Dispersed Uniform Nanoparticles from a Macroscopic Organosilica Powder

Tamara L. Church,† Diana Bernin,‡,§ Alfonso E. Garcia-Bennett,§ and Niklas Hedin*†,

1Materials and Environmental Chemistry, Stockholm University, SE-106 91 Stockholm, Sweden
2Swedish NMR Centre, University of Gothenburg, Box 465, SE-405 30 Göteborg, Sweden
3Department of Chemistry and Biomolecular Sciences, Australian Research Council Centre for Nanoscale Biophotonics, Macquarie University, Sydney, New South Wales 2109, Australia

ABSTRACT: A colloidal dispersion of uniform organosilica nanoparticles could be produced via the disassembly of the non-surfactant-templated organosilica powder nanostructured folate material (NFM-1). This unusual reaction pathway was available because the folate and silica-containing moieties in NFM-1 are held together by noncovalent interactions. No precipitation was observed from the colloidal dispersion after a week, though particle growth occurred at a solvent-dependent rate that could be described by the Lifshitz–Slyozov–Wagner equation. An organosilica film that was prepared from the colloidal dispersion adsorbed folate-binding protein from solution but adsorbed ions from a phosphate-buffered saline solution to a larger degree. To our knowledge, this is the first instance of a colloidal dispersion of organosilica nanoparticles being derived from a macroscopic material rather than from molecular precursors.

INTRODUCTION

Hybrid materials of nanostructured silica, organosilica, and organics can be used as precursors for porous materials or as vehicles for a controlled delivery of molecules and display useful optical and electronic properties.1,2 The internal structures of such hybrid materials can be tuned by varying the fractions of their components as well as by moderating the intermolecular interactions among the components during the formation of the hybrid material. We have synthesized and studied the NFM-1 family of such hybrid materials, which consists of silica and positively charged organosilica interacting with microphase-separated organic domains of stacked Hoogsteen-bonded tetrads of folate.3,4 Folate is a B-vitamin (B9) and is relevant to the detection and targeting of B9 and is relevant to the detection and targeting of various hybrid materials are also relevant to applications in biomedicine and other fields.9–11 Their nanoscopic dimension allows them to be dispersed in solvents and to be assembled into mesoscaled structures, even in a crystalline manner.12 Typically, organosilica nanoparticles are synthesized from small-molecule organosilanes, R2Si(OR)3−x (R may be a bifunctional bridge or contain other functional groups), under sol–gel conditions10,13 in analogy to the Stöber approach that has been quite successful in the synthesis of monodisperse nanoscale particles of silica14 and mesoporous silica.15,16 The nanoscale dimension is controlled via the synthetic parameters (solvents, concentration, pH, etc.).

Important to the evolution of coarsening silica and organosilica nanoparticle dispersions are, among other things, the interparticle interactions and the concentration of the nanoparticles. The former are typically described by the Derjaguin–Landau–Verwey–Overbeek (DLVO) theory, and the extent of the repulsive contributions will effectively control the aggregation tendencies.17 Nevertheless, the stability of silica particle dispersions in particular is often larger than what the DLVO theory would predict.18 In the case of Ostwald ripening, the solubility and diffusivity of the chemical entities constituting the nanoparticles dictate the evolution of particle size.19,20 The synthesis and specifics of the colloidal stability of monodisperse particles of silica and organosilica (based on condensed aminopropyltriethoxysilane) have been studied by van Blaaderen and Vrij.21 They showed that Si(OEt)4 and H2N(CH2)3Si(OEt)3 when combined with an ammonia catalyst, formed organosilica particles. Aminooalkyl-substituted Si atoms were present throughout the particles, rather than
simply forming a layer on their surfaces, and the particles were less dense than expected for analogous silica particles. Extending these studies, we here present a solution-based method to treat macroscopic powder of the mesostructured organic−organosilica−silica hybrid NFM-1 (Figure 1) to give a suspended silica-rich solid and dispersed nanoparticles; this constitutes the first synthesis of dispersed organosilica nanoparticles from a macroscopic organosilica material. The chemical composition and the stability of the dispersed nanoparticles were studied, as was the use of thin films derived from the coarsening dispersion in the microgravimetric detection of folate-binding protein (FBP).

**RESULTS AND DISCUSSION**

The nanostructured composite NFM-1 was synthesized from folic acid, Si(OEt)₄, and H₂N(CH₂)₃Si(OEt)₃ in water. To understand how this yellow organosilica powder could be dispersed as nanoparticles, we briefly discuss the mechanism of its formation, which Atluri et al. have examined using X-ray diffraction (XRD), small-angle X-ray scattering, and conductivity measurements. Folic acid is poorly soluble in H₂O but dissolves upon the deprotonation of its glutamate moieties in base. Thus, when a mixture of Si(OEt)₄ and H₂N(CH₂)₃Si(OEt)₃ (both in excess relative to folic acid) is added to a suspension of folic acid in H₂O, some of the amines are protonated, yielding H₃N⁺(CH₂)₃Si(OEt)₃ and water-soluble folate ions. Aqueous folates associate into columns of stacked hydrogen-bonded tetramers, with the aromatic pterin-based moieties inside the columns and the charged glutamate residues on the outside (Figure 1a). During the synthesis of NFM-1, this process takes minutes. The positively charged H₃N⁺(CH₂)₃Si(OEt)₃ ions are electrostatically attracted to the folate stacks and are therefore concentrated around them. In slower processes, the −SiOEt moieties from the protonated H₂N(CH₂)₃Si(OEt)₃ ions, as well as from Si(OEt)₄ and H₂N(CH₂)₃Si(OEt)₆, are hydrolyzed to give ≡SiOH groups that subsequently condense to form siloxane bonds (Figure 1b). The result is a composite material in which folate tetramer stacks are arranged in a hexagonal lattice, with the glutamate moieties of the folates being associated with ammonium groups that are in turn connected via alkyl groups to an organosilica−silica hybrid; the degrees of alkoxysilane hydrolysis and silica condensation, and therefore the relative fractions of organosilica and silica, depend upon postsynthetic treatment.

![Figure 1. The synthesis of NFM-1 and colloidal dispersions derived from NFM-1 in HCl(aq)−THF.](image-url)
NFM-1 composite synthesized and studied here was not subjected to postsynthesis hydrothermal or calcination treatments, and as a result, the silica portion of the material was not very highly condensed; single-pulse and quantitative solid-state $^{29}$Si NMR spectroscopy (Figure S1) revealed that approximately 55% of the Q sites (Si atoms connected to four O atoms) were fully condensed $Q^2$ sites. Alkylated Si atoms (i.e., those bearing propylamine or propylammonium chains; T sites) made up 49% of the Si atoms in the sample (cf. 24% in hydrothermally treated sample). By mass, NFM-1 was primarily composed of an organic material and condensable hydroxyl groups, as only 32% of its mass remained after combustion to 850 °C in air (thermogravimetric analysis, TGA; Figure S2). Nevertheless, the powder XRD pattern of NFM-1 (Figure S3) displayed sharp peaks evincing the stacking of folic acid tetramers and the existence of a mesoscale hexagonal lattice, as well as the broad wide-angle X-ray scattering peak associated with amorphous SiO$_2$. The IR spectrum of NFM-1 (Figures 4 and S4) was consistent with the one reported, and the solid was also fluorescent, displaying emission spectra similar to those of folic acid (Figure S5).

Hydrothermally treated NFM-1 (NFM-1-h) can be heated at 60 °C overnight in HCl–EtOH to give a white solid, indicating the removal of the folic acid component. On the other hand, we recently observed that treating the as-synthesized NFM-1 with HCl(aq) and THF yielded a near-homogeneous suspension. Thus, heating NFM-1 in a mixture of 11.9 v/v HCl(aq, 6.5 wt %) and THF (this mixture is hereafter denoted “HCl(aq)–THF”) for 2 h at 60 °C produced a mixture from which only a small amount of solid could be filtered. Here, the term “hydrothermal” refers to the mixture prior to filtration and “dispersion” to the clear bright yellow filtrate. The IR spectrum of the very pale yellow filtered solid (Figures 2 and S4) showed it to be primarily silica. The solid retained some IR absorbance in the region 1700–1420 cm$^{-1}$, evincing organic compounds; however, these absorbance bands were significantly less intense relative to the ν(Si–O) bands compared to the case of NFM-1. The solid retained 59% of its mass following combustion to 850 °C (Figure S2a), and mass loss occurred primarily between 200 and 300 °C (Figure S2b), indicating that it was mostly due to the decomposition of alkoxy- and alkylsilane groups and, potentially, to the glutamate tails of folic acid molecules. Unlike NFM-1, the filtered solid showed no increase in the rate of mass loss above 470 °C, indicating that it had a lower aromatic (i.e., the pterin “heads” of folic acid) content.

The bright yellow filtered dispersion that formed after heating NFM-1 in HCl(aq)–THF fluoresced, like aqueous folic acid, with $\lambda_{\text{max}} = 450$ nm when irradiated with near-UV light (Figure S6). To investigate the chemical nature of the dispersed particles, a freshly prepared and filtered sample was cooled in an ice bath, and the solvent was removed in vacuo to give a dark yellow solid. This solid could be combusted almost completely, leaving a residue of 8.8 wt % as a white solid (Figure S2). Nevertheless, both its IR (Figures 2 and S4) and its $^{29}$Si NMR (Figure S1) spectra showed that it contained silica. Further, solid-state $^{29}$Si NMR revealed that the silica in the evaporated colloidal dispersion was more condensed than in NFM-1, as expected given that the heat and low pH applied in the suspension favor the condensation of silicic acid moieties. Monoalkylated Si atoms (T sites) formed a slightly greater proportion of the Si atoms in the evaporated colloidal dispersion than in the original NFM-1 (Figure S1). This difference is consistent with a molecular structure of NFM-1 that contains silica-like domains that are not dispersed upon heating in HCl(aq)–THF but instead form a silica-rich precipitate that is removed by filtration. The presence of such silica-like domains is also consistent with the observation that the solid filtered from the suspension contained a greater fraction of inorganics than either NFM-1 or the evaporated colloidal dispersion (postcombustion residues of 59, 32, and 8.8 wt %, respectively, Figure S2a), as well as with both the mechanism of NFM-1 formation and the observation that calcination of NFM-1-h in air yields an ordered mesoporous silica with channels in place of the folic acid stacks.

The IR spectrum of the evaporated colloidal dispersion derived from NFM-1 in HCl(aq)–THF (Figures 2 and S4) contained new bands at 1718 and 1322 cm$^{-1}$, consistent with pteroic acid. Thus, the amide bonds of at least some folic acid molecules were hydrolyzed during the treatment with HCl(aq)–THF, as has been observed under more severe conditions. The decarboxylation of pteroic acid has also been observed under acidic conditions, and we cannot rule out its occurrence here. The hydrolysis of folic acid separates its pterin-based “heads”, which lay in the center of the organic folate stacks in NFM-1, from their glutamic acid “tails” (Figure 1c). On the basis of TGA (Figure S2), we estimate (see the Supporting Information for details) that a minimum of 26% of the folic acid was hydrolyzed, with the liberated glutamic acid likely being adsorbed on the solid that was filtered from the suspension. Glutamic acid forms hydrogen bonds with silica, and the adsorbed material can nucleate the formation of glutamic acid crystallites on silica; this would favor the adsorption of glutamic acid on the silica-rich solid.

The scission of folic acid molecules to give pteroic acid is not necessarily required to separate a suspended silica-rich solid from the dispersion of nanoparticles containing primarily an organic matter that is formed by heating NFM-1 in HCl(aq)–THF. The folate and silica-rich domains of NFM-1 itself are not held together by covalent bonds; rather, electrostatic and van der Waals interactions mediate the association between the folate ions and the alkylammonium-substituted Si compounds.

Figure 2. Attenuated total reflectance IR spectra of folic acid and NFM-1, as well as of the products of NFM-1 suspension in 11.9 v/v HCl(aq, 6.5 wt %)–THF: the solid filtered after heating in 11.9 HCl(aq, 6.5 wt %)–THF, the dispersion following evaporation at 0 °C, and the precipitate formed from the dispersion following 20X dilution in H$_2$O. Arrows indicate bands assigned to pteroic acid.
Further, the acidic medium causes nonhydrolytic changes to the NFM-1. It is formed under mildly basic conditions (pH early in the synthesis was 8.5); acidification of the solid below the pKₐ values of the carboxylic acids (pKₐ = 2.155 and 4.324 for the α- and γ-carboxylic acids, respectively, in glutamic acid⁵) converts folate to folic acid. Pteroic acid (pKₐ ≈ 2.29⁶) is also expected to be in its acid (i.e., protonated) form at the pH of the colloidal dispersion derived from NFM-1 in HCl(aq)–THF. No sharp ν(O–H) band indicating isolated –OH groups was visible in the infrared spectrum of the evaporated colloidal dispersion (Figure S4), indicating that the carboxylic acids interacted with other species; nevertheless, changes in the protonation states of various species in the solid could be important in disrupting the interactions that hold the organic and inorganic portions of NFM-1 together. As mentioned, folic acid has been removed influencing its formation, we examined the colloidal dispersion derived from NFM-1 in HCl(aq)–THF immediately after filtering.

Although the filtrate formed by dispersing NFM-1 in HCl(aq)–THF appeared homogeneous to the naked eye, dynamic light scattering (DLS) revealed dispersed colloidal particles. As the initial colloidal dispersion had a concentration close to 5 mg/mL and was prepared in a solvent mixture, it was diluted 20× in deionized H₂O to give a more dilute sample in a primarily aqueous medium for DLS measurements; the diluted dispersion was 391:9 v/v HCl(aq), 0.33 wt %–THF and is hereafter labelled “dilute HCl(aq)–THF”. The diluted dispersion contained nanoparticles whose average initial radius was ~90 nm (Figure 3), with a low polydispersity index (PDI) of ~0.15 (Figure S7a). The nanoparticles were therefore more than an order of magnitude larger than the hexagonal unit cell in NFM-1⁷ or than the length or width of a single folic acid tetramer in H₂O.²⁵,³⁵ They were only slightly larger than the nanoparticles formed when folic acid alone was dispersed in HCl(aq)–THF for 2 h at 60 °C (initial radius ≈ 80 nm, PDI ≈ 0.06; see Figure S8). On the basis of their size and content, the particles are expected to be made up of columns of folic/pteroic acid tetramers intermingled with domains of moderately condensed alkyl- and alkoxy silanes. The powder XRD pattern of the evaporated dispersion (Figure S3) indicates that some long-range order is maintained in these particles. The order was also evident in some particles observed in transmission electron microscope images of evaporated dispersion (Figure S9).

The time evolution of the average radius ⟨r⟩ of the particles dispersed from NFM-1 could be described by the Lifshitz–Slyozov–Wagner (LSW) equation¹⁹,²⁰,³⁶ (Figure 3). Plots of ⟨r⟩ versus the cube root of time were linear for two timescales, each relevant to a different medium. Here, τ is the time elapsed since the NFM-1 was dispersed in HCl(aq)–THF, and t is the time elapsed since the sample was diluted in deionized H₂O for DLS. The particle radii maintained a low PDI throughout (Figure S7). Ackerson and co-workers³⁷ and Penders and Vrij³⁸ observed that the average radii of particles in destabilized dispersions of stearil-functionalized silica in benzene also grew with the cube root of time, at least after the initial 20–30 s. The adherence of the ripening of NFM-1 particles dispersed in dilute HCl(aq)–THF to the LSW equation (i.e., the dependence of ⟨r⟩ on the cube root of t) suggests that our system is steered by physics similar to that applicable in the systems of Ackerson and co-workers³⁷ and Penders and Vrij³⁸ in diluted and coarsening dispersions of NFM-1, the apparent LSW slopes for particle growth after dilution increased with t (Figure 3a). The dependence of ⟨r⟩ on t was evaluated in two ways. First, the earliest data point measured following each dilution (i.e., ⟨r⟩₀ at 5 min) was linearly correlated with t¹/₃ (R² = 0.85). The same was true a longer time after dilution; for example, ⟨r⟩₀ at 90 min was also linearly correlated with t¹/₃ (R² = 0.96). Alternatively, the intercept ⟨r₀⟩ of the LSW plot for a diluted and coarsening colloidal dispersion (Figure 3a) could be used as a proxy for the aggregation of particles in the undiluted dispersion. However, ⟨r₀⟩ was poorly linearly correlated with t¹/₃ (R² = 0.11, Figure 3b). The much better correlation of ⟨r⟩ versus t¹/₃ when the former is measured after, for example, t = 5 min, rather than extrapolated to t = 0 for each dilution suggests that the particle growth may not exhibit the LSW behavior immediately after dilution, which would also be consistent with the observations of Ackerson and co-workers³⁷ and Penders and Vrij.³⁸

The ⟨r⟩ increased more rapidly with t than with τ; the slopes of the LSW plots of ⟨r⟩ versus t¹/₃ (Figure 3a) were 5–20× greater than the one for the plot of ⟨r⟩₀ versus t¹/₃ (Figure 3b). Therefore, the particles ripened more rapidly in the diluted
391.9 v/v HCl(aq, 0.33 wt %)—THF medium than in the initial 11.9 v/v HCl(aq, 6.5 wt %)—THF. Considering the LSW description of particle ripening in dispersion and assuming that the molar volume of the dispersed material is independent of solvent, the different LSW slopes with respect to $t$ and $r$ must be related to changes in the surface energies, solubilities, and diffusivities of the subparticles or constituent molecular entities. The relevant diffusion coefficients are not known, but the ratio of viscosities of the initial and diluted solvent mixtures (i.e., without contributions from the particles themselves) can be estimated as $\sim 2.1$ (see the Supporting Information for details). In this analysis, differences in surface energies and solubilities contribute to a 3–10× greater rate of ripening in the diluted colloidal dispersion. The low pH of the matrix produced a small positive surface charge on the particles (a diluted sample with $t = 2$ min and $r = 300$ min had $\zeta$-potential of $+17$ mV), and the differences in particle growth in the initial and diluted dispersions can therefore also be rationalized in terms of screening potential and interparticle interactions. We speculate that the primarily aqueous dilute HCl(aq)—THF matrix provided greater electrostatic screening than the initial HCl(aq)—THF mixture and thus better facilitated particle growth. This effect would however be mitigated by the greater concentration of dissolved ions (i.e., HCl(aq)) in the undiluted dispersion. A particle dispersion prepared from NFM-1 in more concentrated HCl(aq), that is, HCl(aq, 11.2 wt %)—THF, and then diluted for measurement, contained polydispersity particles.

The concentration of THF in the medium not only decreased the rate of particle growth in the dispersion derived from NFM-1 but was also decisive in the rate of sedimentation. The colloidal dispersion formed upon heating NFM-1 in HCl(aq)—THF for 2 h at 60 °C and subsequent filtration could be left to stand at room temperature for at least a week, and no turbidity or precipitation was observed. When this same dispersion was diluted 20× in H$_2$O to give dilute HCl(aq)—THF, folic acid precipitated (IR spectrum Figure S10) precipitated from the undiluted HCl(aq)—dioxane dispersion was too slow to be reliably evaluated. These observations support the hypothesis that the ether co-solvent contributes to the stability of the dispersion by poorly shielding electrostatic repulsion between the positively charged surfaces of the organosilica particles. Alternatively, or possibly consistent with the LSW-based explanation, the differences in the behavior of the nanoparticles in the diluted THF- and dioxane-containing dispersions could relate to changes in the surface energies, solubilities and diffusivities of subparticles or constituent molecular entities.

Thermogravimetric and IR spectroscopic data indicated that the colloidal dispersion produced by heating NFM-1 in HCl(aq)—THF contained primarily not only folic and pteroic acids but also silica and organosilica, and we therefore investigated the possibility that films could be formed from the coarsening dispersion derived from NFM-1. The generation of thin films from colloidal suspensions has several advantages over other methods, with technical simplicity and the ability to control microstructure being especially important.

Thin films formed from suspensions of silica nanoparticles in particular have been used, for example, as antireflective coatings and to encourage the growth of cells on surfaces. Films containing folic acid have proven useful for the detection of a 5-methylcytosine-genomic content (i.e., DNA from cancer cells), cancer cells, and FBP (which is overexpressed in multiple types of tumor cells). A cracked film (Figure S13) could be obtained by placing a few drops of dispersion on a glass substrate and allowing it to dry, indicating that film formation was possible, and we therefore attempted to deposit a thin film of dispersed NFM-1 on an Au sensor. Savran and coworkers have reported a folate-modified sensor that, when monitored in a quartz crystal microbalance (QCM), could be used to detect as little as 30 nM FBP, and this detection limit could be lowered to 50 pM FBP following additional modifications of the sensor. Thus, a diluted dispersion of NFM-1 was spin-coated onto an Au sensor (see the Supporting Information for details). Regions of yellow color that were distinct from the Au sensor were visible near the outside of the coated sensor. An IR spectrum of a yellow region occurred more slowly in the diluted mixture containing 1,4-dioxane than in the one containing THF, and particle growth in the undiluted HCl(aq)—dioxane dispersion was too slow to be reliably evaluated. These observations support the hypothesis that the ether co-solvent contributes to the stability of the dispersion by poorly shielding electrostatic repulsion between the positively charged surfaces of the organosilica particles. Alternatively, or possibly consistent with the LSW-based explanation, the differences in the behavior of the nanoparticles in the diluted THF- and dioxane-containing dispersions could relate to changes in the surface energies, solubilities and diffusivities of subparticles or constituent molecular entities.

To test the hypothesis that the lower polarity (and thus screening potential) of THF compared to that of H$_2$O stabilized the organosilica dispersion by slowing particle aggregation, we repeated the decomposition of NFM-1 in a mixture of aqueous acid and 1,4-dioxane, a cyclic dialkyl ether that is less polar than THF. Thus, NFM-1 was heated in 11.9 HCl(aq, 6.5 wt %)—1,4-dioxane (hereafter labelled “HCl(aq)—dioxane”) for 2 h at 60 °C, then filtered to give a yellow dispersion. DLS measurements demonstrated that a diluted colloidal dispersion contained smaller particles than those dispersed in HCl(aq)—THF (Figure 4). Particle ripening
was recorded on an IR microscope, as was a spectrum of a region on which only the sensor was visible, and both contained $\nu$(Si–O), $\nu$(O–H) and $\nu$(C–H) bands (Figure S14), suggesting the film derived from NFM-1 covered the sensor even when it was not visible in the microscope. The IR spectra also displayed interference, a characteristic of thin-film samples.

The response of the NFM-1-derived film to aqueous solutions of FBP was examined in a QCM apparatus with dissipation monitoring (Figure S15). The film-loaded chip did not respond to pM concentrations of FBP, but very slight changes in the chip vibration frequency were observed upon exposure to 35 and 70 nM FBP solutions, and a 350 nM FBP solution produced a clear drop in the frequency of the chip. Thus, the film derived from NFM-1 did increase in mass upon exposure to FBP, presumably because of the binding of this protein to folic acid, and the chip showed a detection limit on the same order of magnitude as the sensor described by Savran and co-workers.\(^{45}\) A much larger response was noted when the film-coated sensor was exposed to a phosphate-buffered saline (PBS) solution, indicating that the film readily adsorbed one or more of the Na\(^+\), K\(^+\), or H\(_2\)PO\(_4\)^{(3–x)–} (x = 1 or 2) ions. This response occurred regardless of whether the film had already been exposed to FBP and was reversible upon washing with deionized water. Although this marked response to aqueous salts would likely preclude the use of thin films derived from NFM-1 in the microgravimetric detection of FBP in biological fluid, it may offer further information regarding the structure of the suspended nanoparticles formed when NFM-1 is dispersed in HCl(aq)—THF. Tetramers of molecules based upon folic acid\(^{37,48}\) and the related S’guanosine monophosphate\(^{39}\) readily accommodate Na\(^+\) and K\(^+\) ions in their central channels, which could account for some of the mass gain for the coated sensor upon exposure to the PBS. However, in further investigations (Figure S15S), only a small mass change occurred when the film was exposed to NaCl(aq, 50 mM), and similar results were obtained for KCl(aq, 50 mM). A solution containing Na\(_2\)HPO\(_4\)(aq) and KH\(_2\)PO\(_4\)(aq) in the concentrations used in PBS buffer, but without NaCl or KCl, produced a larger weight change in the film, but the response to PBS buffer was several times greater, suggesting the synergistic uptake of ions, and possibly of water, from that solution.

### CONCLUSIONS

Already upon its development, NFM-1 was an unusual organosilica composite in that it was held together by multiple weak interactions between folates and protonated amionic propylsilicates rather than by covalent bonds, and it represented the synthesis of mesoporous silica via a nonsurfactant mechanism.\(^{3}\) We now report that, because of the interactions that adhere the microphase-separated inorganic and inorganic–organic portions of NFM-1, the solid could be decomposed in a mixture of aqueous acid and an ether co-solvent such as THF or 1,4-dioxane. The result was a small amount of insoluble solid composed primarily of SiO\(_2\), as well as a dispersion of monodisperse particles with diameters ranging from 90 to 150 nm. The particles were composed primarily of an organic material but also contained a significant inorganic fraction consisting of silica and organosilica, indicating that the folic acid was not simply washed out of the composite following the protonation of its folate groups.

The particles ripened in solution at a rate that depended on the amount and identity of the ether cosolvent. Both a larger fraction of ether in the medium and a less-polar ether solvent slowed ripening, indicating that the poor electrostatic shielding provided by the ether solvent contributed to the stability of the dispersion. Further, although some hydrolysis of folic acid to pteric acid was observed, the suspended particles also contained intact folic acid molecules. Thus, the decomposition of NFM-1 in HCl(aq)—ether allows a macroscopic organosilica to be decomposed to form a dispersion of organosilica nanoparticles. The primary mechanism of suspension was not the breaking of covalent bonds but rather the pH-driven alterations of the weak interactions that held the material together.

Organosilica films could be derived from the dispersion and could take up FBP, although they took up more PBS.

### EXPERIMENTAL SECTION

#### Synthesis of NFM-1

NFM-1 was synthesized according to published procedures.\(^{44,45}\) Thus, folic acid (0.680 g, 1.54 mmol) and deionized H\(_2\)O (49 mL, 2.7 mol) were combined with a magnetic stir bar in a capped jar, and the mixture was sonicated for 5 min, then allowed to stand at room temperature. Separately, tetraethyl orthosilicate (2.6 mL, 12 mmol) and 3-aminopropyltriethoxysilane (0.90 mL, 3.8 mmol) were combined in a vial. After the folic acid/H\(_2\)O mixture had stood undisturbed for 1 h, it was stirred vigorously while the silicon-containing precursors were added, and then for 30 min more. The mixture was then allowed to stand without stirring for 40 h before it was filtered through a glass frit. The yellow-orange solid was washed with an ether solvent mixture of THF and 1,4-dioxane to remove any unreacted amine, and then dried in a vacuum oven at room temperature. Finally, the solid was ground to a powder and suspended in THF or NFM-1 (50 mg) or folic acid was weighed into a 25 mL round-bottomed flask, and a magnetic stir bar was added. In a separate flask, concentrated hydrochloric acid (HCl(aq), 35.9 wt %, 1.0 mL, 12 mmol), deionized water (4.5 mL, 250 mmol), and tetrahydrofuran (THF, 4.5 mL, 35 mmol) were combined to form a homogeneous liquid (denoted “HCl(aq)—THF”). This mixture was then poured into the flask containing NFM-1. The flask was fitted with a condenser and lowered into an oil bath that was held at 60 °C. After 2 h, the mixture was removed from heat and allowed to cool to room temperature, then filtered through a filter paper that retained particles having $d \geq 2 \mu$m. An analogous procedure was used to suspend NFM-1 in HCl(aq),
except that the addition of THF was omitted. Thus, only 5.5 mL solution (HCl(aq)) was added to the solid. An analogous procedure was also used to suspend folic acid in the same medium; in that case, 17 mg folic acid was combined with 5 mL HCl(aq)—THF.

**ASSOCIATED CONTENT**

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.langmuir.7b03705.

Full experimental details, additional characterization data for NFM-1 and its dispersion products, and estimates of viscosity and degree of folic acid hydrolysis (PDF)

**AUTHOR INFORMATION**

Corresponding Author
E-mail: niklas.hedin@mmk.su.se.

Diana Bernin: 0000-0002-9611-2263
Niklas Hedin: 0000-0002-7284-2974

Author Contributions
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Notes
The authors declare the following competing financial interest(s): Alfonso E. Garcia-Bennett is the co-founder of Muir.7b03705.

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