A New Design Strategy for Molecular Recognition in Heterogeneous Systems: A Universal Crystal-Face Growth Inhibitor for Barium Sulfate

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Controlling crystallization in both chemical production and product formulations is well-known.[1−4] As well as composition and temperature, specific additives can also exert a powerful influence on both crystal nucleation and growth rates. Current design strategies of such additives are based on a molecular recognition[5] in which the additive binds selectively to a single growing crystal surface. Herein, we report on a new conceptual approach to heterogeneous recognition based on the rational design of a molecule which can bind all growing faces of barium sulfate, resulting in a highly active modifier of barium sulfate crystal growth in practice.

Eight different faces are thought to be important in the growth of barium sulfate crystals.[6] Since the spacing between nearest-neighbor sulfate−sulfate sites in each of these faces is different (see Supporting Information), designing an additive which is capable of inhibiting all crystal growth faces is a challenging problem.[2,7] The solution is to design a molecule which is capable of recognizing and binding to *all* possible growing crystal faces. This could be achieved in theory by either (a) designing a molecule with a large number of binding motifs, so that at least one or two of the groups coincide with binding sites on any particular crystal surface (schematically shown in Figure 1),[8] or

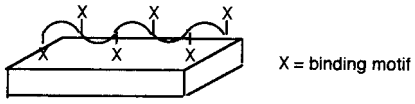

Figure 1. Schematic of a single-face binding agent.

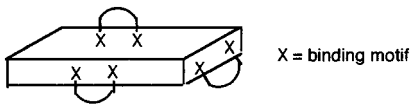

Figure 2. Schematic of a universal face-binding agent.

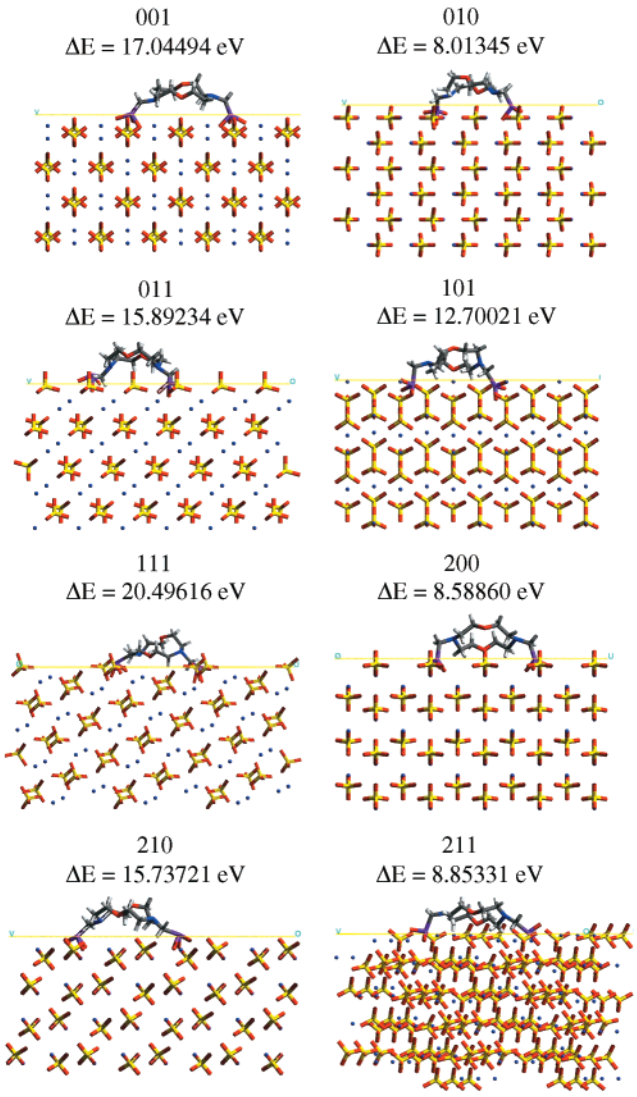

Figure 3. 1,7-Dioxo-4,10-diaza-12-crown-4-*N*,*N*′-dimethylenephosphonate **6** (in vacuo energy −4402.45141 eV) binding to each of the crystallographic faces[11] of barium sulfate indicated, together with relative energies (Δ*E*) for each conformation. Length scale is shown in parentheses in each image. Each snapshot is captured after 10 ps of molecular dynamics performed at 300 K, following energy minimization. Color key: gray, carbon; white, hydrogen; red, oxygen; blue in modifier, nitrogen; pink, phophorus; blue in crystal lattice, barium; yellow, sulfur.

(b) designing a molecule with a small number of binding motifs, but which can easily adopt several conformations (preferably of similar energy) to enable binding to growing surfaces (Figure 2). The disadvantages of (a) is that large molecules need to be made and many of the binding motifs might be superfluous by not taking part in binding. Therefore, the design of a flexible, universal face-binding agent is more attractive, especially if the molecular weight

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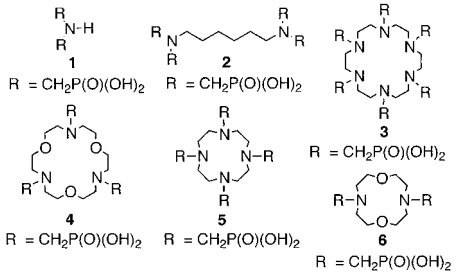
and number of binding functions can be minimized. It is inherently more difficult to achieve this goal because it necessarily requires a more detailed knowledge of the conformational flexibility of the molecule—an exacting test of predictive computational molecular design.

The design of this new class of flexible crystal growth inhibitors started with a search for candidate molecular structures. The basic structural fragment considered was the poly-aminomethylphosphonate system, since such molecules (e.g. **1** and **2**) are barium sulfate scale inhibitors due to replacement of some of the sulfate sites in the growing crystal by their phosphonate groups.[7] Taking up a theme exemplified by earlier work on the inhibition of crystallization of ettringite,[3,4,9] we examined a range of related macrocyclic aminomethylphosphonates **3**−**6**. This earlier work



showed that molecular modeling can be applied to the rational *a priori* design of novel compounds, which acted as efficient inhibitors of crystalline ettringite formation.[9,10]

Energy minimization and molecular dynamics simulations at 300 K[11] of the binding of molecules **1**−**6** (among others) on the different surfaces of barium sulfate revealed that most of these molecules (**1**−**6** and related structures)[2] showed good recognition for at least one or two faces.[2] However, no molecules showed complementary binding (i.e. all phosphonate groups were capable of binding into vacant sulfate sites in the lattice) to three or more faces, the outstanding exception being macrocycle **6**. Compound **6** was capable of recognizing and binding to all eight crystal faces of the barium sulfate lattice without attendant formation of high-energy, unfavorable conformations (i.e. all conformations accessible at 300 K). This achievement stems from the fact that molecule **6** is sufficiently flexible to be able to adopt a wide range of energetically similar conformations, wherein the relative separation of the phosphonate groups adjusts to match sulfate−sulfate distances on each different crystal face. The results of these simulations are displayed in Figure 3.

Following the prediction that macrocycle **6** should be a highly efficient barium sulfate binding agent, the synthesis and evaluation of **6** was undertaken. The synthesis was accomplished using literature-related methods.[12,13] (Scheme 1) and N-phosphonoalkylation.[14] The effect of macrocycle **6** on the growth of barium sulfate crystals was then studied by performing crystallization experiments in the presence of varying concentrations of **6**.[8]

To assess the success of our design methods, we prepared crystals of barium sulfate[8] both with and without additive **6**, to compare any morphological changes with those reported[7,8] for linear additives (e.g. **1** and **2**). Our criterion for success was that whereas additives of type **1** and **2** act anistropically, yielding morphologies in which faces in the [001] zone are selectively inhibited,[7,8] additive **6** is expected to act isotropically, simultaneously modifying the growth faces in all three orthogonal zones.

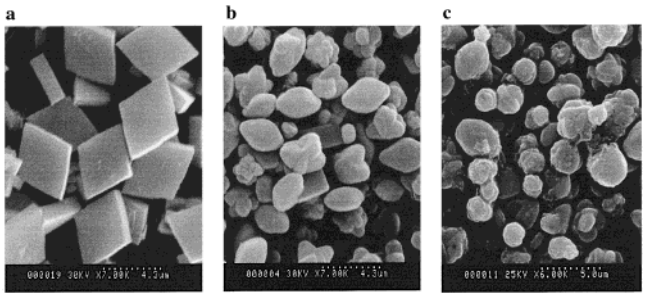
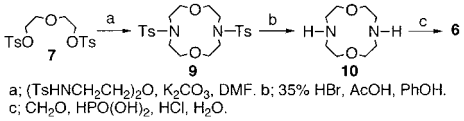


Figure 4. SEM images showing the effect of additive **6** on $BaSO_4$ morphology: (a) native $BaSO_4$; (b) $BaSO_4$ crystallization in the presence of 0.048 mM **6**; (c) $BaSO_4$ crystallization in the presence of 0.096 mM **6**. All crystallization were carried out under identical conditions; precipitates were formed at 70 °C by mixing solutions of $BaCl_2$ and Na_2SO_4 according to literature methods.[7,8]

Scheme 1



a; $(TsHNCH_2CH_2)_2O$, K_2CO_3, DMF. b; 35% HBr, AcOH, PhOH. c; CH_2O, $HPO(OH)_2$, HCl, H_2O.

The consequence of this should be that the well faceted {001} rhombs found in pure solutions will be replaced by crystals in which the growth rates in all directions will be inhibited and anisotropy of the growth disappears. Such crystals are expected to be increasingly spherical as the concentration of additive **6** is increased. Figure 4 shows the comparison. In Figure 4a rhombic plates grown with additive can be seen; Figure 4b corresponds to 0.048 mM of **6** with the rhombic outline still evident but with facets largely absent and a partially spherical morphology; Figure 4c at a loading of 0.096 mM shows crystals which as expected are virtually spherical and no evidence of faceting remains. These data are totally consistent with our expectations and fulfill our success criterion. We note that the spheres produced here are quite clearly the result of a gradual loss of faceting of single crystals, in marked contrast to the spheres which are formed from high loadings of **1** and **2** which are known to be ordered aggregates of nanocrystals.[15] The reduction in sizes with additive concentration suggests that the crystallization process is inhibited with nucleation becoming the dominant process.

In summary, we have designed macrocycle **6** which, according to computer simulations, should recognize and bind to all the important crystal growth faces of barium sulfate. Subsequent crystallization experiments clearly show that all faces are modified by the formation of spherical single crystals, thus showing the viability of the novel design strategy inherent (Figure 2), i.e., the application of a universal crystal-face blocking agent. Such an approach should prove invaluable as a general protocol for the design of not only new crystal growth inhibitors, but of novel heterogeneous systems and materials.

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Supporting Information Available: Experimental procedures and data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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