Journal of Structural Biology 196 (2016) 260–287

Contents lists available at ScienceDirect

Journal of Structural Biology

journal homepage: www.elsevier.com/locate/yjsbi

Nonclassical crystallization *in vivo et in vitro* (II): Nanogranular features in biomimetic minerals disclose a general colloid-mediated crystal growth mechanism

Carlos Rodríguez-Navarro [a,*], Encarnación Ruiz-Agudo [a], Joe Harris [b], Stephan E. Wolf [b,c]

[a] Dpto. Mineralogía y Petrología, Universidad de Granada, Fuentenueva s/n, 18071 Granada, Spain
[b] Department of Materials Science and Engineering, Institute of Glass and Ceramics (WW3), Friedrich-Alexander-University Erlangen-Nürnberg, Martensstrasse 5, 91058 Erlangen, Germany
[c] Interdisciplinary Center for Functional Particle Systems (FPS), Friedrich-Alexander University Erlangen-Nürnberg (FAU), Haberstrasse 9a, 91058 Erlangen, Germany

ARTICLE INFO

Article history:
Received 29 January 2016
Received in revised form 5 September 2016
Accepted 7 September 2016
Available online 9 September 2016

Keywords:
Biomimetics
Calcium carbonate
Amorphous precursor
Dense liquid precursors
PILP
Nanogranular
Nonclassical crystallization
Nanoparticle-mediated crystal growth

ABSTRACT

Recent research has shown that biominerals and their biomimetics (i) typically form via an amorphous precursor phase, and (ii) commonly display a nanogranular texture. Apparently, these two key features are closely related, underlining the fact that the formation of biominerals and their biomimetics does not necessarily follow classical crystallization routes, and leaves a characteristic nanotextural imprint which may help to disclose their origins and formation mechanisms. Here we present a general overview of the current theories and models of nonclassical crystallization and their applicability for the advance of our current understanding of biomineralization and biomimetic mineralization. We pay particular attention to the link between nonclassical crystallization routes and the resulting nanogranular textures of biomimetic $CaCO_3$ mineral structures. After a general introductory section, we present an overview of classical nucleation and crystal growth theories and their limitations. Then, we introduce the Ostwald's step rule as a general framework to explain nonclassical crystallization. Subsequently, we describe nonclassical crystallization routes involving stable prenucleation clusters, dense liquid and solid amorphous precursor phases, as well as current nonclassical crystal growth models. The latter include oriented attachment, mesocrystallization and the new model based on the colloidal growth of crystals via attachment of amorphous nanoparticles. Biomimetic examples of nanostructured $CaCO_3$ minerals formed via these nonclassical routes are presented which help us to show that colloid-mediated crystal growth can be regarded as a wide-spread growth mechanism. Implications of these observations for the advance in the current understanding on the formation of biomimetic materials and biominerals are finally outlined.

1. Introduction

Biominerals display complex shapes, a hierarchical structure, and an exquisite organization at multiple length-scales, which along with the right combination of rigid (mineral) and elastic/-plastic (organic) materials, provide them with unmatched functionality and physical-mechanical properties (Cölfen and Yu, 2005; Gómez-Morales et al., 2015; Gower, 2008; Hendley et al., 2015; Lowenstam and Weiner, 1989; Mann, 2001; Meldrum and Cölfen, 2008; Nudelman and Sommerdijk, 2012). These features enable biominerals to, for instance, offer protection and structural support (Lowenstam and Weiner, 1989), act as equilibrium, optical or sensing (orientation or navigation) devices (Aizenberg et al., 2001; Faivre and Schüler, 2008; Lowenstam and Weiner, 1989), provide structural color (Li et al., 2015), and act as ion reservoirs (Sato et al., 2011). Inspired by nature and in a quest to reproduce *in vitro* the superior properties and functionality of biominerals, chemists and material scientists have tried to replicate them in the laboratory via bottom-up, mild synthesis routes (Aizenberg and Fratzl, 2009; Arakaki et al., 2015; Imai et al., 2006; Liu and Jiang, 2011; Meldrum and Cölfen, 2008; Munch et al., 2008; Sanchez et al., 2005; Sommerdijk and de With, 2008; Wegst et al., 2015; Xu et al., 2007; Yao et al., 2014). This bio-inspired or biomimetic synthesis approach is not only aimed at replicating abiotically the size, shape, orientation, composition and hierarchical organization of existing biominerals, but also strives to learn guiding principles and ideas that nature has mastered through

* Corresponding author.
E-mail address: carlosrn@ugr.es (C. Rodríguez-Navarro).

http://dx.doi.org/10.1016/j.jsb.2016.09.005
1047-8477/

billion years of evolution (since early microbial biomineralization; see for instance Wright and Oren, 2005) and use them for the synthesis of novel functional materials (Xu et al., 2007). Indeed, as indicated by Gómez-Morales et al. (2015) "what is really important in biomimetic and bio-inspired studies is not the devices themselves, but to understand the mechanisms that life uses to produce them". Interestingly, the synthesis and analysis of biomimetic minerals is in turn yielding important results that are helping to shed light on the mechanisms of biomineralization. Some of these results, particularly those referring to the nanotextural features of biomimetic calcium carbonate minerals and their relationship to nonclassical crystallization routes, are reviewed here.

Growing experimental evidence is showing that biominerals and their biomimetic counterparts commonly display two key features that seem to be related and might be general (Gal et al., 2014, 2015; Gower, 2008): they form via amorphous precursor phases (Addadi et al., 2003; Aizenberg et al., 2003; Beniash et al., 1997, 2009; DeVol et al., 2015; Gal et al., 2010; Gong et al., 2012; Gower, 2008; Killian et al., 2009; Lowenstam and Weiner, 1985; Mahamid et al., 2008; Politi et al., 2004, 2008; Rodriguez-Navarro and Ruiz-Agudo, 2013; Rodriguez-Navarro et al., 2015a,b; Seto et al., 2012; Towe and Lowenstam, 1967), and display a nanogranular texture, typically made up of oriented nanocrystals less than 100 nm in size (for an extended list of contributions, see the first part of this review and references therein -Wolf et al., 2016a, or, for instance Böhm, 2016; Dauphin, 2001, 2008; Cuif et al., 2011; Gal et al., 2013, 2014, 2015; Miyajima et al., 2015; Oaki et al., 2006; Rodriguez-Navarro et al., 2015b; Ruiz-Agudo et al., 2016; Sethmann et al., 2006; Seto et al., 2012; Sondi et al., 2011; Stolarski and Mazur, 2005; Wolf et al., 2012, 2015a). These two key features underline the fact that the formation of biominerals and their biomimetics does not seem to follow classical crystallization routes/pathways. Furthermore, their nonclassical crystallization and subsequent coarsening via an aggregation-based growth mechanism where precursor nanoparticles, liquid or solid, amorphous or crystalline, are the building blocks, as opposed to monomers (as postulated by classical crystallization theory), leaves a characteristic nanotextural imprint (Fig. 1) which may help to disclose their formation mechanisms and may also aid in the recognition of biotic signatures in the geologic record.

Here we review some of the key structural and textural (nanogranular) features of biomimetic minerals, as well as their nonclassical nucleation and growth mechanisms. For this, we first present a brief description of the fundamentals of classical nucleation (CNT) and growth (CGT) theories. Afterwards we introduce the Ostwald's step rule, and discuss the different (thermodynamic and kinetic) theories put forward to explain its origins. The Ostwald's step rule helps us to put into context the following sections in which we present the current models for nonclassical nucleation (stable prenucleation clusters, liquid and solid amorphous precursors) and colloid-mediated, aggregation-based nonclassical crystal growth. We show that the formation of amorphous (liquid and solid) precursor phases, in conjunction with the presence (and effects) of organic additives, along with a general colloid-mediated nonclassical crystal growth mechanism, helps to explain the nanogranular features of a range of biomimetic minerals. Several examples of biomimetic materials with nanogranular features are presented and described here which help us to show that a colloid-mediated crystal growth might be a general growth mechanism *in vitro* (and *in vivo*, too; see Wolf et al., 2016a). We focus our review on calcium carbonate biomimetic minerals for two main reasons: (i) calcium carbonates are the most abundant biominerals and their biomimetics have been the subject of extensive research; and (ii) significant progress in our current understanding of nonclassical crystallization has recently taken place studying the $CaCO_3$-H_2O system. Finally, implications of these observations for the advance in the current understanding on the formation of biomimetic materials and biominerals are outlined.

2. Classical crystallization theory

Crystallization in solution is a first order phase transition which takes place via two distinctive processes: a) nucleation of a solid phase (a crystal embryo) and b) its subsequent spontaneous growth (Mullin, 2001). According to classical nucleation theory (CNT), as defined among others by Volmer and Weber (1926) and Becker and Doring (1935), based on Gibbs's works (Gibbs, 1876, 1878), the driving force for nucleation is the overall reduction in Gibbs free energy of a system, ΔG which can be expressed as:

$$\Delta G = -\frac{\frac{4}{3}\pi r^3}{v} kTln\left(\frac{IAP}{k_{sp}}\right) + 4\pi r^2\gamma \quad (1)$$

where r is the radius of a cluster (assumed to be spherical), v its molecular volume, k is the Boltzmann's constant, T is the absolute temperature, IAP is the ion activity product, and k_{sp} is the solubility product (of a relevant phase), being $\ln(IAP/k_{sp})$ defined as the supersaturation, σ of the system, and γ the interfacial (or surface) energy of the crystal embryo in contact with the solution. The first term of Eq. (1) accounts for the energy released by the formation of the bulk solid phase (due to the reduction in chemical potential upon incorporation of a monomer into a cluster), while the second term accounts for the energy penalty associated with the creation of a solid-solution interface. The competition between bulk and surface free-energy terms leads to the existence of a free-energy barrier that has to be overcome for a cluster to grow (via incorporation of monomers) rather than to shrink. This free energy barrier, $\Delta G*$ is overcome when the clusters reach a critical radius, that is, when $d\Delta G/dr = 0$, and is given by (García-Ruiz, 2003):

$$\Delta G^* = \frac{16\pi v^2\gamma^3}{3\left[kT\ln\left(\frac{IAP}{k_{sp}}\right)\right]^2} \quad (2)$$

Eq. (2) enables the calculation of the free energy barrier for homogeneous nucleation in solution. In most systems, however, a preexisting surface or an interface typically exists (e.g., solid particles, membranes or organic matrices). In these cases, the heterogeneous nucleation of crystal embryos on a substrate is favored. The presence of an interface significantly reduces the Gibbs free energy barrier for nucleation (Sommerdijk and de With, 2008). This occurs because the relevant surface free energy term is the sum of the nucleus-liquid and nucleus-substrate interfacial energies minus that of the liquid-substrate interface, whereas in the case of homogeneous nucleation the only relevant interfacial energy is that of the nucleus-liquid interface (Travaille et al., 2005). Heterogeneous nucleation is thus the generally preferred crystallization route in a range of biomineralization and biomimetic scenarios (e.g., template-directed crystallization, see for instance Aizenberg et al., 1999; Mann, 2001; Sommerdijk and de With, 2008; Tremel et al., 2007).

According to CNT, it is assumed that clusters are spherical (which is not the case for polyhedral crystals) and their γ equals that of the bulk macroscopic crystals. The latter is the so-called "capillary assumption" (Dillmann and Meier, 1989, 1991; Ford et al., 1993; Gebauer et al., 2014), which is largely responsible for the strong deviations between calculated and experimental values of nucleation rates, J^* given by (García-Ruiz, 2003; Mullin, 2001),

$$J^* = Aexp\left(-\frac{\Delta G^*}{kT}\right)exp\left(-\frac{E_a}{kT}\right) \quad (3)$$