

resulting precipitates were characterized by Infrared Spectroscopy, X-ray diffraction and the morphology of crystals was observed by an optical microscope and a scanning electron microscope.

The results showed that SOM influences not only on the agglomeration, morphology, size and polymorphism of the CaCO_3 crystals but also narrows the range of calcium and carbonate critical concentrations necessary to induce nucleation, the "Crystals-Growing Space". Thus, it appears evident that in gelling environment the SOM is able to select a specific calcium and carbonate concentration. That, respecting the supersaturation laws, confines the nucleation and growth processes.

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Keywords: biomineralization, organic matrix, gelling environment

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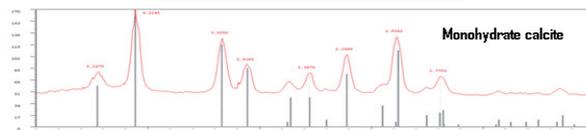
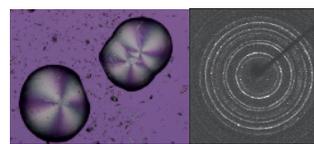
Self-assembled crystalline materials of calcium carbonate and silica

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Biom mineralization is a widespread crystalline phenomenon among living systems which provides superior microscopic and macroscopic material properties, which has aroused a great deal of interest and in vitro studies throughout the past years [1]. Moreover, the self-assembly of alkaline-earth metal carbonates in the presence of silicate is an outstanding example in biomineralization, as purely inorganic precursors cooperate in this case to constitute special structures and shapes strongly reminiscent of biological forms [2]. This kind of completely inorganic, self-assembled silica-carbonate aggregates showing a wide range of non-crystallographic, biomimetic morphologies and sizes from a much simpler system compare to living organisms [3]. However, the precipitation of calcium carbonate (CaCO_3) in basic silica has not produced the similar forms characteristic of biomorphs in the absence of any additives at room temperature until now.

Here we report an experimental study of the crystallization of calcium carbonate in silica gel at ordinary temperature and pressure. The experiments have been performed by diffusion-reaction technique in a diffusion cell, without the presence of organic additives. The concentrations of CaCl_2 and Na_2CO_3 have been varied from 0.05M to 0.2M in equimolar amounts and the gel pH value from 9.0 to 10.5. The crystals have been characterized by XRD, SEM and optical microscopy. After the screening of pH we have specially studied the crystallization at pH=10.5.

At this pH the results are the precipitation of the following crystalline phases with the increase in reagent concentrations: monohydrate calcite, calcite and aragonite. Microscopic observation of these crystalline phases reveals that monohydrate calcite is formed as peanut-like and hemispheric crystals in the liquid part of the system (see figure) whereas calcite (rhombohedral and sheaf of wheat morphologies) and aragonite (flower-like and lamellar morphology) are found out in the gel part. The formation mechanisms and specially the way in which silica interact with calcium carbonate to produce these morphologies is being deeply investigated.



[1] H. Colfen, *Curr. Opin. Colloid Interface Sci.* **8** **2003** 23. [2] J.M. Garcia-Ruiz, S.T. Hyde, A.M. Carnerup, A.G. Christy, M.J. Van Kranendonk, N.J. Welham, *Science* **2003** *302*, 1194. [3] A.E. Voinescu, M. Kellermerier, B. Bartel, A.M. Carnerup, A.K. Larsson, D. Touraud, W. Kunz, L. Kienle, A. Pfitzner, S.T. Hyde, *Crystal Growth and Design* **2008** *8*, 5, 1515-1521.

Keywords: silica gel, monohydrate calcite, calcite, aragonite

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Coordination polymers of *N,N'*-bis(pyridin-4-ylmethyl)hexanediamide (L): Ligand conformation and the effect of metal to ligand ratio

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The X-Ray crystal structures of four coordination complexes namely: $[\text{Cd}(\text{L})_{1.5}(\text{NO}_3)_2]_n$ **1**, $\{[\text{Cd}(\text{L})(\text{H}_2\text{O})_4](\text{NO}_3)_2(\text{H}_2\text{O})_2\}_n$ **2**, $\{[\text{Zn}_2(\text{L})(\text{H}_2\text{O})_5](\text{NO}_3)_2(\text{H}_2\text{O})_2\}_n$ **3** and $\{[\text{Zn}(\text{L})(\text{H}_2\text{O})_4](\text{NO}_3)_2(\text{H}_2\text{O})_2\}_n$ **4** are described. It was found that the ligand conformation [1] and the metal to ligand ratio [2] play an important role in determining the structure of the resulting complex. By varying the metal to ligand ratio and keeping other experimental factors constant, different coordination complexes were obtained.

Complex **1** was grown from cadmium nitrate and *N,N'*-bis(pyridin-4-ylmethyl)hexanediamide (L) in a metal ratio of 2:1. The complex consists of 2-D networks which are linked by self complementary amide hydrogen bonds. Complex **2** was grown from cadmium nitrate and L in a metal to ligand ratio of 1:1 and it consists of 1-D chains that are interlinked by hydrogen bonding via the nitrate anion. The three independent ligands in complex **2** adopt the AAA (anti-anti-anti) and GAG (gauche-anti-gauche) conformations while the ligands in complex **2** adopt the GAG conformation. Complexes **3** and **4** were grown from zinc nitrate and L in metal to ligand ratio of 1:2 and 1:1 respectively. Complex **3** consists of discrete and dinuclear units that are linked by hydrogen bonding via the coordinated water molecules. Complex **4** consists of 1-D chains that are interlinked by hydrogen bonding via the nitrate counter ions. The ligands in complex **3** are arranged in the AAA conformation while the ligands in complex **4** are arranged in the GAG conformation.

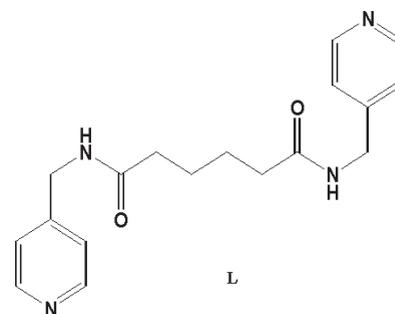


Fig 1. *N,N'*-bis(pyridin-4-ylmethyl)hexanediamide (L).

[1] H-L. Hu, Y-F. Hsu, C-J. Wu, C-W. Yeh, D. M. Proserpio and J-D. Chen, *CrystEngComm*, **2009**, *11*, 168. [2] D. J. Kleinhans, L. Dobrzanska and L. J. Barbour, *New J. Chem*, **2008**, *32*, 813-819.

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Crystal structures of histone chaperone CIA/ASF1-containing complexes

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The nucleosome, which is a fundamental repeating unit of chromatin, consists of about 200 base pairs of DNA and a histone octamer. Since the interactions between the histone proteins and DNA in the nucleosome hamper enzymes' access to DNA, disassembly of nucleosomes is required for nuclear reactions such as transcription. Histone chaperones, which facilitate nucleosome assembly and disassembly, are therefore considered to play a critical role in transcription. Indeed, biological analyses have suggested that the histone chaperone CIA/ASF1, which is the most conserved histone chaperone in eukaryotes, is involved in histone eviction at the promoter regions in the transcriptional activation process. Other biochemical and biological studies have revealed that a critical signal of transcription activation is histone acetylation, which seems to function as a signal for the nucleosome disassembly in transcription. The acetylation signal is therefore likely to be transferred to histone chaperone CIA/ASF1. However, its molecular mechanism has remained elusive. In 2002, the Horikoshi group showed that CIA/ASF1 physically and genetically interacts with the double bromodomain (DBD) of CCG1 in the TFIID complex [1]. This result suggests that the interaction between CIA/ASF1 and DBD plays a key role in connecting the histone acetylation and site-specific nucleosome disassembly.

In order to elucidate this molecular mechanism at the atomic level, we determined the crystal structures of two molecular complexes containing CIA/ASF1. Initially, we determined the crystal structure of the CIA/ASF1-H3-H4 complex at 2.7 Å resolution [2]. This crystal structure showed that CIA/ASF1 interacts with the histone H3-H4 dimer and that the interaction inhibits nucleosome formation, suggesting that this complex occurs in the nucleosome disassembly process. In addition, the genetic analysis suggested that the interaction between CIA/ASF1 and histone H3 is involved in the transcription initiation process in yeast.

Next, we determined the crystal structure of the CIA/ASF1-DBD complex at 3.3 Å resolution [3]. The genetic analysis, combined with structural information, showed that the interaction between CIA/ASF1 and DBD is also involved in the transcription initiation process in yeast. A ChIP analysis using a structurally designed DBD mutant suggested that CIA/ASF1 is recruited to promoter regions through the interaction with DBD and induces site-specific histone eviction around the promoter regions, leading to transcriptional activation. Our biochemical results showing that CIA/ASF1 can change its interacting partner from DBD to the histone H3-H4 dimer also supports this model. This is the first structure-based model of the biological signaling from histone modifications to structural change of the nucleosome (hi-MOST model) [3].

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Keywords: histone chaperone, chromatin, transcription

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Methylation by CARM1: A structure based approach to design inhibitors and peptide mimics

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Post-translational methylation of arginine is a widespread epigenetic modification found in eukaryotes that is catalyzed by the protein arginine methyltransferases (PRMTs). PRMTs have been implicated in a variety of biological processes, such as regulation of transcription, translation and DNA repair. At least nine members of PRMTs (PRMT1 to PRMT9) have been identified and classified into two main classes. Coactivator-associated arginine methyltransferase 1 (CARM1, also known as PRMT4) was identified as an enhancer of the transcriptional activation by several nuclear hormone receptors. CARM1 is a crucial protein involved in many biological processes including the regulation of chromatin structure and transcription via methylation of histones and many transcriptional cofactors. Since deregulation of these processes appears to be implicated in the pathogenesis of different diseases such as human cancers, CARM1 and other PRMTs represent potential new targets for which compounds can be developed and that can be exploited to provide new therapies against cancer. As such, understanding the detailed mechanism of action of this protein at the structural level is important and has implications ranging from pure structural information to potential way of regulating gene expression via inhibitor design. Understanding the mechanism of action of CARM1 at the atomic scale is therefore crucial both for fundamental biology and pharmacological applications.

The work presented here combine chemistry, molecular modeling and X-ray crystallography with the aim to address two challenges in the field. The first one is to understand at the atomic level the mode of binding of substrate/product arginine-containing peptides, reflecting states prior and subsequent to methylation. The second one is to design, synthesize and improve by structure based-drug design compounds that can inhibit CARM1 methylation activity. We have previously solved several crystal structures corresponding to three isolated modules of CARM1. Crystal structures of the CARM1 catalytic module revealed large structural modifications and have shown that the NH₂-terminal and the COOH-terminal end of CARM1 catalytic module contain molecular switches that may inspire how CARM1 regulates its biological activities by protein-protein interactions. Moreover, our recent structural and functional studies have shown that peptides outside the catalytic core of CARM1 are essential for substrate binding and recognition.

Extensive works on PRMTs did not succeed yet to reveal the mode of mode of binding of substrate/product arginine-containing peptides, reflecting states prior and subsequent to methylation. This is certainly due to the weak or transient nature of the peptide/enzyme interaction. We have developed a novel approach to tackle this challenge and therefore understand how CARM1 and more generally PRMTs recognize and bind their peptide substrate. We have synthesized analogs or mimics of the transition state of the methylation reaction where the substrate/product is linked to the S-adenosyl-L-methionine cofactor. Full detailed analysis of new structures of CARM1 in the presence of substrates mimics will be presented. We have used the same approach