Supporting Information

Small-Molecular-Weight Additives Modulate Calcification by Interacting with Prenucleation Clusters on the Molecular Level

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Experimental Details

Materials
The following chemicals were used without further purification: calcium chloride, 1 M volumetric standard solution, analytical grade (Honeywell, Morristown, New Jersey, USA); sodium bicarbonate, 1 M volumetric standard solution, analytical grade (Alfa Aesar, Haverhill, Massachusetts, USA); sodium carbonate, 0.5 M volumetric standard solution, analytical grade (VWR, Radnor, Pennsylvania, USA); sodium hydroxide, 0.01 M volumetric standard solution, analytical grade (Alfa Aesar, Haverhill, Massachusetts, USA); ethylenediaminetetraacetic acid tetrasodium salt dihydrate, 99% (AppliChem GmbH, Darmstadt, Germany); etidronic acid monohydrate, 95% (Sigma-Aldrich, St. Louis, Missouri, USA); potassium tripolyphosphate, 95% (Sigma-Aldrich, St. Louis, Missouri, USA); cis,cis,cis-1,2,3,4-cyclopentanetetracarboxylic acid, 98% (Alfa Aesar, Haverhill, Massachusetts, USA); N,N-bis(carboxymethyl)-DL-alanine trisodium salt, 90%, (Sigma-Aldrich, St. Louis, Missouri, USA); sodium tripolyphosphate, 5% (Sigma-Aldrich, St. Louis, Missouri, USA); sodium tripolyphosphate, 99% (Sigma-Aldrich, St. Louis, Missouri, USA). In all experiments, ultra-pure water was used (Merck Milli-Q Direct 8 with UV photooxidation, 18.2 MΩ cm⁻¹).

ACC synthesis and ripening / ageing experiments
Amorphous calcium carbonate (ACC) was synthesized by a metathesis reaction: while stirring, 3.5 mL of a CaCl₂ solution (80 mM) was dosed into 50 mL of a sodium carbonate/bicarbonate buffer (80 mM, pH = 9.75) within 5 s. In additive-controlled reactions, the additive was dissolved in the buffer at a concentration of 0.8 mM. The forming suspension was immediately filtered and washed with ethanol, the residue was dried in a desiccator over fresh silica gel. Control experiments were carried out under identical conditions, employing a pure and additive-free carbonate buffer. The as retrieved "non-ripened" precipitates were stored over silica and were used for further characterization, e.g., XRD, SEM, ssNMR, DSC, or SANS.

For assessing the stability against phase transformation, i.e., crystallization, ripening experiments were performed. The mixing time of the initial suspensions was extended to 15 minutes in their mother liquors before collecting the solid reaction products for further characterization, e.g., SEM and XRD. Additionally, ageing experiments were performed: Five mg of the non-ripened and confirmed amorphous powders were re-suspended in 5 mL distilled water and stirred for 15 min before collecting the solid reaction products for further characterization by SEM and XRD.

Ca-binding and mineralization profiling experiments
Profiles were obtained by closely following protocols reported in the literature. For all steps of the experiment, decarbonated Milli-Q Water was used which was obtained by purging water over night with a constant stream of nitrogen. Solutions and buffers were kept under CO₂-deprived atmosphere. All titration experiments were conducted under a CO₂-free atmosphere at 24.0± 0.1 °C using a Metrohm Titrandos setup (Titrandos 905 equipped with up to 2 Dosino 800, 2 dosing units 807, a flat membrane pH electrode and a Ca ion selective electrode, and controlled by the titration software tiamo v2.5; Metrohm GmbH, Herisau, Switzerland). In all profiling experiments, the pH was held at 9.75 throughout the measurement by counter-titration of 10 mM NaOH. Buffer and additive solutions were pre-adjusted to a pH value of 9.75 by titrating a 10 mM sodium bicarbonate solution with a 10 mM sodium carbonate solution. Electrodes were calibrated before each measurement session; if more than three profiles were performed in one session, an additional calibration was conducted.

Ca-binding profiles were recorded by measuring calcium activity of 25 mL of a 100 µM solution of the additive in pure water while adding 10 mM CaCl₂ at a constant rate of 0.01 mL min⁻¹. The pH was constantly kept at 9.75 ± 0.03. Reference experiments were conducted without additive. Mineralization profiles were recorded in a similar fashion by measuring the Ca activity of 25 mL of a 10 mM sodium carbonate buffer pre-adjusted to 9.75, which contained the additive of interest at a concentration of 100 µM, while adding 10 mM CaCl₂.
CaCl\textsubscript{2} at a constant rate of 0.01 mL min\textsuperscript{-1}. The pH was constantly kept at 9.75 ± 0.01 by counter-dosing of 10 mM NaOH. For reference experiments, no additive was used.

For visualizing the median of the references curve and the experimental spreading of reference curves, which is an expected consequence of the stochastic character of nucleation processes, we fitted the reference curves to a parametrized model representing a standard LaMer curve\textsuperscript{[8]}. We chose a representation which consist of an initial linear function \(g(x)\) which is converted into a constant value \(c\) using an asymmetric sigmoid function \(s(x)\). The resulting fit function is therefore

\[
\begin{align*}
    f(x) &= g(x) \ast s(-x) + a \ast s(x) \\
    g(x) &= m \ast x + a \\
    s(x) &= 1 - \left(1 + e^{\frac{x}{a}}\right)^{-b}
\end{align*}
\]

with the linear function:

\[
g(x) = m \ast x + a
\]

and the asymmetric sigmoid function:

\[
s(x) = 1 - \left(1 + e^{\frac{x}{a}}\right)^{-b}
\]

All fit parameters are positive, with \(m\) as the constant initial slope before burst nucleation; \(d\) as the free calcium concentration at the maximum, \(c\) as the free calcium concentration in the final equilibrium stage. By varying the fit parameters, a range of relevant LaMer curves can be represented, see below. The median reference curve was obtained by using the arithmetic average of the fit parameters; the envelope curves were received using the minimum/maximum values of the obtained fit parameters. If not stated otherwise, following values are used: \(a = 20\), \(b = 10\), \(c = 300\), \(\delta = 10\), \(m = 0.3\)
Characterization of amorphous and crystalline products

**X-ray diffraction (XRD)** measurements were performed using a D8 Advance Eco (Bruker) with Cu Kα radiation (λ = 1.5406 Å).

**Scanning electron microscopy (SEM)** micrographs were taken with a GeminiSEM (Carl Zeiss) with an accelerating voltage of 1.0 kV applied.

**Differential scanning calorimetry (DSC)** was accomplished with a DSC 8500 (PerkinElmer) and a constant heating rate (20.00 °C/min) from 30.0 °C to 500.0 °C was chosen. Nitrogen served as carrier gas at a constant flow of 20 ml min⁻¹. The following steps were performed during each DSC measurement: (1) Hold for 2.0 min at 30.00 °C, (2) Heat from 30.00 °C to 500.00 °C at 20.00 °C min⁻¹, (3) Hold for 2.0 min at 500.00 °C, (4) Cool from 500.00 °C to 30.00 °C at 40.00 °C min⁻¹, (5) Hold for 1.0 min at 30.00 °C.

**Thermogravimetric analysis (TGA)** was performed with a STA 449 F3 Jupiter (Netzsch) applying a constant heating rate of 5 °C/min under nitrogen atmosphere until a maximum temperature of 800 °C was reached. To remove adherent water from ACC surfaces, all samples were dried at 145 °C for 2 h before the actual TGA measurement. For the determination of the additive content, the step-like mass loss around 400 - 450 °C was used. As TPP- and HEDP-ACC show a deviant behavior, indicating a thermonduced reaction, a different quantification was applied. XRD of samples annealed to 900 °C showed only the presence of calcium oxide and hydroxyapatite and the absence of any crystalline carbonate species. Therefore, the additive content for these samples was assessed by assuming a thermonduced reaction of water-free calcium carbonate and Ca-TPP or HEDP yielding calcium oxide and hydroxyapatite. The determined mass fractions are given in Fig. S3B; the value for EDTA-ACC and MGDA-ACC are below the resolution limit of this technique.

**Small and very-small angle neutron scattering (V/SANS)** experiments were conducted at two beamline instruments (KWS-2 and KWS-3, operated by Jülich Centre for Neutron Science JCNS) at the Heinz Maier-Leibnitz Zentrum (MLZ) in Garching, Germany. The focusing SANS instrument KWS-3 provides scattering vectors $Q$ from 0.0001 to 0.35 Å⁻¹ at sample-to-detector distances of 9.2, 1.25, 0.25 and 0.05 m using a toroidal mirror with focus-to-focus distance 22 m, entrance aperture 2x2 mm², wavelength $\lambda=12.8$ Å ($\Delta\lambda/\lambda=17$), and two-dimensional position-sensitive scintillation detector with diameter 9 cm and pixel size 0.32 mm. The scattering statistics above $Q = 0.02$ Å⁻¹ were improved by additional experiments using the classical pinhole SANS instrument KWS-2 at sample-to-detector distances of 2 and 8 m (corresponding collimation length of 4 and 8 m), and wavelength of $\lambda=5$ Å ($\Delta\lambda/\lambda = 10\%$). With these configurations, KWS-2 allows a $Q$-range from 0.01 to 0.45 Å⁻¹. Quartz cuvettes with a path length of 0.1 mm were used for sample mounting. Data reduction, analysis, background subtraction and fitting were performed by means of the software QtiKWS (V. Pipich, 2019, http://www.qtiKWS.de). A multi-level Beaucage fit was applied.

**Solid-state nuclear magnetic resonance spectroscopy (SS-NMR)** 75.4 MHz $^{13}$C, 121.85 MHz $^{31}$P solid state MAS NMR measurements were carried out on a 3-channel, solid state AVANCE III NMR spectrometer (Bruker), operating at 300.01 MHz for $^1$H, equipped with triple-resonance probe with a 4 mm spinning module. Samples, ~40 mg, obtained by immediate filtration after solutions mixing and subsequent drying, were packed after 4-16 days in 4 mm (o.d.) zirconia rotors; rotors were kept closed (airtight caps prevent exchange of water content) until all NMR measurements for each sample were done. The two excitation schemes employed are cross polarization (CP) from hydrogen to either $^{13}$C or $^{31}$P, and direct excitation (DE) of $^{13}$C. Both schemes used chemical shift refocusing with echo interval identical to the rotor period, $T_R$. Detection used $^1$H SPINAL decoupling with rf level of 100 kHz. CP matched Hartmann–Hahn rf levels at 50 kHz for $^{13}$C and $^{31}$P, and ramped $^1$H CP (30–70 kHz) for 1msec contact time, using 3sec relaxation delay between experiments. DE experiments used 2400 sec relaxation delay for $^{13}$C. To obtain satisfactory S/N up to 8K transients were acquired.
$^{13}$C($^{31}$P) CP-REDOR experiments$^{[12,13]}$ were conducted using the CP excitation scheme and REDOR pulse sequence with refocusing $\pi$ pulses at the completion of each rotor period ($T_R$) on the observed channel ($^{13}$C) and recoupling $\pi$ pulses at the middle of each rotor period on the non-observed nucleus ($^{31}$P); these were followed by an additional 2$T_R$ period with a refocusing $\pi$-pulse after $T_R$ to form simultaneously the chemical shift and rotational echoes. Both the refocusing and recoupling $\pi$ pulses employed the xy-8 phase cycling$^{[14]}$. Data acquisition employed an alternating block scheme, collecting a single $S_0$ transient with recoupling pulses turned off, followed by acquiring $S_R$ transient with recoupling pulses turned on. Each part was processed separately to yield the respective spectra. The REDOR $S_0$ spectra, obtained without dipolar recoupling, show reference spectra with unperturbed peaks that account for all $^{13}$C species. The REDOR $S_R$ spectra acquired with the dipolar interaction turned on show peaks of attenuated intensities for carbon species with P-atoms in their immediate vicinity; attenuation extent, $\Delta S$, obtained by $S_0 - S_R$ subtraction (integrated peak areas subtraction) depends on the interatomic distance and on the length of the recoupling period $nT_R$. The dependence of the relative attenuation on recoupling length, $\Delta S/S_0$, vs. $nT_R$, forms the REDOR curve. The REDOR experiments used the CP excitation scheme. All measurements used sample spinning speed 10,000 Hz. The simulated REDOR curves were adopted from Akiva-Tal et al.$^{[15]}$ for orthophosphate surrounded by spherical shells, 1 Å thick, of CaCO$_3$:H$_2$O 1:1. This model ignores the larger volume occupied by HEDP or TPP, hence introducing a 12-4% error in calculating the weighted $\Delta S$ contributions.

**Molecular Dynamics Simulations**

To investigate the behavior of additives in calcium carbonate solution, we employed molecular dynamics simulations using the LAMMPS simulation software$^{[16]}$. For all molecular dynamics simulation runs, a time step of 1 fs was used, along with a 0.11 nm distance cut-off for evaluating all intermolecular interaction potentials. For Coulombic interactions, we chose a damped shifted force potential with a damping parameter of 0.05 Å$^{-1}$. Following the approach of Demichelis et al., we set up a cubic simulation box with 10 nm dimensions mimicking an aqueous 0.5 M CaCO$_3$ solution at pH=10; the molecular composition is given in Table S1A below.$^{[17]}$ In individual simulation runs performed for EDTA, MGDA, CIT, CPTC, HEDP and TPP, we explored the evolution of the calcium carbonate solution in the presence of additives. The protonation state of the additives was chosen i) on the basis of the pK$_A$ values as known from experiments in carbonate-free solutions (table S2A) and ii) considering substantial lowering of the effective pK$_A$ values upon association of calcium ions. For each of these systems, 10 additive molecules (~0.02 M) along with the corresponding number of sodium ions needed for charge neutralization were introduced. For calcium, carbonate, and bicarbonate, we employed the well-established forcefield of Gale et al., along with a flexible SPC/Fw water model.$^{[17-19]}$ In turn, the general amber force field (GAFF) was used for the additives and the sodium ions, respectively.$^{[20,21]}$ For the former, atomic point charges were identified by means of a restrained electrostatic potential fit to quantum calculations of the isolated ionic species. The quantum calculations were performed at the HF/6-31G* level using the Gaussian09 package.$^{[22]}$

Molecules and ions were first placed at random positions. The system was then allowed to relax by steepest decent energy minimization, followed by 30 ns equilibration runs at ambient conditions, using the Nosé-Hoover thermostat-barostat algorithm with relaxation times of 0.1 ps and 1.0 ps. The equilibration time was chosen generously large to ensure a dynamic equilibrium of DOLLOP growth and dissociation is reached, hence the number of ions in DOLLOPs and the diffusion coefficients for all ionic species stayed constant. The production runs are based on further 20 ns molecular dynamics simulations.

The complexity and variability of additive coordination by calcium ions can be visualized by 3-dimensional occurrence profiles, as exemplified in Figure S9. Each image is based on 20 ns simulation trajectories whose coordinates were back-mapped with respect to the
orientation of a single additive molecule’s carboxylate/phosphonate group. To illustrate the flexibility of the terminal oxygens of carboxylate/phosphonate groups as well as the dynamics of the coordinated Ca ions, the corresponding O/Ca positions were sampled at 100 ps intervals and then shown cumulatively as a cloud of dots. Note that different dot sizes were used to mark the Ca positions to compensate for the different occurrences stemming from different overall coordination numbers.

To qualitatively measure the association of both calcium and carbonate ions by a given additive, we investigated the radial distribution functions for both ions, Ca$^{2+}$ and CO$_3^{2-}$ in the first and second coordination shell of all additives. For assessing the Ca coordination in the additive’s first shell, we sampled the Ca-C/P distances based on the carboxylate-C / phosphonate-P atoms, as exemplary shown on the left of Figure S8. In turn, the association of carbonate by additives is most reliably assessed by the distance between carbonate-C atoms and terminal O atoms of the additives, i.e., oxygens in carboxylate or phosphonate groups, see the right plot of Figure S8. The radial distribution functions of the Ca-C/P distances show distinct peaks for bi- and mono-dentate Ca-coordination by carboxylates or phosphates. The minima between the first and second coordination shell peaks are given in Table S3; they were used as distance delimiters when identifying the nearest-neighbor coordination numbers of the additives given in Figure S9.

Molecular modelling was also used to estimate the molecular surface of surface-bound additives. For each of the investigated chelant species the molecular surface was computed based on a 3 Å (van der Waals contact) distance delimiter. While this reflects the solvent accessible surface of the chelants, we assume that the contact area of chelants docked to the surface of an ACC precipitate would amount to roughly half of the total chelant surface, yielding values of 74 Å$^2$, 85 Å$^2$, 92 Å$^2$, 91 Å$^2$, 81 Å$^2$, and 121 Å$^2$ for HEDP, TPP, CPTC, MDGA, CIT, and EDTA, respectively. On this basis, the maximum chelant density on a fully covered precipitate (without any additive incorporation) can be estimated by the inverse of the contact area — its values range from 0.8 for the largest (EDTA) to 1.4 nm² for the smallest (HEDP) chelant.

### Table S1. Number of ions and water molecules in simulation cells

| Additive-free | n Additive | n Ca$^{2+}$ | n CO$_3^{2-}$ | n HCO$_3^-$ | n Na$^+$ | n H$_2$O |
|---------------|------------|------------|-------------|------------|----------|----------|
| EDTA$^{4-}$   | 10         | 268        | 134         | 268        | 40       | 59572    |
| MGDA$^{3-}$   | 10         | 268        | 134         | 268        | 30       | 59578    |
| CIT$^{3-}$    | 10         | 268        | 134         | 268        | 30       | 59570    |
| CPTC$^{4-}$   | 10         | 268        | 134         | 268        | 40       | 59564    |
| HEDP$^{4-}$   | 10         | 268        | 134         | 268        | 40       | 59576    |
| TPP$^{5-}$    | 10         | 268        | 134         | 268        | 50       | 59582    |
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**Table S2A** Dissociation constants ($pK_a$) of additives in water.

|          | $pK_{A,1}$ | $pK_{A,2}$ | $pK_{A,3}$ | $pK_{A,4}$ | $pK_{A,5}$ |
|----------|------------|------------|------------|------------|------------|
| EDTA$^{[23]}$ | 2.0        | 2.7        | 6.16       | 10.26      |            |
| MGDA$^{[24]}$ | 1.6        | 2.5        | 10.5       |            |            |
| CIT$^{[25]}$ | 3.13       | 4.76       | 6.39       |            |            |
| CPTC$^{[26]}$ | 2.54       | 3.97       | 5.05       | 9.25       |            |
| TPP$^{[27]}$ | 1          | 2          | 2.13       | 5.75       | 8.65       |
| HEDP$^{[28]}$ | 1.87       | 2.76       | 6.78       | 10.20      |            |

**Table S2B** Theoretical speciation of additives at pH 9.75 in water. The label in the first row indicates the deprotonation state. $H_xL$ denotes the fully protonated additive species, $H_{x-1}L$: the monoanion after release of one proton, $H_{x-2}L^2$: the dianion after the second deprotonation step, etc.

|          | $H_xL$ | $H_{x-1}L$ | $H_{x-2}L$ | $H_{x-3}L$ | $H_{x-4}L$ | $H_{x-5}L$ |
|----------|--------|------------|------------|------------|------------|------------|
| EDTA$^{[23]}$ | 3.1E-19 | 1.7E-11    | 2.0E-4     | 0.76       | 0.24       |            |
| MGDA$^{[24]}$ | 3.4E-16 | 4.8E-8     | 0.85       | 0.15       |            |            |
| CIT$^{[25]}$ | 1.1E-15 | 4.6E-9     | 4.5E-4     | ~1         |            |            |
| CPTC$^{[26]}$ | 4.9E-19 | 8.0E-12    | 4.8E-6     | 0.24       | 0.76       |            |
| HEDP$^{[28]}$ | 1.1E-18 | 8.1E-11    | 7.9E-4     | 0.74       | 0.26       |            |
| TPP$^{[27]}$ | 5.6E-30 | 3.1E-21    | 1.8E-13    | 7.4E-6     | 0.074      | 0.93       |

**Figure S1.** Micrographs of additive-free ACC and products after 15 min of ripening.
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**Figure S2** XRD diffractograms of ACC powders received after different reaction times. (A) After 0 min. All retrieved powders were X-ray amorphous. (B) After 15 min of reaction time. Rietveld refinement analyses showed that additive-free reference experiments predominantly formed vaterite (97.9%) besides traces of calcite. Vaterite also formed preferentially, though to a lesser extent in the presence of EDTA, MDGA, and CIT (95.5%, 97.8%, and 85.1%, respectively). (C) After drying and resuspending 15 min in water. Calcite dominated in the additive-free ACC (76.8%), whereas EDTA-, MDGA-, and CIT-ACC mainly formed vaterite (81.8%, 81.1%, and 63.4%, respectively).
**Figure S3.** Differential scanning calorimetry of the non-ripened ACC powders; $T_x$ denotes the observed crystallization temperature.

**Figure S4.** Thermogravimetric analyses (TGA) of the non-ripened ACC powders. The mass fraction of additives was determined as described in the experimental details; the determined mass fractions for EDTA-ACC and MGDA-ACC are at the resolution limit of this technique.
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**Figure S5.** Further results from SS-NMR spectroscopy on ACC precipitated in presence of additives. (a) 121.85 MHz $^{31}$P CP MAS spectra of CaCO$_3$ precipitated with TPP (bottom) and HEDP (top). The spectrum of TPP shows three broad peaks (centered at 4, -5, -20 ppm) representing the speciation of the hydrolysis products of TPP – $P_1$ (orthophosphate), pyro- and/or terminal phosphate, and internal phosphate, respectively, as incorporated within ACC. (b) 75.4 MHz $^{13}$C CP MAS spectrum of CaCO$_3$ precipitated with citrate (top, black) overlayed that of neat calcium citrate (bottom, red) for a reference. (c) 75.4 MHz $^{13}$C DE (red) and CP (black) MAS spectra of the “as-arrived” additive-free [20%-$^{13}$C]CaCO$_3$ – control sample – showing vaterite as the major component (DE, red trace) and residual disordered vaterite (CP, black trace). (d) Representative $^{13}$C($^{31}$P) CP-REDOR$^{[12,13]}$ spectra (16 $T_R$, 1.6 ms) of HEDP-ACC showing the almost complete attenuation of the auaternary and methyl carbon peaks of HEDP due to the strong intramolecular dipolar interactions (single bond and two bond distances, respectively), and (e) the carbonate peak (64 $T_R$, 6.4 ms) of HEDP- (left) and TPP-ACC (right) precipitates showing attenuation of the carbonate peaks due to weaker intermolecular carbonate-P interactions (27 and 34% attenuation, respectively). $S_0$ denotes reference spectra (black) and $S_R$ denotes REDOR spectra (red). (f) The $\Delta S/S_0$ REDOR evolution as function of the dipolar recoupling time (HEDP - black squares; TPP - green triangles). Curves represent REDOR simulations$^{[29]}$ for a simplified geometric model of a single phosphate centered in a CaCO$_3$ sphere with radii $R = 7$, 8, 9, 10 Å, corresponding to P-concentrations of 6, 4, 3 or 2 P/Ca mol%, respectively$^{[15,30]}$. The 5 and 6 mol% P-concentrations implied for the experimentally measured REDOR evolution for HEDP and TPP, respectively, are corrected to molecular concentrations by division by 2 and 3 to account for the two P atoms.
in HEDP and three in TPP, hence yielding \(~2\text{mol}\% \text{ (additive/CaCO}_3\text{)}\) as a coarse estimate of their occlusion level. Repeated measurements of the same recoupling periods produce a scatter that reflects the noise (uncertainty) that accompanies the $\Delta S/S_0$ determination. As may be seen the scatter is well bound by the 5-6mol\% P/Ca concentration range.

**Figure S6.** Mineralization profile in presence of 800 $\mu$M citrate.

**Figure S7.** Median and standard deviation of reference titration profiles, *i.e.*, in absence of additive.
Figure S8. Representative snapshots of the investigated additives (dark blue) in MD simulations. EDTA and MGDA are shown as close-up pictures with the additive’s oxygen atoms highlighted in light blue. These are forming salt-bridges to calcium (yellow) ions – which in turn may coordinate a small number of carbonate (red) and further calcium ions. The other additive species prefer to interact with PNCs. This preference smoothly shifts from lateral association to integrating into the PNCs with the series of CIT, CPTC, HEDP, and TPP, respectively.
Figure S9. Distribution of carboxylate/phosphonate oxygen atoms (red clouds) of the additives and Ca\(^{2+}\) positions observed within 20 ns runs. Different pixel colors mark Ca coordination to different carboxylate/phosphonate groups, respectively.

Figure S10. (left) Radial distribution functions of the Ca-C/P distances (left) showing calcium association to the carboxylate / phosphonate groups of CIT and HEDP, respectively. (right) The CO\(_3^{2-}\) arrangement with respect to the additives is characterized by sampling the C(carbonate)-O(additive) distances. The minima between the first and second coordination peaks in the radial distribution functions are used as distance delimiters for discriminating nearest neighbor numbers as summarized in Table S3.
**Table S3.** Ca-C/P(additive) and C(carbonate)-O(additive) distance delimiters for identifying the first coordination sphere of the additives, in Å.

|       | EDTA | MGDA | CIT | CPTC | HEDP | TPP |
|-------|------|------|-----|------|------|-----|
| \(\text{Ca}^{2+}\) | 3.8  | 3.8  | 3.1 | 3.8  | 3.4  | 3.4 |
| \(\text{CO}_3^{2-}\) | 4.2  | 4.5  | 4.3 | 4.4  | 4.5  | 4.4 |

**Figure S11.** Occurrence profiles of the number of \(\text{Ca}^{2+}/\text{CO}_3^{2-}\) associated to the additives.
Figure S12. Time-resolved evolution of the simulation system featuring the HEDP-calcium carbonate solution. Additives are shown in blue, \( \text{Ca}^{2+} \) in yellow (magnified spheres in close proximity to additives), and \( \text{CO}_3^{2-} \) in orange. Starting from randomly dispersed ions, HEDP quickly agglomerates several \( \text{Ca}^{2+} \) ions in its immediate proximity. During further relaxation, PNCs grow further, incorporating the additive into their dynamic structure. The finally formed PNCs show a dynamic equilibrium of calcium and carbonate association/dissociation, whilst the HEDP additives remain within the PNC throughout our MD runs.

|      | \( \bar{n}_{\text{Ca}} \) | \( \bar{n}_{\text{CO}_3} \) | classification |
|------|----------------|----------------|----------------|
| EDTA | 3.6           | 1.3            | \( \bar{n}_{\text{Ca}} > \bar{n}_{\text{CO}_3} < 2 \) |
| MGDA | 2.1           | 1.5            |                 |
| CIT  | 3.2           | 2.0            | \( \bar{n}_{\text{Ca}} > \bar{n}_{\text{CO}_3} \approx 2 \) |
| CPTC | 4.9           | 3.3            |                 |
| HEDP | 5.5           | 4.8            | \( \bar{n}_{\text{Ca}} > \bar{n}_{\text{CO}_3} > 3 \) |
| TPP  | 6.4           | 4.9            |                 |

Table S4. Average nearest-neighbor numbers of \( \text{Ca}^{2+} \) and \( \text{CO}_3^{2-} \) ions associated to the different additives as derived from the occurrence plots in Figure S9. The different modes of additive action are not only related to the number of associated \( \text{Ca}^{2+} \) ions but also notably differ in \( \text{CO}_3^{2-} \) association numbers.
Figure S13. (A) SANS scattering profiles collected from non-ripened ACC powders. (B) Multilevel Beaucage-fit exemplified in case of the reference, i.e., ACC generated in absence of additives.

Figure S14. Specific surface area (SSA) of non-ripened ACC powders, as determined from SANS data using the Porod invariant. A simple order-of-magnitude estimate reveals that the additives’ mass fractions (as determined by TGA) are inexplicable by mere surface adsorption but requires additive incorporation (Figure S15).
Table S5. Fitting parameters of the multilevel Beaucage fit based on SANS data shown in Figure S13.

![Comparison of experimentally determined additive mass per unit volume (green) and theoretical additive mass per unit volume at the maximum surface loading capacity (orange). The experimentally determined mass fraction considerably exceeded the theoretical limit of pure surface adsorption. The latter was derived from the specific surface area (SSA, Fig. S14) and the contact area of each additive estimated by MD (see p. 6). The experimental additive mass per unit volume was received from TGA analysis, assuming an ACC density of 2.18 g cm$^{-3}$ [31]. Note that the experimentally determined additive mass per unit volume for ACC-EDTA and ACC-MGDA is below the resolution limit of TGA and can only be seen as an upper bound (mass fraction according to TGA: <0.4%).](image-url)
Supplemental References

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