

Design of a Synthetic Foldamer that Modifies the Growth of Calcite Crystals

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The ordered projection of functional groups plays an important role in controlling the growth of minerals in both biological¹ and artificial systems.² Acidic macromolecules isolated from a variety of biogenic minerals have been shown, *in vitro*, to modify the morphology³ and polymorph⁴ of calcium carbonate crystals. Peptides,⁵ synthetic polymers,^{6,7} monolayers,⁸ and dendrimers⁹ have been designed to display functionality to interact with growing crystal faces; however, few low-molecular weight compounds with the same property have been identified.¹⁰

We have previously used small-molecule scaffolds to disrupt protein–protein interactions through protein surface recognition.^{11,12} Protein–crystal recognition also involves the binding of a large, solvent-exposed surface area by a flat or convex array of functional groups.¹³ One effective scaffold for targeting protein–protein interactions is an oligopyridine foldamer that projects complementary recognition groups in a controlled arrangement.¹² In this communication we describe the application of this foldamer to crystal surface recognition. The ordered projection of carboxylates from the scaffold modifies the morphology of calcite crystals via a specific interaction with the $\{10l\}$ ($0.5 \leq l < 1$) faces.

The tricarboxylic acid derivative, **1**, was synthesized via sequential coupling of the protected acid chlorides and aniline derivatives (see Supporting Information). Compound **3** was synthesized as a monomeric control. The crystal structure of the trimeric nitro derivative, **2**, showed a planar conformation stabilized by two intramolecular bifurcated hydrogen bonds between the amide NHs and their neighboring pyridine N and alkoxy O groups ($N \cdots N$ and $N \cdots O$, 2.6–2.7 Å) (Figure 1).^{14,15} The key consequence of this strand structure is that the three carboxylate groups project from the same face of the molecule separated by ~5 Å. This spacing is well-suited for interaction of the three carboxylates with Ca^{2+} ions on the surface of a growing $CaCO_3$ (calcite) crystal.

Slow diffusion of carbon dioxide (from ammonium carbonate within a desiccator) into a solution containing both the foldamer and calcium chloride, resulted in the slow crystallization of calcium carbonate.³ After 3 days, the resulting crystals were rinsed with water, and examined by both light and scanning electron microscopy. IR spectroscopy of the solid (Supporting Information) showed that in all cases (**1**, **3**, and control) the major phase was calcite. The calcite grown with the trimer, **1** (1 mM), had a saw-tooth morphology that is very different from the equilibrium rhombohedral geometry of control calcite (Figure 2). The angle of the “teeth” was measured consistently both within individual rods and among several rods to be ~35°. In contrast, calcite grown in the presence of monomer **3** (3 mM) was indistinguishable from control calcite (not shown).

These modified crystals resembled calcitic rhombohedra formed by six $\{10l\}$ faces (Figure 2b, inset).^{17,18} To gain more information about the identity of the new faces, overgrowth experiments were performed (Figure 2c–f).¹⁹ The new crystals are completely aligned (showing no rotation around the *c* axis), indicating that each rod is an individual crystal, not aggregates of several crystals (Figure 2d).

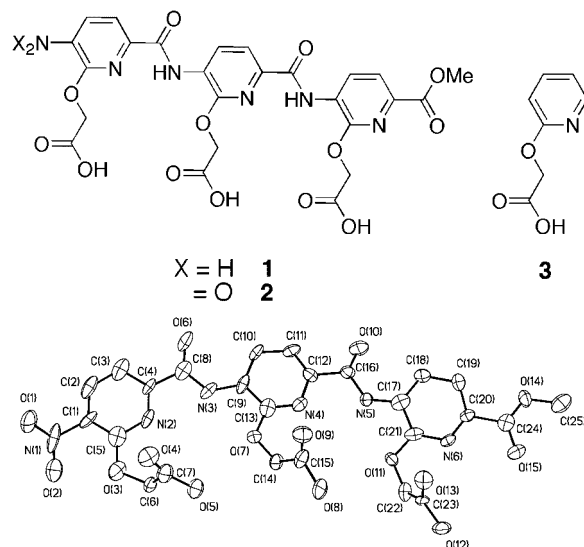


Figure 1. ORTEP representation (30% probability) of the crystal structure of **2**. The hydrogen atoms have been omitted for clarity.

The long axis of the rods is aligned with the *c* axis of calcite, and therefore growth occurs primarily in that direction. The orientation also indicates that the faces forming the “teeth” are in the $\{h0l\}$ family. Finally, the inclination of the overgrowth crystals toward the tip of the underlying crystal (arrows in Figure 2f), distinguishes the new faces as $\{10l\}$ rather than $\{10l\}$. This information, along with the calculated angles for different $\{10l\}$ faces,¹⁸ identifies the faces formed as a result of **1** as the $\{10l\}$ faces where $0.5 \leq l < 1$.

The appearance of $\{10l\}$ faces of calcite has been observed previously from both inorganic^{7,20,21} and biogenic influences.^{3,22} Calcite grown in the presence of magnesium ions develops well-formed $\{101\}$ faces with $\{101\}$ steps. The larger hydration sphere of Mg^{2+} (compared to Ca^{2+}) can presumably be better accommodated into the $\{101\}$ face because the cations on these faces are far enough apart.^{3,20,21} *In vitro*, proteins isolated from both sea urchin spicules and mollusk shells have been shown to induce the formation of $\{101\}$ faces.^{3,22} These faces are roughly parallel to the *c* axis of calcite, and thus, the carbonate ions emerge almost perpendicular to the face (Figure 3). These faces are also good candidates for the interaction of acidic macromolecules with poly-Asp/Glu sequences.²³ That the synthetic foldamer, **1**, with an ordered array of carboxylates promotes the formation of $\{10l\}$ faces is consistent with the previously observed results.^{3,7,21,22} Recent work has suggested that a geometrical match between the angle of the carbonates in the calcite structure and the interacting carboxylic acids promotes binding to specific faces.^{7,24} In this system, the perpendicular projection of carbonates from the $\{101\}$ faces makes them favorable for replacement by the carboxylates projected by **1**. Another possibility is that the $\{10l\}$ faces are actually a combination of two sets of faces, such as the $\{102\}$ and $\{101\}$, as

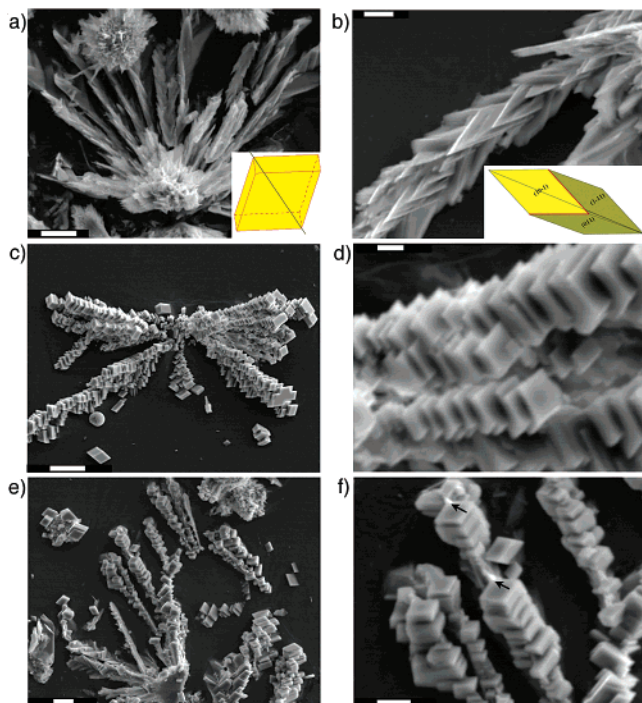


Figure 2. (a, b) SEM images of calcite grown in the presence of **1**. Scale bars: (a) 10 μm , (b) 5 μm . Insets in (a) calcite rhombohedron with the equilibrium morphology of six $\{104\}$ faces and (b) calcite rhombohedron with six $\{101\}$ faces created using SHAPE. (c) Low magnification of rods after overgrowth (100 mM CaCl_2 , 30 min). Scale bar: 20 μm . (d) A magnified view of the upper right-hand portion of (c). Scale bar: 2 μm . (e) Less heavily overgrown rods (25 mM CaCl_2 , 2 h). Scale bar: 10 μm . (f) A magnified view of the middle of (e). Black arrows indicate portions of the original crystal visible under the overgrowth. Scale bar: 5 μm .

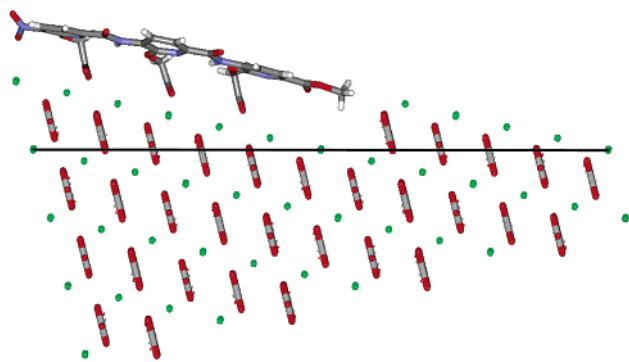


Figure 3. Molecule of **1** docked onto the $(\bar{1}01)$ face of calcite (black line). Notice that the carbonates are projected almost perpendicularly out of the plane and the angle is matched by the carboxylates. Red: oxygen. Blue: nitrogen, White: hydrogen, Gray: carbon, Green: calcium. Manually docked in WebLabViewer (Accelrys Software).

has been proposed for hillocks bounded by $\{\bar{1}01\}$ faces observed by AFM and resulting from dissolution by aspartic acid.²⁵

In conclusion, a synthetic foldamer projecting carboxylates in an ordered fashion has been shown to influence the growth of calcium carbonate. A specific interaction between the growing calcite crystals and **1** results in the formation of new faces (the $\{\bar{1}01\}$) and a unique morphology. The modularity of the synthetic scheme suggests that other minerals may be targeted by this approach. From this, we should gain insight into the strategies used by organisms to control the growth of minerals.

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Supporting Information Available: Complete synthetic experimental details and an IR spectrum (PDF). X-ray crystallographic data (CIF file). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- Crystal data of **1**: pale yellow plates, $T = 150(2)$ K, triclinic, $P-1$, $Z = 4$, $a = 13.6343(14)$ Å, $b = 14.1508(14)$ Å, $c = 23.889(2)$ Å, $\alpha = 86.844(2)^\circ$, $\beta = 82.792(2)^\circ$, $\gamma = 71.115(2)^\circ$, $V = 4325.9(8)$ Å³, $R_1 = 0.1289$, $GOF = 1.479$.
- C—H \cdots O hydrogen bonds may also play a role in stabilizing the structure. C \cdots O, 2.7–2.9 Å.
- A tilting stage was not used; thus, this is only an approximation.
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