Shape Matters: Crystal Morphology and Surface Topography Alter Bioactivity of Bioceramics in Simulated Body Fluid

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The assessment of bioactivity is a pivotal and indispensable step in the development of new biomaterials, e.g., bone-replacing materials such as cement formulations composed of different mineral phases.1–3 As bioactivity is an essential property to achieve bone-bonding, it is of special importance to probe which material traits affect bioactivity. A common and established bioactivity assay involves the incubation of specimens in Kokubo's simulated body fluid (SBF), i.e., a solution that closely resembles the ionic composition of blood and is thus supersaturated concerning the solubility limit of various apatites and calcium phosphates.4,5 As SBF highly simplifies the conditions in vivo—e.g., reduced carbonate concentration and absence of organic solutes—this reductionistic approach has been questioned.6 However, a number of remarkable analogies between bioactivity determined in vivo and SBF assays have been reported.7–9 SBF assays cannot cover the entire complexity of in vivo tests, but they allow the assessment of underlying thermodynamic processes, such as heterogeneous nucleation on substrates, which are fundamental contributors to bioactivity. For instance, SBF assays were used in the prominent Dr. B. Myszka, Prof. A. R. Boccaccini Department of Materials Science and Engineering (WW) Institute of Biomaterials Friedrich-Alexander-University of Erlangen-Nuremberg (FAU) Cauerstrasse 6, 91058 Erlangen, Germany P. I. Schodder, S. Leupold, Dr. M. Schüßler, B. Demmert, J. Biggemann, Dr. T. Fey, Dr. S. E. Wolf Department of Materials Science and Engineering (WW) Institute of Glass and Ceramics Friedrich-Alexander-University of Erlangen-Nuremberg (FAU) Martensstrasse 5, 91058 Erlangen, Germany E-mail: stephan.e.wolf@fau.de

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case of bioglass to reveal that two synergistic effects, both caused by ion leaching, drive hydroxyapatite (HAP) formation: released calcium ions increase the supersaturation with respect to HAP\textsuperscript{[10,11]} and silicate leaching results in a local increase in pH by up to 2 pH units which translates into a decrease in HAP solubility by a ten up to a hundred-fold.\textsuperscript{[5,10–13]} Therefore, valuable insights can be gained even from such rather simple approaches because thermodynamic laws also govern the solution chemistry in vivo. SBF assays thus allow us to hone our fundamental understanding of factors that affect bioactivity and its determination in assays but are, as of yet, unrecognized.

In this contribution, we explore the impact of morphological traits of bioceramics on bioactivity. For this, we exploit calcium carbonate as a chemically simple model system for a generic bioceramic. Calcium carbonate is biocompatible, bioreabsorbable, and osteoconductive,\textsuperscript{[14]} and it features phase-dependent bioactivity in SBF.\textsuperscript{[1,7]} Moreover, nacre has been shown to induce calcium phosphate precipitation in SBF as well as bone formation by activation of cutaneous fibroblasts and human osteoblasts and in vivo.\textsuperscript{[8,15–18]} Also, calcareous bioceramics derived from corals received remarkable attention in past years.\textsuperscript{[19–26]}

The calcium carbonate system features at least seven different polymorphs, ranging from crystalline to amorphous. It is abundant in the biosphere, and, in the last years, it received remarkable attention for its so-called nonclassical crystallization pathways which are fueled by nanoparticle attachment instead of an ion-wise growth.\textsuperscript{[27,28]} These pathways allow, inter alia, for the incorporation of organic material into the crystalline matrix—a speciality which is impressively demonstrated by calcareous biominerals that owe their remarkable toughness to their hybrid nature.\textsuperscript{[29,30]} As calcium carbonate formation is a key contributor to the bioactivity of bioglass,\textsuperscript{[31]} it is of special importance to identify factors that affect calcium carbonate bioactivity as these factors may also impact the bioactivity of bioglass.

In a recent contribution, we charted the bioactivity and phase transformation processes of different calcium carbonate polymorphs when exposed to SBF.\textsuperscript{[7]} We showed clear polymorph-specific behavior. Calcite is essentially bioinert showing near to no bioactivity, whereas all other calcium carbonate polymorphs showed pronounced bioactivity. We found the polymorphs’ bioactivity scale with their solubility. Moreover, we demonstrated that the presence of phosphate ions, as in SBF, strongly suppresses Ostwald–Lussac step ripening of aragonite and vaterite, which considerably extends the lifetime of these metastable polymorphs.\textsuperscript{[7]}

In this contribution, we use these findings as spadework for probing how morphology can impact the bioactivity of bioceramics. Herein, we demonstrate that not only the crystal phase but also the crystal morphology has a distinct impact on bioactivity in SBF. In standard Kokubo assays,\textsuperscript{[9]} rhombohedral calcite appears as bioinert, whereas calcite with deviating crystal morphology, generated by heat treatment of metastable aragonite or vaterite, shows pronounced bioactivity. However, not only the crystal morphology determining the microstructure of a bioceramic is capable of modulating its bioactivity. We show further that simple changes in a surface’s topography, e.g., a simple scratch, locally lower the apparent bioactivity in SBF assays. We rationalize that ion depletion effects caused by limited mass transport lead to a locally reduced nucleation and crystal growth rate. This leads to an apparently counterintuitive behavior of bioactive specimens: crack closure is strongly retarded although the entire specimen readily forms a dense calcium phosphate layer.

Pellets were prepared from three different calcium carbonate phases, i.e., calcite, aragonite, and vaterite. In the first set of experiments that serve as control experiments illustrating a standardized behavior, the specimens were first pelletized and then annealed for 30 min at 100 °C. This mild heat treatment kept the initial mineral phase and crystal shape unaffected but allowed the pellets to sufficiently consolidate so that they stayed intact upon immersion in SBF (see the first row in Figure 1). Pellets show no detectable bioactivity (see the first column of Figure 1). No traces of calcium phosphate could be found after 21 days of immersion by scanning electron microscopy (SEM). Also, after 28 days, neither X-ray diffraction (XRD; see Figure S2, Supporting Information) nor energy-dispersive X-ray spectroscopy (EDS) analyses can trace calcium phosphate formation. This finding tells that calcite is essentially bioinert in SBF—a finding which reproduces our earlier reports and is commensurate with in vivo studies of geological calcite rhomb spars implanted in rabbits’ tibiae.\textsuperscript{[7,12]}

In contrast, aragonite pellets show the formation of calcium phosphate at the pellet surface already after 1 day of incubation in SBF (see the second column of Figure 1). EDS analyses confirmed the formation of a phosphorous-containing compound on the surface of the pellets (see Figure S3, Supporting Information). XRD after 28 days also documented that aragonite did not undergo phase transformation to calcite (see Figure S2, Supporting Information), as one would expect according to Ostwald’s rule of stages. The observed bioactivity and phase stabilization of aragonite is in line with earlier reports on aragonite powders.\textsuperscript{[7,13]} Pellets prepared from vaterite behave comparably, as also reported earlier\textsuperscript{[7]} (see the third column of Figure 1). Distinct bioactivity, i.e., the formation of calcium phosphate precipitates on the pellets’ surface, can be observed both in SEM micrographs and EDS as well as by XRD analyses (see Figure S2 and S4, Supporting Information). Like aragonite, metastable vaterite is stable against phase transformation when immersed in SBF; this correlates well with the case of aragonite and reproduces earlier reports.\textsuperscript{[7]}

These results show that only calcite pellets appear as bioinert in these standardized assays, whereas aragonite and vaterite pellets show the reported bioactivity.\textsuperscript{[7]}

Differences in supersaturation provide a rationalization for the phase-specific bioactivity of calcium carbonate polymorphs in SBF solution. According to solubility calculations performed with geochemical simulation software PHREEQC,\textsuperscript{[34]} Kokubo’s SBF is slightly oversaturated with respect to calcite but undersaturated with respect to aragonite and vaterite (see saturation indices as calculated by in Table S1, Supporting Information). Although calcite is expected to grow, aragonite and vaterite should undergo redissolution and Ostwald step ripening. Their redissolution leads to a temporarily (and locally) increased calcium and carbonate activity which facilitates the formation of apatite.
The rate of dissolution of calcium carbonate can be conveniently traced by monitoring the pH development because carbonic acid is a weak acid, featuring $pK_a$ values of 6.3 and 10.3. Thus, carbonates act as strong bases: when carbonate is released into solutions at $pH < 13$, a distinct fraction of carbonates undergoes protonation which leads to an increase in $pH$. When calcium carbonate is immersed in water, the increasing $pH$ value is both a measure for the release of carbonate and, indirectly, of calcium ions because equimolar amounts of calcium and carbonate dissolve (see Section 2, Supporting Information). We thus tested differences in dissolution rates when the three calcium carbonate polymorphs were exposed to water (see Figure S5, Supporting Information). These in situ $pH$ measurements show that the dissolution rate is a function of the solubility. The differences in release rates can be seen from the different $pH$ values, taking calcite as a reference, and from the first time-derivative of the $pH$. As in SBF solution no redissolution of calcite is expected, it becomes clear why aragonite and vaterite show bioactivity in SBF. To ensure comparability, the pellets consisting of rhombohedral calcite were treated in a similar way. The intensified heat treatment triggered phase transformation of both aragonite and vaterite to calcite (see Figure S1, Supporting Information). Nevertheless, the respective pellets’ microstructure and, thus, the individual crystallite morphology are preserved in all cases (see the first row in Figure 2). Aragonite-derived pellets show still the characteristic lath-like morphology, although XRD demonstrates that calcite is the only crystal phase that is present. In the case of the microstructure of vaterite-derived pellets, the spheroids of vaterite are preserved, although XRD could find no traces of vaterite.

These heat-induced solid-to-solid phase transformations are so-called paramorphic phase transformations which generate calcite crystals with morphologies that are characteristic for a different calcium carbonate polymorph but represent atypical and nonequilibrium crystal morphologies of calcite. All pellets are entirely composed of calcite but feature different microstructures and crystal habits, depending on which polymorph they derived from.

The bioactivity of the paramorphic calcite pellets, i.e., those derived from aragonite or vaterite, was compared with the bioactivity of the rhombohedral calcite pellets by strictly following the same protocol as for the reference experiments. Calcite-derived pellets, i.e., those with the typical rhombohedral crystal habit, show no distinct bioactivity—matching the results of the control experiments shown earlier (see the first row in Figure 2). In stark contrast, aragonite-derived calcite pellets and vaterite-derived calcite pellets show pronounced bioactivity, although they are composed of calcite (see the second and third row in

![Figure 1. Pellets prepared from different calcium carbonate polymorphs (columns) after different incubation times in SBF (rows).](image-url)
Figure 2). After 28 days, a complete and homogeneous layer of calcium phosphate is generated on these samples, whereas near to no calcium phosphate could be found in the case of rhombohedral calcite; XRD and EDS analyses corroborate this observation (see Figure S2, Supporting Information). Specific surface area measurements and Scherrer analyses showed that pellets prepared from rhombohedral calcite are comparable in their characteristics with pellets composed of paramorphic calcite (see Table S2 and S3, Supporting Information); thus, we exclude that a change in surface area or crystallite size accounts for the paramorphs’ bioactivity. Moreover, XPS analyses excluded the presence of surficial contaminants which might affect heterogeneous nucleation rates (see Figure S6, Supporting Information).

At first sight, these results appear to be counterintuitive and inconsistent because all pellets of the second set consist of calcite and, thus, all pellets feature the same nominal bulk solubility. However, our results evidence that calcite bioactivity is not only governed by crystal morphology but also by an interplay between crystal morphology and crystal phase. How can we rationalize these seemingly paradoxical observations? The important point is to realize that paramorphic phase transformation leads to the formation of calcite with nonequilibrium morphology, thus calcite expressing high-energy facets. According to Wulff’s theorem, crystals in nonequilibrium morphologies will promptly undergo morphological relaxation which eventually leads to their equilibrium morphology[35]. This intensive crystal remodeling proceeds by regress of high-energy facets and further advancement of low-energy facets. Eventually, the crystal’s habit is dominated by lowest-energy and slowest-growing facets. Thus, when paramorphic calcite is exposed to water, pronounced redissolution and further crystal reshaping will take place until this final state is achieved. The remodeling calcite undergoes enhanced ion exchange with the SBF solution which results in a locally increased calcium and carbonate concentration. In analogy to the case of vaterite and aragonite, this should be reflected in pH shift.

To evaluate these considerations, we also performed in situ pH measurements which corroborated the above rationalization (see Figure S7, Supporting Information). Although all samples are composed of calcite, both paramorphs show a faster initial increase in pH than rhombohedral calcite, as clearly reflected in ΔpH values. Both paramorphs reach a higher but remarkably comparable plateau level than rhombohedral calcite. Vaterite-derived spheroidal calcite initially shows a faster redissolution kinetics, as shown by the evolution of δpH/δt values. It should be pointed out that these measurements only reflect the redissolution dynamics at early stages; as these systems are not equilibrated, they do not necessarily imply that the bulk solubility of paramorphic calcite is higher than that of rhombohedral calcite. The system is still out of the equilibrium, as shown by the negative slope of the plateau (see Figure S7B, Supporting Information). To conclude, the paramorphs show an increased initial redissolution kinetics when immersed in liquids; this is the source of their increased bioactivity in SBF compared with equilibrium-shaped calcite. The increase in calcium concentration and the
concomitant increase in pH facilitate, similar to the prominent case of bioglass, the formation of a hydroxyapatite layer on the pellets. This observation thus substantiates that already a minor change in microstructure can remarkably alter the bioactivity of a crystalline biomaterial in SBF assays.

It should be clarified that the nonequilibrium shape of paramorphic materials only modulates its (initial) bioactivity concerning its bulk polymorph—here calcite. In the control set—see the second and third column in Figure 1—both vaterite and aragonite pellets show a pronounced formation of calcium phosphate deposits already after 7 days of incubation in SBF. In contrast, aragonite- and vaterite-derived calcite pellets only show minor traces of calcium phosphate deposition after 7 days of incubation (see the second and third column in Figure 2). When revisiting the results of the reference system, it becomes apparent that already the exposure of high-energy facets is sufficient to increase bioactivity, although very locally. In the reference experiments, although only after 28 days, minute deposits of calcium phosphate can be detected even in case of rhombohedral calcite, but these minimal deposits only form at damaged calcite crystallites. This specifically localized nucleation can be rationalized by considering that mechanical damage can also lead to the creation of high-energy surfaces.

We conducted a third set of experiments to assess whether this principle is also perpetuated on larger length scales. Thus, we tested whether simple surface modifications such as scratches affect bioactivity in SBF. For this, we used an expanded set of samples, thus pellets composed of vaterite, aragonite, rhombohedral calcite, aragonite-derived lath-like calcite, and vaterite-derived spheroidal calcite. After adequate heat treatment, these pellets were manually scratched before incubation in SBF. We followed then the closure of the applied surficial scratch upon exposure to SBF as a function of time (see Figure 3). In the case of essentially bioinert rhombohedral calcite, no crack closure was observed. As the crystallites in the scratch experienced additional damage, a higher but still small number of calcium phosphate deposits were found within the groove (see inset in Figure 3). In the case of the highly bioactive aragonite and vaterite, the scratches were filled—occasionally, the scratches could not even be localized by SEM anymore. The scratch closure appears to take place mainly by crystal overgrowth from both sides of the trench and not by crystals forming and growing within in the scratch (see Figure S8, Supporting Information).

In the case of the pellets with medium bioactivity, i.e., those composed of lath-like and spheroidal calcite, the undamaged pellet surface was entirely covered by a continuous layer of calcium phosphate except for the scratch. Even after 28 days in SBF, the scratches showed only a small number of calcium phosphate spherules, thus a much smaller particle number density compared with the undamaged surface of the pellets. This finding

![Figure 3](image_url). The scanning electron micrographs show pellets composed of different calcium carbonate polymorphs and paramorphs after 28 days of incubation in SBF. The pellets were scratched before incubation, and the micrographs show the crack closure as a function of calcium carbonate poly- or paramorph. In the case of aragonite pellets, it was impossible to relocate the crack due to the intense overgrowth of the pellet; the aragonite inset shows a representative micrograph of the calcium phosphate coating. The colored scheme visualizes how growing crystals deplete the activity product (AP) in their vicinity; the lower AP, the lower the nucleation rate. In direct vicinity to the growing crystal, AP approaches the solubility limit $K_{SP}$. In the case of scratched surfaces, crystals growing beside groove (lower scheme) deplete the ion concentration also in the trench volume, which leads to reduced bioactivity and a suppressed crack closure.
is, at first sight, perplexing as one would expect that the bioactive substrate would especially favor calcium phosphate formation within the scratches because the efflux of ions from the trenches should ease nucleation. Our finding contrasts this expectation and implies that mass transport has a dominant and general impact on the bioactivity of uneven substrates tested in SBF assays.

As soon as heterogeneous nucleation of calcium phosphate takes place at an arbitrary place, the mass transport feeding its growth depletes the concentration of relevant ions in the crystals’ vicinity (see colored scheme in Figure 3). This reduction in ion concentration leads to a massive reduction in rates of nucleation in the near surrounding of the growing crystal, considerably impeding formation as well as the growth of new neighboring crystals. This vicinal impediment of crystal nucleation and growth is described in established surface growth models. It has also been experimentally demonstrated for crystal growth from solution on flat but chemically patterned self-assembled monolayers. In the present case of scratched surfaces, nucleation of exposed sites—thus the even, unscratched pellet surface—is preferred because mass transport can occur without restriction from the bulk solution. However, within the scratches, crystals growing at the surface and the rim of the scratch deplete the supersaturation and limit mass transport to the bottom of the trench. As crystal growth and nucleation critically depend on the level of supersaturation, crack closure is inhibited because calcium phosphate nucleation and growth within the scratch is impeded. This rationalization is also corroborated by the observation that scratch closure on highly bioactive aragonite and vaterite pellets proceeds by crystal overgrowth from both sides of the trench and not by crystals forming and growing within in the scratch (see Figure S7, Supporting Information).

When taken together, our results presented in this contribution reveal that—apart from nominal solubility of the bulk material—bioactivity in SBF can also be strikingly altered by simple morphological alterations.

Uneven sample surfaces can lead to a considerable but local reduction in bioactivity. When crystals grow in the vicinity of pits, small trenches, or scratches, these topographical features may form bottlenecks for mass transport. Then, they lead to a spatially restricted depletion in relevant ions which locally reduces rates of nucleation and crystal growth. In our model system of calcium carbonate, this prevented crack closure. In general, such topographical features, e.g., caused by damaging a biomaterial during implantation, might also impede ingrowth of implants; future studies should aim at evidencing this also in vivo.

Moreover, we demonstrated that changes in crystal morphology, e.g., crystals with nonequilibrium morphologies such as paracrystals, can turn an essentially bioinert material such as calcite into a bioceramic with distinct bioactivity. Our finding thus reveals that bioactivity of bioceramics could be conveniently tailored via tuning their microstructure and grain morphology.

Finally, it is worth pointing out that we exploited an established bioactivity test for our experiments, i.e., immersion in Kokubo’s SBF, which is broadly used as a convenient in vitro assay for potential biomaterials. However, our results show that in these tests already simple morphological changes can profoundly impact the actual bioactivity on different length scales. Thus, our findings should also raise our awareness for the complexity of the underlying, intricate crystallization mechanisms which allow us to test “bioactivity” in this simple but simplifying in vitro test. However, once these hidden factors have been unraveled and understood as important cofactors modulating bioactivity, they might also guide us to a better understanding and fine-tuning of the bioactivity of biomaterials such as ceramics, bioglass, or cement.

Supporting Information
Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest
The authors declare no conflict of interest.

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