# Electronic Supplementary Information for

# Identifying Alkali Metal Inhibitors of Crystal Growth: A Selection Criterion based on Ion Pair Hydration Energy

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### **S1. Experimental methods**

*Materials.* The following reagents for calcium oxalate monohydrate crystallization were purchased from Sigma Aldrich (St. Louis, MO) and were used without further purification: sodium oxalate ( $Na_2C_2O_4$ , >99%), calcium chloride dihydrate (ACS Reagent, 99+%), potassium chloride (SigmaUltra, 99+%), lithium chloride (ACS Reagent, 99+%), and cesium chloride (ReagentPlus®, 99+%). Sodium chloride was purchased from JT Baker (Center Valley, PA).

*Calcium oxalate monohydrate (COM) crystallization.* We prepared COM crystals using a previously reported protocol.<sup>1</sup> COM crystals were grown in solutions with molar composition 0.7 mM CaCl<sub>2</sub>: 0.7 mM Na<sub>2</sub>C<sub>2</sub>O<sub>4</sub>: x mM MCl (x = 150 - 500) where M<sup>+</sup> = alkali metal. Growth solutions were prepared by first dissolving the alkali chloride salt in deionized water. To this solution was added 10 mM CaCl<sub>2</sub> stock solution. The sample was placed in an incubator at 60°C for one hour followed by the addition of 10 mM Na<sub>2</sub>C<sub>2</sub>O<sub>4</sub> stock solution dropwise while stirring. The sample was returned to the incubator for three days to allow complete crystallization. Cleaned glass slides were placed at the bottom of the vials to collect the crystals for microscopy. The alkali metals selected for this study were Li<sup>+</sup>, Na<sup>+</sup>, K<sup>+</sup>, and Cs<sup>+</sup>. COM crystals prepared in the presence of 150 mM salt is referred to as the *reference (or control)*, which was used to compare the relative effects of electrolytes at higher concentration.

Analytical methods. The dimensions of bulk COM crystals within the basal (100) plane were measured by optical microscopy in reflectance mode using a Leica DM2500-M microscope. The length and width were measured along the [001] and [010] directions, respectively. We report the average dimensions of approximately 200 crystals prepared from 3 different batches. The crystal habit was assessed by scanning electron microscopy (SEM) using a FEI 235 Dual-Beam Focused Ion-Beam instrument equipped with a SEM sample extraction probe. COM crystals on glass slides were transferred to carbon tape by gently pressing the slide to the tape followed by coating the samples with a layer of carbon (ca. 25 nm). COM crystals were characterized by powder X-ray diffraction (XRD) using a Siemens D5000 X-ray diffractometer with Cu Ka radiation (40 kV, 30 mA). The approximate number density of crystals was obtained by counting the number of COM crystals (per unit area) that were collected on glass slides in each synthesis vial. The crystal number density reported here is an average of 3 measurements from separately prepared crystal batches. In each experiment, we analyzed 50 regions on the glass slide ( $324 \times$ 242  $\mu$ m<sup>2</sup> area at each location) for statistical sampling. This simple assay does not account for (i) crystallites too small to sediment to the bottom of the vial, (ii) crystals that adhere to the sides of the synthesis vial, or (iii) crystals that are removed from the glass slide during gentle rinsing with deionized H<sub>2</sub>O prior to analysis by optical microscopy.

The growth rate of COM crystallization was measured *in situ* using a calcium ion-selective electrode (ISE) from Orion (model 9720BNWP). The depletion of free calcium ions in supersaturated growth solutions was analyzed at room temperature using an initial solution of composition 0.5 mM CaCl<sub>2</sub>:0.5 mM Na<sub>2</sub>C<sub>2</sub>O<sub>4</sub>:*x* mM alkali metal chloride (x = 100 - 500) with continuous stirring at 1,200 rpm. The slope of ISE curves was used to assess the rate of Ca<sup>2+</sup> depletion, *r*. The relative growth rate was calculated as the growth rate at a specific alkali chloride concentrate ( $r_{electrolyte}$ ) divided by the growth rate at 150 mM of the same alkali chloride ( $r_{reference}$ ).

#### S2. COM nucleation

The homogenous nucleation rate J (i.e., number of nuclei formed per unit volume per time) can be estimated using the Arrhenius relationship,

$$J = A \exp(\frac{-\Delta G}{RT}) \tag{S1}$$

where A is the frequency constant,  $\Delta G$  is free energy of nucleation, R is the universal gas constant, and T is the absolute temperature (selected as 298.15 K for this calculation). The influence of salt concentration is reflected in the supersaturation ratio, S, where changes in ionic strength impact the free energy of nucleation. The homogeneous nucleation rate can be estimated using the following equation,<sup>2</sup>

$$J = A \exp\left[-\frac{\beta \gamma^3 v_m^2 N_A}{R^3 T^3 (\ln S)^2}\right],$$
(S2)

For our calculation we used a frequency constant  $10^{33}$  nuclei cm<sup>-3</sup> s<sup>-1</sup>, <sup>3</sup> which is an average value reported in the literature (values are reported in the range  $10^{30} - 10^{36}$  nuclei cm<sup>-3</sup> s<sup>-1</sup>).<sup>4</sup> The parameter  $\beta$  is a geometric factor ( $16\pi/3$  for a spherical nucleus),  $\gamma$  is the surface energy (7.14 mJ/m<sup>2</sup> for COM),<sup>4</sup>  $v_m$  is the molecular volume (66.42 cm<sup>3</sup>/mol for COM),<sup>4</sup> and  $N_A$  is Avogadro's number. There are three variables that predominantly influence the rate of nucleation: T, S, and  $\gamma$ .<sup>2</sup> Equation S2 is valid for growth solutions with S > 1.<sup>2</sup> For example, El-Shall et al. examined the effect of S ranging from 1.6 to 2.2 on COM nucleation,<sup>4</sup> and their study revealed that the nucleation rate decreases with decreasing S (i.e., increasing ionic strength). Here, we used Equation S2 to predict the effect of alkali chloride concentration on J. As shown in Figure S1, there is a monotonic decrease in J with increasing alkali chloride (electrolyte) concentration.



Figure S1. COM nucleation rate J calculated as a function of increasing alkali chloride concentration at 25°C. Equation S2 predicts an approximate 2-fold decrease in J with increased electrolyte concentration.

An increase in electrolyte concentration decreases the supersaturation ratio S, which in turn reduces the rate of COM nucleation J. This general trend for COM nucleation (Figure S1) qualitatively agrees with our experimental measurements, which are shown in Figure S2. We observed an approximate order of magnitude reduction in the number density of COM crystals, suggesting Na<sup>+</sup> influences the rate of COM nucleation beyond simply altering the supersaturation of growth solutions.



**Figure S2.** Number density of COM crystals on glass slides extracted from growth solutions as a function of NaCl concentration. We observed a decrease in the number of COM crystals as the NaCl concentration increased (i.e., as the supersaturation ratio *S* decreased). The reduction in supersaturation resulted in fewer and larger COM crystals, as shown in the optical micrographs (inset images). Each experimental data point (symbol) is the average number density estimated from the total number of COM crystals per unit area measured on the glass slide. The solid line is interpolated to help guide the eye.

#### **S3. COM bulk crystallization**

We used SEM images to characterize changes in COM bulk crystal habit in the presence of different alkali metals. COM crystals prepared in the presence of Na<sup>+</sup> tend to have a relatively uniform morphology (i.e., hexagonal platelets). Representative scanning electron micrographs of the (100) and (010) surfaces of COM crystals prepared with 150 mM NaCl are shown in Figure S3 A and C, respectively. Crystallization in the presence of KCl, LiCl, and CsCl produced unique morphologies that were not observed in the presence of NaCl. For example, COM crystals with a diamond-shaped (100) surface and elongated {12-1} surfaces were observed. SEM images of these crystals at two different viewing angles are shown in Figure S3 B and D. Additional examples of distinct COM crystal morphologies observed in the manuscript (see Figure 3).



**Figure S3.** Scanning electron micrographs of COM crystals prepared from growth solutions containing 150 mM concentrations of (A and C) NaCl, (B) LiCl, and (D) CsCl. COM crystals in the presence of NaCl exhibit relatively uniform hexagonal morphology, as shown in A (view of basal surface) and C (side view). Substituting NaCl with other alkali metal salts (e.g., KCl, LiCl, and CsCl) results in the formation of COM crystals with different morphologies, such as diamond-shaped crystals (shown in B) and extended {12-1} faces (shown in D). Scale bars for all SEM images equal 10 µm.

Modifications to COM crystal size and habit in the presence of different alkali metals were assessed by optical microscopy. COM crystals prepared in the presence of 150 – 500 mM NaCl exhibit nearly identical hexagonal morphology (Figure S4, left column). As shown in Figure S3, the presence of KCl, LiCl, and CsCl can lead to changes in crystal habit. Figure S4 contains representative optical micrographs of COM crystals prepared at different salt concentrations using NaCl, KCl, LiCl, and CsCl. In addition to observing morphologies that differ from the common hexagonal shape, we also observed fewer and larger COM crystals with increasing alkali chloride concentration, irrespective of the alkali metal (see Figure S4).



**Figure S4.** Optical micrographs of COM crystals prepared in the presence of 150 - 500 mM NaCl (first column), KCl (second column), LiCl (third column), and CsCl (fourth column). We observed a general trend in COM crystallization, irrespective of the alkali metal selected, wherein an increase in ionic strength decreased the number density of crystals on the glass slides and increased the average crystal size. We also observed different crystal morphologies in the presence of K<sup>+</sup>, Li<sup>+</sup>, and Cs<sup>+</sup> with increasing salt concentration. The scale bar (bottom right) applies to all optical micrographs.

We quantified the change in bulk crystal habit as a function of NaCl concentration by measuring the aspect ratio, which we define as the relative ratio of [001] length to [010] width. As shown in Figure 1 of the manuscript, we observe that COM crystal size increases with NaCl concentration, but the aspect ratio remains unaffected by increasing ionic strength (Figure S5). For instance, we observed a constant length-to-width aspect ratio of COM crystals at NaCl concentrations spanning 150 to 500 mM. This observation suggests that Na<sup>+</sup> does not exhibit a preference for binding to a particular COM crystal surface.



**Figure S5.** Effect of NaCl concentration on the bulk habit of COM crystals prepared at 60°C. The aspect ratio reported here is the ratio of [001] length to [010] width measured within the (100) basal plane. An increase in NaCl concentration does not have an appreciable effect on the overall morphology of COM crystals (i.e., the aspect ratio is nearly constant at all NaCl concentrations). Each data point is an average of 200 crystals on glass slides extracted from at least 3 separately prepared crystal batches. Error bars equal one standard deviation.

Thermodynamic relationships predict that an increase in alkali metal concentration alters the solubility of COM, C<sub>e</sub>, according to the following equations,

$$CaC_2O_4 \cdot H_2O_{(S)} \longleftrightarrow Ca^{2+}_{(aq)} + C_2O^{2-}_{(aq)} + H_2O_{(l)}$$
 (S3)

$$K_{sp} = \gamma_{Ca^{2+}} [Ca^{2+}] \gamma_{C_2 O_4^{2-}} [C_2 O_4^{2-}]$$
(S4)

$$C_{e} = \sqrt{K_{sp} \left( \gamma_{Ca^{2+}} \gamma_{C_{2}} o_{4}^{2-} \right)^{-1}}$$
(S5)

The solubility product  $K_{sp}$  of COM crystals is  $1.7 \times 10^{-9} \text{ mol}^2 \text{ L}^{-2}$  at 25 °C.<sup>5</sup> We calculated the activity coefficients  $\gamma_i$  using the Davies equation,<sup>6</sup>

$$\log \gamma_i = -0.5 \, z_i^2 \left( \frac{\sqrt{\mu}}{1 + \sqrt{\mu}} - 0.2 \mu \right) \tag{S6}$$

where  $z_i$  and  $C_i$  are the ion valence and concentration, respectively, and  $\mu$  is the ionic strength ( $\mu = 0.5 \sum z_i^2 C_i$ ). The COM growth solutions used in this study were prepared with equimolar concentrations of calcium and oxalate:  $C_{CaOx} = C_{Ca^{2+}} = C_{C_2O_4}^{2-}$ . In the manuscript, the concentration of calcium oxalate is often reported as the supersaturation ratio,  $S = C_{CaOx}/C_e$ .

#### S4. Effect of alkali metals on COM crystal growth rate

The temporal reduction of  $Ca^{2+}$  concentration during COM growth was monitored *in situ* using a calcium ion-selective electrode (ISE), which measures the concentration of free  $Ca^{2+}$  ions in solution. ISE measurements revealed a monotonic decrease in the rate of COM crystal growth (i.e., slope of the free  $Ca^{2+}$  ion concentration versus time) with increasing alkali metal concentration. Classical models of crystallization predict that the kinetic rate of bulk crystal growth is proportional to the driving force (i.e., supersaturation  $\Delta C = C_{CaOx} - C_e$ ), according to the following equation,<sup>7,8</sup>

$$r = \frac{dC_{CaOx}}{dt} = k \Delta C = k \left( C_{CaOx} - C_e \right)$$
(S7)

where *r* is the rate of calcium oxalate depletion (ppm/min) and *k* is the kinetic rate constant. In the manuscript we refer to the relative growth rate (RGR), which is the ratio of growth rates for different electrolyte concentrations,  $r_{MCL}$ , divided by the reference at 150 mM,  $r_{150mM}$ .

$$RGR = \frac{r_{MCl}}{r_{150mM}} = \frac{k (C_{CaOx} - C_e)_{x MCl}}{k (C_{CaOx} - C_e)_{150 MCl}} = \frac{(C_{CaOx} - C_e)_{x MCl}}{(C_{CaOx} - C_e)_{150 MCl}}$$
(S8)

Here, we assume that the kinetic rate constant is independent of salt concentration. In our study, we found that the effect of monovalent cations on the rate of COM crystallization was not identical for all alkali metals (see Figure 2A). In the manuscript, we discuss the effects of COM growth inhibition in relation to the ionic radius, r (*pm*), and the hydrated ionic diameter,  $\alpha$  (pm), of alkali metals. In Table S1, we compare these radii with those of calcium and chloride ions.

Ion	r (pm) <sup>a</sup>	α (pm) <sup>b</sup>
Ca <sup>2+</sup>	100	600
Li <sup>+</sup>	76	600
$Na^+$	102	450
$K^+$	138	300
$Cs^+$	167	250
Cl	181	300

Table S1. Ionic sizes of ions at 25°C

<sup>a</sup> Effective radius (coordination number = 6)  $^{9-11}$ 

<sup>b</sup> Hydrated ion diameter obtained from the Harris 1948 reference <sup>12</sup>

#### **S5.** Ion selective electrochemistry

Ion selective electrochemistry (ISE) is used in a wide range of applications as a means of quantifying ion concentration in aqueous solution. Ion selective electrodes have two basic components – a reference cell and a sensing half-cell – as illustrated in Figure S6. Improvements in their design have led to the development of combination electrodes where both sensing and reference half cells occupy the same compartment.<sup>14</sup>

9720BNWP Calcium Combination Electrode



**Figure S6.** Schematics of (A) the combination electrode used in  $Ca^{2+}$  ion selective electrochemistry and (B) the sensing module occupying the lower portion of the electrode. Individual components of the electrode are labelled in each schematic. The combination electrode has both the sensing and reference half cells in the same compartment. The tip of this electrode contains the ion sensitive area, which is a porous membrane that selects and detects the activity of free  $Ca^{2+}$  ions in solution. These schematics were adapted from the ISE instrument manual.<sup>14</sup>

When the electrode comes in contact with an ionic solution, a potential develops across the ionexchange membrane. The potential depends on the activity of the sensed ion in solution, which refers to free  $Ca^{2+}$  in this manuscript. The activity is also influenced by the ionic strength of the solution (i.e., ions that impose interference effects). ISE is designed to be highly selective for the sensed ion and robust to withstand high concentrations of interference ions. When the ionic strength is greater than *ca*. 100 mM, the electrode should be calibrated to account for the effects of interference ions (see Section S6). In general, the use of ISE requires electrode calibration wherein standards are used to obtain electrode slopes prior to sample measurement.<sup>13,14</sup> For example,  $Ca^{2+}$  electrode slopes must be around 25 mV per decade to ensure that free  $Ca^{2+}$  ion readings are within experimental error.

ISE offers the advantage of measuring temporal changes in free Ca<sup>2+</sup> concentration *in situ*; however, there are several sources of error that contribute to experimental variability in measurements of the sensed ion concentration. Potential sources of error may be attributed to the following: (i) degradation of the instrument (i.e., meter, electrode, or reference electrode) with time; (ii) drift due to repeated exposure of the ISE electrode to solutions without continual calibration; and (iii) errors in preparing the calibration standards.<sup>14,15</sup> Approaches to minimize these errors have been developed by ISE manufacturers and are made available to end users.

#### S6. Calcium ion-selective electrode calibration

The effect of ionic strength on the calcium ion-selective electrode reading was tested by preparing a total of 20 calibration solutions. Five MCl salt concentrations were prepared with a range of ionic strength that spanned the values tested in the manuscript: 150, 200, 300, 400, and 500 mM MCl. At each salt concentration, we prepared four different concentrations of calcium: 0.3, 0.4, 0.5, and 0.6 mM CaCl<sub>2</sub>. ISE readings were taken and the data was plotted with the electrode ("elect") reading as the y-axis (units of ppm) and the concentration of CaCl<sub>2</sub> solution ("soln") as the x-axis (units of mM). For each ionic strength sample, we performed linear regression analysis by setting the y-intercept to zero. The slope from each calibration curve is given by the following relationship:

$$m\left(\frac{ppm}{mM}\right) = \frac{\Delta C_{Ca, elect}}{\Delta C_{Ca, soln}}$$
(S9)

ISE measurements are corrected for interference ion effects by scaling the relative growth rate (Eq. S8) with the calibration slopes for the reference solution  $m_{150 MCl}$  (150 mM MCl) and each ionic strength  $m_{x MCl}$  (x > 150 mM MCl). This correction converts the concentrations measured by the electrode (ppm) to the actual change in calcium concentration (mM).

$$RGR = \frac{(C_{CaOx} - C_e)_{x \ MCl, \ elect}}{(C_{CaOx} - C_e)_{150 \ MCl, \ elect}} \cdot \frac{m_{150 \ MCl}}{m_{x \ MCl}}$$
(S10)

Figure S7A is an example calibration curve using LiCl. All alkali chloride calibration curves in this study exhibited excellent linearity (i.e.,  $R^2 > 0.98$ ). The calibration slopes, *m*, are plotted in Figure S7B as a function of alkali chloride concentration.



**Figure S7.** Calcium ISE calibration data for alkali chloride solutions at room temperature. (A) Example calibration curves for LiCl at five different salt concentrations (150, 200, 300, 400, and 500 mM LiCl) in solutions containing 0.3 - 0.6 mM CaCl<sub>2</sub>. The calcium content measured by the ISE electrode (ppm) is plotted on the y-axis, and the concentration of the prepared calcium solution (mM) is plotted on the x-axis. The solid lines are linear regression (R<sup>2</sup> > 0.98) where the slope *m* is used to calibrate the kinetic data (RGR values) according to Eq. S10. (B) Calibration slopes (ppm/mM) for each MCl salt (M = Li<sup>+</sup>, Na<sup>+</sup>, K<sup>+</sup>, and Cs<sup>+</sup>) are plotted as a function of alkali chloride concentration. Dashed lines are interpolations for visual clarity.

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