S7	') .								

L-Alanine	Number of	Induction time: Mean ±	Supersaturation ratio:	
concentration / M	devices	Standard Deviation / s	Mean \pm Standard Deviation	
1.6	3	461 ± 28	1.38 ± 0.05	
1.2	3	653 ± 33	1.40 ± 0.08	
0.8	3	841 ± 17	1.42 ± 0.07	
0.4	3	992 ± 27	1.23 ± 0.17	
0.2	3	1087 ± 8	1.10 ± 0.07	



Fig. S8 The recorded curves over time with the evaporation of D-Mannitol droplets with concentrations of (A) 0.1 M, (B) 0.2 M, (C) 0.4 M, (D) 0.6 M, (E) 0.8 M and (F) 1 M.

D-Mannitol	nnitol Number of Induction time: Mean		± Supersaturation ratio:		
concentration / M	devices	Standard Deviation / s	Mean ± Standard Deviation		
1	3	279 ± 32	1.11 ± 0.04		
0.8	3	453 ± 34	1.10 ± 0.05		
0.6	3	555 ± 24	0.95 ± 0.04		
0.4	3	829 ± 57	1.12 ± 0.18		
0.2	3	1000 ± 7	1.02 ± 0.03		
0.1	3	1105 ± 29	1.12 ± 0.37		

Table S3 Statistic of the induction time of D-Mannitol droplets with different concentrations

 (see also Figure S8).

S3. Raman spectroscopy of glycine crystals

Individual Raman spectra were measured in 15-20 points across the whole crystallization area, as indicated by the circles in Figure S9 A. The polymorphs identification by Raman spectroscopy is based on the peak positions of the symmetric and asymmetric stretches of the C-H bonds, which are distinct for different polymorphs (α -, β - and γ -) of glycine.³

Figure S9 B shows a representative Raman spectrum from our measurements. This is characterized by two peaks at 2972 and 3007 cm⁻¹, which corresponds to the formation of the α -polymorph of glycine.



Fig. S9 (A) Picture of the crystals obtained from the evaporation of 1 M glycine solution on the interdigitated electrode platform. The red circles are showing where the Raman measurements were taken. (B) Representative Raman spectrum of the crystals. The peaks centered at 2972 and 3007 cm⁻¹ correspond to the α -glycine.

S4. Tentative model of the molecular transport during crystallization

Glycine is a neutral molecule, but in aqueous solution it mainly exits as zwitterion form ($^+H_3N-CH_2-COO^-$).⁴ In aqueous solution, hydronium (H_3O^+) and hydroxide (OH⁻) also exit as ion intermediates. With the driving force from the electric field between the two electrodes, glycine zwitterion, H_3O^+ and OH⁻ are distributed at the interfaces of the electrode/electrolyte, forming the electron double layer (EDL). According to the Gouy-Chapman-Stern model,⁵ the distribution of ions in the EDLs is shown in Figure S10. In the inner layer, there is a compact layer at the interface of the electrode, a monolayer of glycine zwitterion and OH⁻ formed the compact layer, while in the negative electrode, glycine zwitterion and H_3O^+ formed the influence of electric attraction and thermal motion.⁵ In this model, the capacitance of the EDL

is the series of the capacitance of the compact layer and the diffusion layer. As glycine zwitterion exist in the EDLs at the interface of positive and negative electrodes, heterogeneous nucleation events may happen randomly at both electrodes. Here we only discuss the possible nucleation event on the positive electrode.

Initially, the recorded current decreases almost linearly with time (Fig. 3A and Fig. S5), which is ascribed to the decrease of the droplet area, upon the solvent evaporation. With the evaporation going on, the solution at the edge of the droplet, i.e. at the liquid-solid-gas interface, reaches the highest evaporation rate,⁶ leading to a supersaturation value higher than 1.08, leading to nucleation. As the gold electrode surface is much more hydrophilic than that of the PEN substrate, the ions are likely to start nucleating on this surface. To support the growth of the nuclei, large quantities of glycine zwitterion in the EDL will be transferred to the nucleation area, as indicated by the dashed lines 1-3 in Figure S10. To stabilize the EDL, the ions in the bulk solution will also be transferred to the EDL as outlined by the dash lines 4 and 5 in Figure S10. Some nuclei may also dissolve and release glycine zwitterion into the EDL. These events could possibly lead to the sharp current increase observed at the induction time. After this time, many sharp peaks (spikes) in the current were also observed (Fig. 3A and 3B), which may be assigned to the formation of new nuclei, causing fast change in the distribution of the ions close to the electrodes.⁷

In the case of L-Alanine and D-Mannitol, the recorded temporal current curves by IES show similar trends to that measured for glycine solutions (Fig. 3 and Fig. 4), therefore the above tentative model can also be extended to L-Alanine and D-Mannitol.



Fig. S10 Schematic illustration of the ion transportation in the electrolyte during early stage of crystallization as monitored by IES.

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