Can sustainable monodisperse spherical silica be produced from biomolecules? A review

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Abstract

Spherical silica is a fundamentally important material with uses across a wide and diverse range of areas. However, the synthetic routes to producing spherical silica – typically Stöber processes – are inherently unsustainable and environmentally damaging. Petrochemical surfactants, alcoholic solvents, and ammonium hydroxide, which are commonly used, each have their own associated environmental problems. Demand is growing to find new, more sustainable ways, to synthesise spherical silica. Bioinspired and biomimetic silica, produced using knowledge learned from natural silica production methods such as biomineralisation, is an ever-growing field of research, that provides a possible route to more sustainable industrial silica production. Biomolecules can be used to shape and form spherical silica instead of petrochemical surfactants. Water-based chemistries can be used instead of alcohol solvents and ammonium hydroxide. This review establishes the parallels between the natural silica biomineralisation process and Stöber processes and focuses on the physicochemical properties necessary for biomolecules to synthesise spherical silica. Recent biomolecule-based syntheses are highlighted, and an outlook is given on further developments in the field.

1 Introduction

Spherical silica is one of the most important contemporary industrial materials. It has many integral uses across a diverse range of areas such as catalysis, adsorption, chromatography, sensors, and drug delivery, to name just a fraction (Brown 1990; Narayanan and El-Sayed 2003; Miyake et al. 2007; Slowing et al. 2008; Pagliaro 2009). However, like many industrial materials that are fundamental to modernity, there are issues with how spherical silica is currently produced. Since the Industrial Revolution, rates of anthropogenic pollution have rapidly increased in tandem with, and with profound causal links to, the innovation and advancement of industrial production. Throughout this period, right up to the present day, little regard in industry has been given to environmental consequences of inefficiencies and wastes of industrial processes.

In an attempt to address this failing the concept of Green Chemistry was formalised in the 1990s. One of its key facets is the "design of chemical products and processes to reduce or eliminate the use and generation of hazardous substances" (Anastas and Eghbali 2010). In essence, this means developing processes that are more sustainable, by using reagents which cause minimal environmental damage. Ideally, these reagents come from natural and renewable sources, that are either biodegradable or environmentally benign. This must become the guiding principle for industrial development, and silica manufacturing is no exception.

The ubiquity of spherical silica necessitates the manufacture of vast quantities of it annually to meet worldwide demand. The global market for precipitated silica, including spherical silica, was valued at USD 1.96 billion in 2018 and is expected to continue to grow (Grand View Research 2019). However, industrial spherical silica production methods currently use vast quantities of environmentally damaging reagents such as alcohols, alkoxysilanes, and oil-derived surfactants (Isomaa et al. 1976; Nakashima et al. 1994; Nałęcz-Jawecki et al. 2003). These embedded

environmental costs render the processes unsustainable. Thus, finding environmentally friendly alternative production methods for spherical silica is critical. Learning from Nature's own silica production method, *biomineralisation*, may offer the means to do so.

Biomineralisation is the process by which certain plants and animals create complex, hierarchical, mineral structures, often out of silica, from simple starting materials (Mann 2001). For hundreds of millions of years plants have been using silica for structural supports and pathogen defence (Trembath-Reichert et al. 2015). Animals also use silica on a vast scale, with radiolaria, sponges, molluscs, and diatoms among those which have mastered the biomineralisation process (Knoll 2003; Hildebrand 2008; Schoeppler et al. 2018; Tang et al. 2019). Diatoms are particularly interesting to materials scientists. These creatures are single-celled algae that can construct labyrinthine structures out of silica with ease. They have become model organisms for studying the silica biomineralisation process. The level of detail and control achieved in diatom silica structures has not been matched by materials science. The complexity of the bottom-up silica production processes of diatoms makes *in vitro* replication of their silica constructs profoundly difficult. But biomimetic materials research has attained some understanding of the fundamentals of biomineralisation processes. This knowledge can be used to produce biosilica – silica particles synthesised via biomimetic processes – using environmentally friendly means.

Since the discovery and isolation of the biomolecules responsible for biomineralisation there have been numerous attempts to use this knowledge to replicate the process in vitro to create various silica structures (Coradin et al. 2004b; Jackson et al. 2015; Piletska et al. 2017; Wang et al. 2020). While some of these studies have attempted to produce spherical silica particles, discrete and monodisperse particles produced via a truly sustainable biomimetic synthesis is yet to be achieved. Identifying the parallels between biomineralisation and the current industrial methods of silica

production, based upon the Stöber process and its derivatives, may be the key to this morphological control. Another key advantage of synthesising spherical silica biomimetically is the reduced environmental impact, due to the relatively mild synthesis conditions, compared to the current methods (Jackson et al. 2015). When the Stöber processes use templating agents to control the particle morphology, these are often petrochemical surfactants. Extraction and refinement of fossil fuels, such as petroleum – from which traditional surfactants are derived – causes severe damage to ecosystems, local environments, and the climate (Höök and Tang 2013; Rebello et al. 2014). Biopolymers offer a less problematic alternative. They are renewable, naturally occurring, environmentally benign, and their production and use generates less CO_2 (Hayes and Smith 2019). As with traditional polymers, there is a great, and ever growing, variety of highly refined biopolymers available. This stems from their widespread use in many materials science applications (Mann et al. 1993; White et al. 2011; Yu et al. 2012; Li et al. 2012; Alatalo et al. 2015), and particularly in the medical field, for drug delivery and wound healing applications (Patil 2003; Kogan et al. 2007; Oh et al. 2009; Park et al. 2017; Tematio et al. 2017). Biopolymers have also been extensively used in food technology, mainly as films, coatings, and emulsion stabilisers (Tang et al. 2012; Othman 2014; Scholten et al. 2014; Ghanbarzadeh et al. 2015; de Azevedo et al. 2020). Now, green chemistry aspirations are accelerating the use of biopolymers into further fields.

This review lays out the parallels between the established Stöber processes and the emerging field of biomimetic silica, with a view to bridging the gap between the two. The focus will be on the physicochemical characteristics of the specific biomolecules responsible for biomineralisation in creatures such as diatoms and how they relate to the surfactants used in the Stöber processes. These properties are then used to identify biomolecules readily available from sustainable sources that

may fulfil the role of the surfactants in the Stöber processes and enable the synthesis of spherical silica particles. Spherical silica is a material of great importance, and there is a growing need for its production to be sustainable. While the process of biomineralisation, with its complex structures and granular control, and the Stöber processes may seem distinct from one another, the underlying formation process is strikingly similar (**Section 4**). This review looks at whether the unsustainable traditional spherical silica syntheses can be replaced with sustainable, biomolecule-based ones. Firstly, we will focus on a background of spherical silica formation in the Stöber processes, and the inherent environmental problems associated with them. Secondly, explaining biomineralisation, the biomolecules responsible for the formation of silica in vivo, and physicochemical properties of biomolecules which are conducive to this. Thirdly, the parallels between the Stöber processes and biomineralisation are investigated and highlighted, and examples are given of attempts to produce silica in a biomimetic way using these parallels. Lastly, the future outlook is given on using biomolecules to create sustainable spherical silica, looking at specific examples of attempts to create spherical silica using biomolecules, and any potential barriers to this are explored.

2 Spherical silica

There are a number of key ways in which natural silica production in organisms is paralleled by industrial silica production. One can use biomolecules to take advantage of those parallels to make silica more sustainably. But, to do this, one must first understand current industrial spherical silica production methods. There is a single historical point of origin for all modern spherical silica manufacture – *the Stöber process.*

2.1 Stöber process

The origin of spherical silica production begin in 1968 when Stöber et al. (1968) reported a process for the controlled growth of spherical non-porous silica particles of uniform size. Since then, the field has grown drastically to include modified versions of this process to give highly porous, high surface area silica particles, which extends the applications into areas such as drug delivery and high performance liquid chromatography (Hayes et al. 2014; Liberman et al. 2014). The particles obtained via this method ranged in size from 50 nm to 2000 nm in diameter. The relatively simple procedure involves mixing a silica precursor, an alkyl silicate, with ammonia, in a water/alcohol solution. The alkyl silicate is hydrolysed to give silicic acid, which subsequently condenses to yield monodisperse silica particles. Ammonia is used as a base catalyst and influences the morphology of the particles to render them spherical. A key aspect of the Stöber process is the ability to produce monodisperse particle sizes by altering the reaction conditions, i.e., type of alcohol/alkyl silicate and concentrations of the various reagents. During their systematic study of these conditions, Stöber et al. found that the rate of hydrolysis and condensation is fastest in methanol, giving smaller particles, and slowest in n-butanol, giving larger particles. The choice of alkyl silicate also influences particle size. Fastest reaction rate and smallest particle sizes were observed with tetramethyl orthosilicate, while slowest reaction rate and larger, fewer uniform particles were observed for tetrapentyl orthosilicate. The reason for this is that smaller alkyl chains are more sterically accessible, while larger chains are sterically hindered. The concentration of water influences the rate of hydrolysis and thus, the final particle size. Ammonia affects the morphology of the final particles. Absence of ammonia leads to irregularly shaped particles, indicating that it acts as a morphological catalyst. Control of particle size and morphology was a key step forward in silica production. Thus, key to forming discrete spherical silica particles is the

presence of a morphological-control agent, aka, structure-directing agent (SDA). In this case, the SDA is ammonia. But as the process for creating spherical silica evolved, petrochemical surfactants such as CTAB were used as the SDA. The reason why, and mechanism by which, these surfactants work is explained subsequently, but for now it suffices to say that it is these same properties that allow certain biomolecules to also create spherical silica particles.

2.2 Modified-Stöber process

After Stöber's seminal work on non-porous particles, surfactants were incorporated into the synthesis to create porous particles. These modified-Stöber processes broaden the utility of the particles by opening new applications. The role of the surfactants is to control the morphology, size, and porosity of the particles. This surfactant-templated approach enables a high degree of control of the these physical properties (Anderson et al. 1998). The most commonly used templating agents are long-chain amine molecules such as hexadecylamine (HDA) and cationic surfactants such as cetyltrimethylammonium bromide (CTAB), which is even more widely used. The surfactants form micelles in solution and under basic conditions the negatively charged silica oligomers interact with the positively charged or neutral surfactants. The surfactant acts as an SDA controlling the formation of the pores and size of the particles (Hoffmann et al. 2006). The surfactant is then removed post-synthesis by calcination to reveal the pores. The synthesis can also be done in acidic conditions with triblock copolymer templates (Zhao et al. 1998). In either case mesoporous silica particles are formed.

2.3 Structure-directing agents

The structure and shape of the silica particles is highly dependent on the interactions between the silicate species and SDA during synthesis (Hoffmann et al. 2006). The SDA controls the morphology of the final silica particles. In the case of the Stöber synthesis, the morphological

control comes from the ammonium hydroxide. Under basic conditions the surface of the forming particles is negatively charged, and the cationic ammonium ion is electrostatically attracted to the surface. This attraction prevents aggregation of the particles and allows discrete spherical particles to grow. Such colloidal stability is generally well described by DVLO theory (Trefalt et al. 2014), which describes the interaction of particles in a liquid medium as the sum of van der Waals and double layer interactions. The van der Waals forces arise from the fluctuating dipoles of atoms and molecules (Luo et al. 2014), and are typically attractive forces. The electrical double layer forms on the surface of the particles with the first layer consisting of NH_4^+ ions attracted to the negatively charged silica surface and the second layer being made up of negatively charged ions such as OH^-. Thus the electrical double layer describes the repulsion force between particles because when two double layers overlap, electrostatic repulsion increases (Trefalt et al. 2016). Whether particles aggregate together, or remain stable and do not aggregate, depends on the net potential energy, which is a sum of the van der Waals and double layer forces. If van der Waals forces dominate, the particles will aggregate, and if the double layer forces dominate, the particles will be repulsed. Ionic strength, pH, and surfactants have a direct influence on these forces, and therefore, colloidal stability (Zareei et al. 2019).

In modified-Stöber syntheses, the principle is the same although the way in which the SDA acts differs slightly. As mentioned, non-ionic or cationic surfactants are typically used in modified-Stöber syntheses. At high concentration, the surfactant forms micelles to lower the system entropy (Zhao et al. 1996). The concentration above which these micelles form is known as the critical micelle concentration (cmc). Inside the micelle core, which is essentially liquid hydrocarbon, there is greater freedom for movement and so the entropy associated with the hydrocarbon tails also increases, which promotes the formation of micelles (Alothman 2012). The electrostatic

interaction between the surfactant and the growing network of silica depends on the pH of the reaction conditions. **Fig. 1** shows three of these possible interactions.

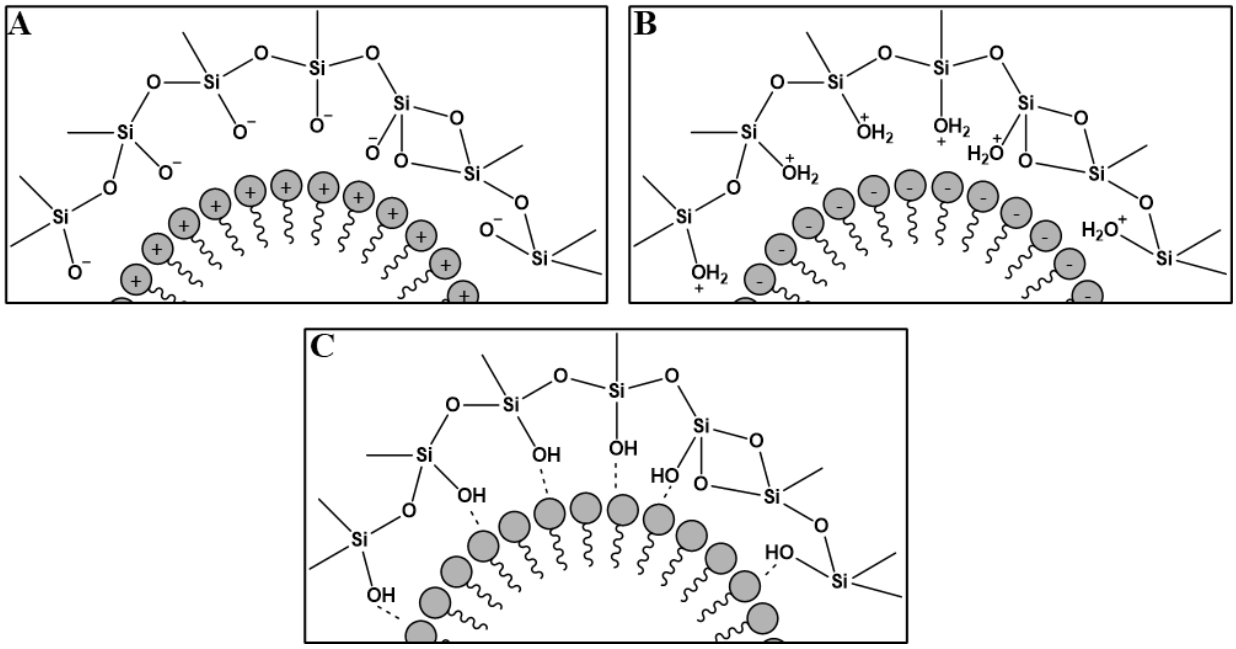
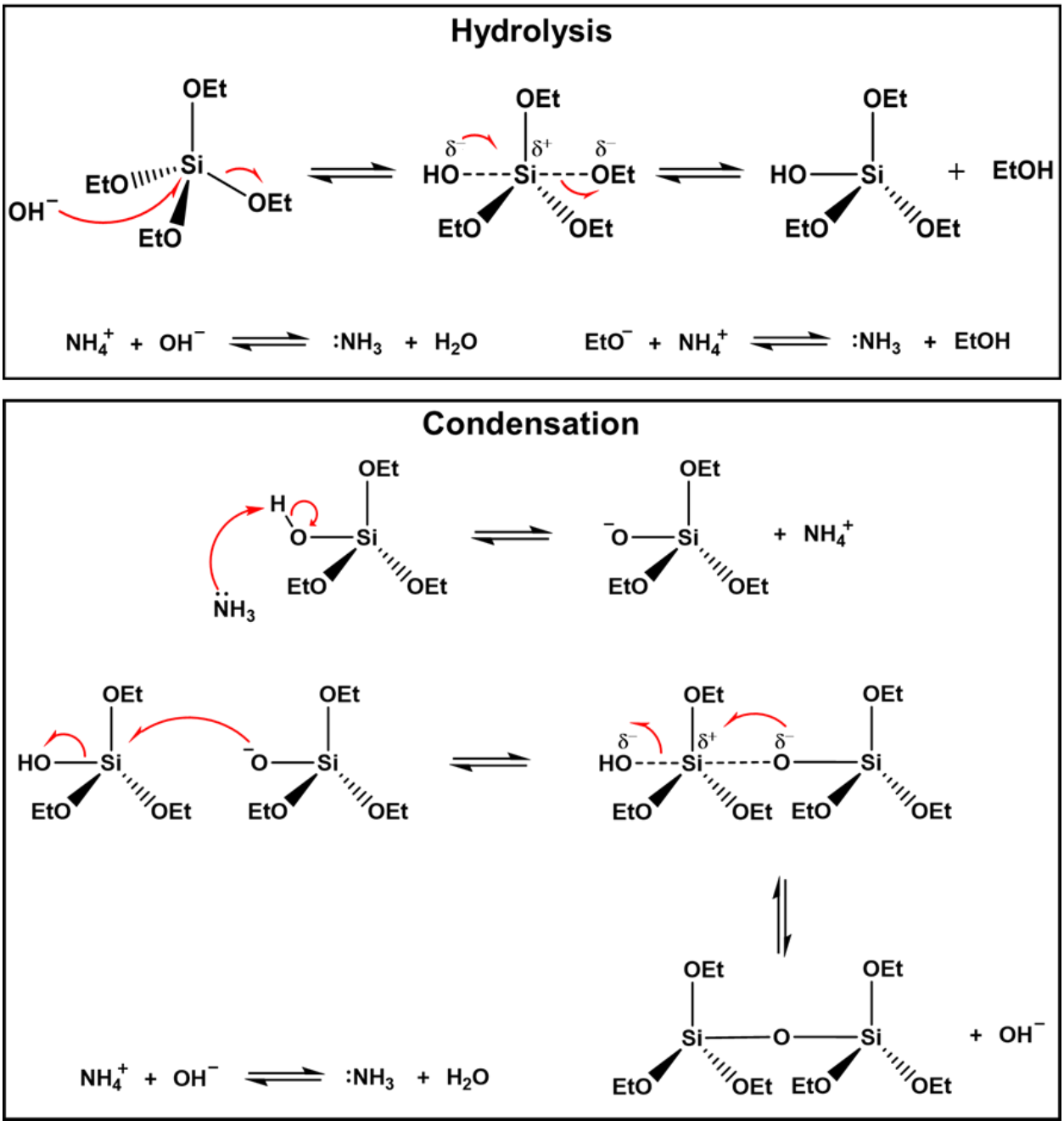


Fig. 1 Example of (a) interaction of cationic surfactant with negatively charged silicate species in basic conditions, (b) interaction of anionic surfactant with positively charged silicate species in acidic conditions and (c) interaction of non-ionic surfactant with silica through hydrogen bonding. Note: other types of interactions exist, shown here are the three most common. Adapted from Alothman (2012)

The electrostatic interactions bring the silica oligomers into greater proximity with each other and as a result the silica network condenses around the surfactant micelles (see **Fig. 3**). These electrostatic interactions also prevent aggregation of the particles and discrete monodisperse particles are produced. Non-ionic surfactants such as HDA interact with the silica surface through hydrogen bonding. This hydrogen bonding occurs between the amine hydrogen and the oxygen, and the hydroxyl hydrogen and the nitrogen (Spencer et al. 1985). Again, the silica condenses around the surfactant, while preventing aggregation. A more detailed explanation of the growth mechanism is provided in the proceeding sections.

2.4 Hydrolysis and condensation

The growth of silica particles in the Stöber process is, at its most fundamental, controlled by two reactions: (1) the hydrolysis of TEOS [$Si(OEt)_4 \rightarrow Si(OEt)_{4-x}(OH)_x$], where x = 1 - 4. (2) condensation of the $Si(OEt)_{4-x}(OH)_x$ monomers into the siloxane network. **Scheme 1** shows the mechanism of the hydrolysis and condensation processes. The hydrolysis of the silica precursor can take place under acidic or basic conditions. At basic pH, the formation of spherical particles is promoted, while silica gels generally form under acidic pH (Iler 1979). The reason for this difference is that under acidic conditions, the forming silica particles bear little surface charge and aggregation into a gel network is more likely (Hench 1998). Whereas under basic conditions, electrostatic repulsion inhibits aggregation. The Stöber process uses ammonium hydroxide as the base catalyst to accelerate the hydrolysis and condensation of TEOS, as shown in **Scheme 1**. The initial hydrolysis step is the slowest and rate-determining step, but the rate increases as more ethoxy groups are removed due to increased positive charge of the silicon and reduced steric hindrance around the silicon (Ghimire and Jaroniec 2021). The condensation reaction is similar to the hydrolysis reaction in that it involves a nucleophilic substitution reaction transitioning through a pentacoordinate intermediate which forms the siloxane network. The hydrolysis and condensation reactions, and the degree to which either one dominates, have a significant impact on the size and morphology of the final particles, as discussed below.



Scheme 1 Mechanism of hydrolysis and condensation of TEOS in the presence of ammonia (Stöber process). TEOS is hydrolysed to give the oligomeric precursor species. Note that the hydrolysed precursor shown here is only one of the possible structures formed. For a more detailed description of these intermediaries, see Trinh et al. (2006) Condensation of these oligomers leads to the generation of small primary seed/sub-particles. These nucleation events precede the formation of the final particles. The final particles are formed typically via coalescence and/or Ostwald ripening of the seed particles. Mechanism adapted with permission from Ghimire and Jaroniec (2021). Copyright (2020) Elsevier Inc.

Two prominent mechanisms have been proposed to describe the growth of the silica particles – the monomer addition (Matsoukas and Gulari 1988, 1989), and aggregation models (Bogush and Zukoski 1991a, b). Briefly, the monomer addition model suggests that monomers continue to form until above a certain critical supersaturation level, a burst nucleation event occurs. This nucleation event consumes the monomers until the concentration of monomers falls below the nucleation threshold. After this, monomers preferentially deposit onto the growing siloxane network resulting in particle growth. The aggregation model suggests that particle growth occurs via the aggregation of particles that are formed during nucleation. Smaller particles are colloidally unstable due to their high interfacial energy and therefore aggregate together, resulting in particle growth. These two models provide two distinct growth mechanisms; however, they may not be mutually exclusive.

Recent research by Han et al. (2017) has tried to reconcile the relationship between the two growth models by looking at the kinetic balance between them. They describe two pathways (see **Fig. 2**) to growth in the Stöber process, Pathway I: hydrolysis of the silica precursor into silanol monomers which initially nucleate to form seeds for growth; and Pathway II: condensation of newly-formed silanol monomers onto the seeds formed in Pathway I, which results in augmentation of the silica particles. They found that monodisperse silica nanoparticles were only formed in concentrated ammonia solutions ($\geq$ 0.95 M), which increased the hydrolysis of the silica precursor. At lower ammonia concentrations, the hydrolysis rate is slowed and polydisperse particles are formed.

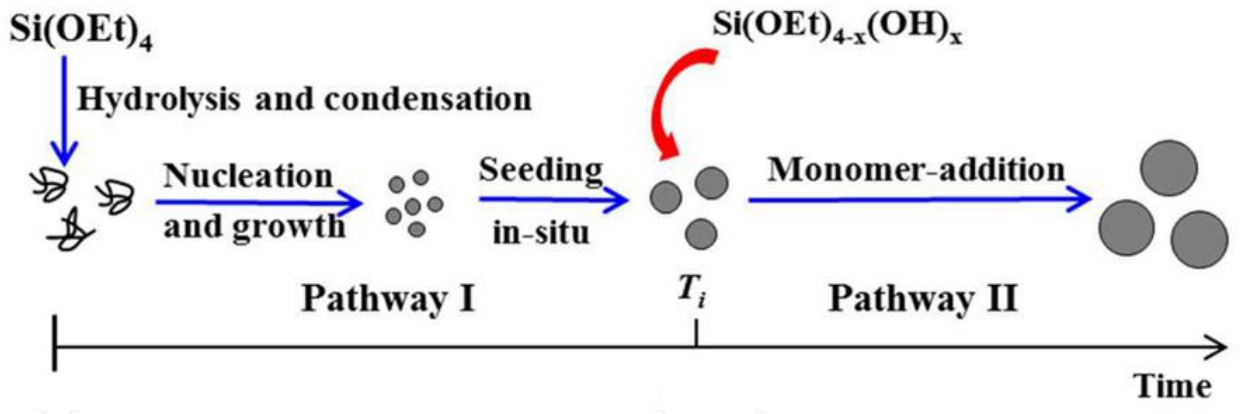


Fig. 2 Particle growth can be divided into two consecutive stages, Pathway I (nucleation-growth) and Pathway II (monomer addition) at high ammonia concentration (≥ 0.95 M); or Pathway I (nucleation-growth), Pathway I+II (continuous nucleation and monomer addition) at low ammonia concentration (< 0.95 M). Reprinted with permission from Han et al. (2017). Copyright (2017) American Chemical Society

The growth mechanism for silica particles in the presence of an SDA such as CTAB can be described by similar monomer addition and aggregation models. **Fig. 3** shows these two pathways. The monomer addition (upper pathway) describes the adsorption of silicate anions onto the surface of the micelles followed by condensation around the micelle, forming primary particles. Growth then occurs by addition of monomeric or oligomeric silica and surfactant molecules, with mesophase structuring occurring through rearrangement of the aggregated species from a non-ordered agglomerate (Edler 2005). The aggregation model (lower pathway) describes the adsorption of polymeric silica onto individual micelles (primary particles) which then aggregate together to form the mesostructure (Nooney et al. 2002). In both cases, the adsorption of silicate species onto the surface of the micelle reduces electrostatic repulsion between the micelles, allowing them to aggregate and subsequently form particles. CTAB has also been shown to form bilayers on the surface of silica particles, which allows for charge stabilisation (Zhang et al. 2012; Liu et al. 2013). This provides colloidal stability to the particles, similar to the way in which NH_4^+ acts in the Stöber synthesis.

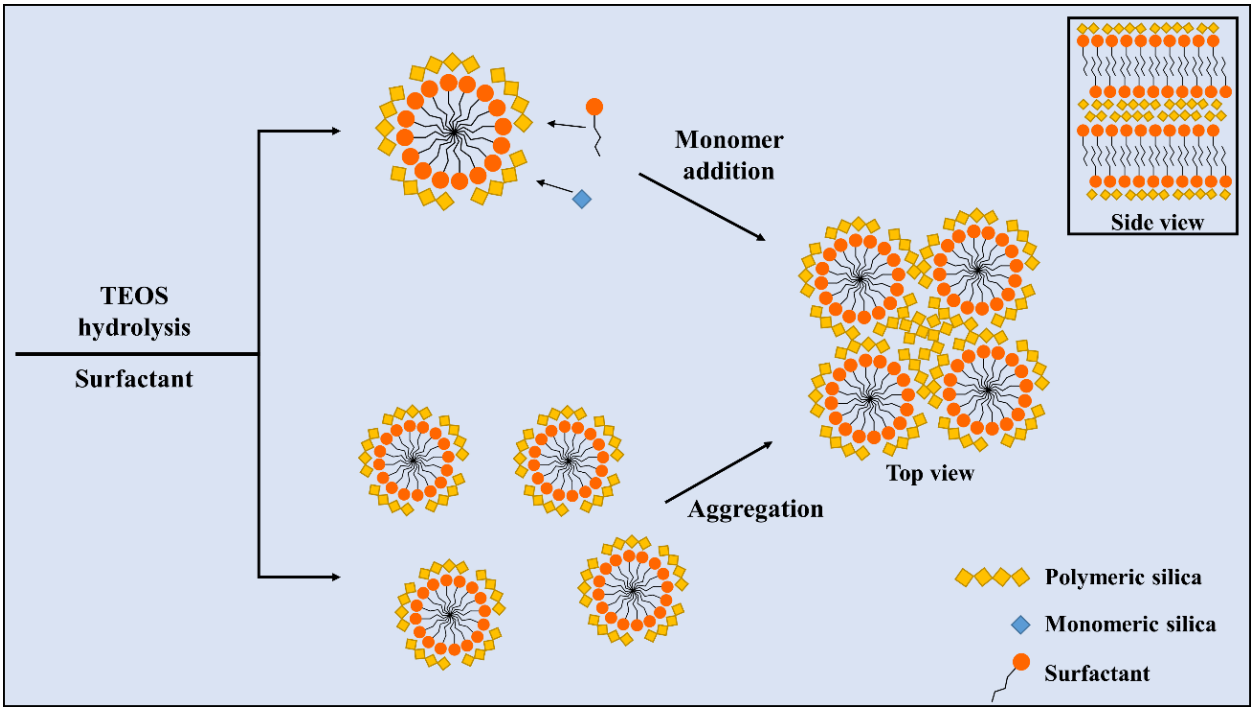


Fig. 3 Proposed mechanisms for the formation of surfactant-templated silica. The upper pathway corresponds to a monomeric silica addition mechanism. The lower pathway corresponds to aggregation of seed particles to form larger particles. Adapted with permission from Nooney et al. (2002). Copyright (2002) American Chemical Society

Another proposed mechanism for particle growth is through a phase-separation process. Initially, TEOS is located in the core of the surfactant micelle due to its immiscibility with water. The ethanol used in the synthesis is thought to act as a cosurfactant inside the surfactant micelles, involved in the formation of phase-separated seed particles (Edler 2005). Then the ethanol acts as a cosolvent decreasing the rate of hydrolysis of TEOS. This decreased hydrolysis rate slows down the production of anionic silicate species, which allows the electrostatic repulsion between surfactant headgroups to increase, elongating the micelles (Lebedev et al. 2004). These elongated micelles then aggregated together, resulting in particle growth. However, SANS and molecular simulation data indicate that the likely mechanism of formation follows that of **Fig. 3** (Hollamby et al. 2012; Chien et al. 2017).

2.5 Ostwald ripening and coalescence

A complementary process of particle growth occurs via Ostwald ripening, which is a coarsening process which occurs in the late stage of phase transformation (Ostwald 1900). In general, when particles are formed from a homogeneous solution, a phase transition occurs. This transition causes an interfacial area to be created between the solid and liquid phases. Smaller particles have a higher surface-to-volume ratio than larger particles, and thus have higher surface energies associated with them. As such, any process which produces larger particles at the expense of smaller particles will be thermodynamically favourable. In order to grow, reactive units (either monomers or small aggregates) must diffuse to the surface, followed by subsequent reaction at the surface, of the particles. The coarsening can be described as occurring via diffusion-limited growth or reaction-limited growth. The most prominent Ostwald ripening process is that of diffusion-limited growth which was given a mathematical description by Lifshitz and Slyozov (1961) and Wagner (1961), the so-called LSW theory. Ostwald ripening can be identified in particle size distributions by a characteristic Gaussian curve. Coalescence is the fusion of two or more particles together, leading to particle growth. This process also results in a lowering of the interfacial energy between the particles and the solution. However, unlike Ostwald ripening which tends to produce size-monodisperse particles, coalescence tends to produce polydisperse particles. This is due to the non-homogenous fusion of particles and is characterised by a log-normal curve in particle size distributions. Ostwald ripening dominates in typical silica production methods. **Fig. 4** shows some example silica particles prepared via the Stöber process.

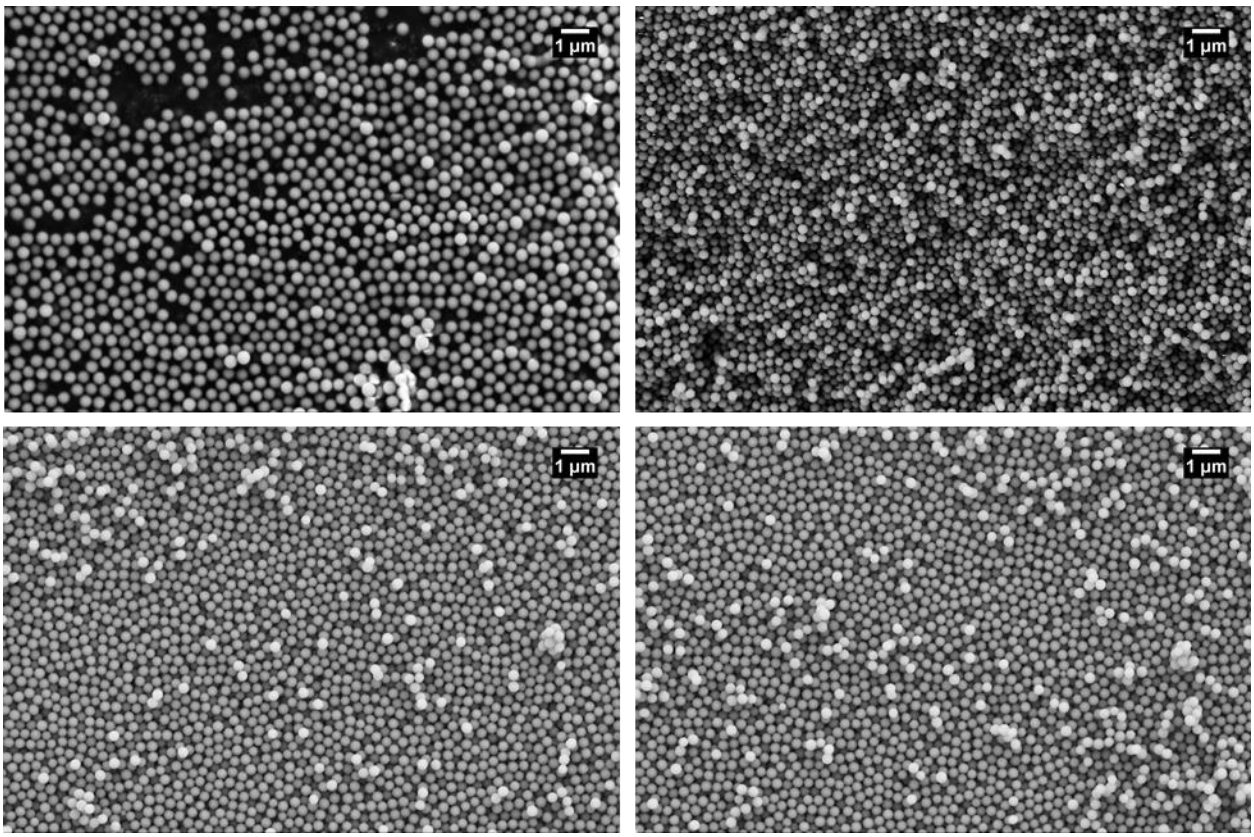


Fig. 4 Scanning electron microscopy images of silica nanoparticles prepared via the Stöber process. Scale bar = 1µm. Images from author's own work

In summary, spherical silica particles can be readily achieved via Stöber processes. The key additive that enables and promotes the spherical morphology is an SDA. The silica precursor is first hydrolysed, and the SDA interacts with the hydrolysed silicate species primarily through electrostatic and/or hydrogen bonding interactions. These interactions along with the growth process described above, leads to the formation of spherical silica. The SDA also prevents aggregation of the forming particles through these same electrostatic and/or hydrogen bonding interactions, as discussed previously.

3 Environmental problems of Stöber silica production

While spherical silica production is important, the production process is problematic. A typical Stöber process, and its derivatives, uses some combination of the following categories of reagents: an alkoxysilane as the silica precursor, ammonia, surfactant, water, and an alcohol. The most commonly used silica precursor is tetraethyl orthosilicate (TEOS), but others such as tetramethyl orthosilicate (TMOS), tetrapropyl orthosilicate (TPOS), and tetratbutyl orthosilicate (TBOS) are also used. The main environmental problem associated with these compounds is their toxicity when they are released into the environment. This release may be accidental or deliberate, through inadequate waste disposal. Numerous studies of alkoxysilane toxicity have been conducted, with renal failure, and acute tubular necrosis, and even fatalities in some animal models among the most serious observations (Okamura 1992; Nakashima et al. 1993, 1994; Nakashima 1994). Ammonium hydroxide can also be toxic if released into the environment and is classed as H400 (very toxic to aquatic life) by the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations 2019). Ammonium hydroxide in water exists in equilibrium with the free ammonia form, which is more toxic than the ionised form (Thurston et al. 1981). Numerous studies on the effect of ammonia on aquatic life have reported an LC50 (lethal concentration, 50%) in the range of just μg L^{-1} to mg L^{-1}. A comprehensive list of these studies is available in this USEPA report (1998). Ethanol is commonly used as pesticide (microbicide, fungicide, etc.) with a well-established toxicological profile – its use and inadequate disposal can pose ecological and environmental problems (U.S. Environmental Protection Agency 2007). Surfactants such as cetyltrimethylammonium bromide (CTAB) and hexadecylamine (HDA) are commonly used in the manufacture of silica particles. These petrochemically-derived compounds pose a high risk to the environment and health (Pang et al. 1997; Timmer et al. 2019). CTAB is listed as H400 by the

GHS. HDA is also listed as H400, with further classification as H410 (very toxic to aquatic life with long lasting effects). Aside from the toxicity of these compounds, the fact they are derived from petrochemical resources means they are finite. Most synthetic surfactants are synthesised from petrochemical feedstocks (Knepper and Berna 2003), alkyl silicates such as TEOS are typically produced by reaction of $SiCl_4$ with ethanol (Sánchez-Ramírez et al. 2018), while ethanol is industrially produced by the acid-catalysed hydration of ethene, which is a petroleum product (Scully and Orlygsson 2019). Thus, it is clear that the environmental problems associated with the manufacture of spherical silica particles need to be addressed. Aside from reducing the environmental impact of silica synthesis, biomimetic approaches also provide potential economic advantages by reducing and/or eliminating the need for organic solvents, reducing waste, and simplifying processes by using less reagents and water-based chemistries (Patwardhan 2011). Such water-based reactions would reduce the capital expenditure needed for solvent recovery, while also reducing running costs as biomimetic silica can be produced under ambient conditions, making for a far more sustainable and economic processes at-scale. An excellent overview of eco-design in silica synthesis is provided by Baccile et al. (2009) The next sections look at how we can draw inspiration from the natural biomineralisation process to achieve these economic and sustainability benefits.

4 Natural silica production

Natural silica occurs, of course, in Earth's crust and rocks but, it is also found in plants as phytoliths, and is even utilised by certain animals. Animal uses of silica range from the complex, gene directed layering of proteins and silicates in the shells of certain molluscs (Kaplan 1998; McDougall and Degnan 2018), to the intricate, fragile structures of glass sponges like the Venus flower basket (Sundar et al. 2003; Birkbak et al. 2016), and incredibly diverse microalgae such as

diatoms (Malviya et al. 2016; Piredda et al. 2018). These applications of silica are of great interest to science because of the degrees of structural sophistication achieved through these bottom-up processes. Diatoms provide a particularly intriguing example of silica biomineralisation. These fascinating single cell creatures, though seemingly rudimentary, can create a visually stunning arrays of intricate structures that even the most advanced materials science techniques cannot match. These structures are assembled by diatoms at a variety of scales, from a few nanometres up to several hundred microns (Lopez et al. 2006). The apparent ease with which these extraordinary creatures are able to create their cellular structures, acting as a protective shield while they wander the Earth's rivers and oceans, makes them especially interesting.

Diatoms are model organisms for studying biomineralisation processes. This is because the diatom species *Thalassiosira pseudonana* and *Cylindrotheca fusiformis* have been characterised in great detail (Hildebrand et al. 1998; Bertermann et al. 2003; Magaletti et al. 2004; Sumper and Brunner 2008; Brembu et al. 2017). This has enabled a greater understanding of the mechanisms by which they use biomineralisation to create such intricate structures (Kröger 2007). Nanofabrication of silica in diatoms occurs under ambient conditions at slightly acidic pH and results from specific interactions between biomolecules and silicic acid derivatives (Sumper et al. 2003). Isolation and extraction of biomolecules in *T. pseudonana* and *C. fusiformis* has revealed some that are directly involved in silica fabrication. Some of the first discovered were cationically charged proteins called silaffins, all of which are rich in serine and lysine residues (Pamirsky and Golokhvast 2013). Other important molecules isolated from various diatoms are long-chain polyamines (LCPAs). These silaffins and LCPAs are species-specific molecules, but both have been shown to induce rapid silica condensation in vitro (Kröger et al. 2000). All these things – pH, electrostatic interactions, functional groups, condensation – play important roles in Stöber processes too. The

compounds that play these roles in diatom biomineralisation have functional equivalents in Stöber processes, though it is often not immediately apparent that this is so. The critical role to understand is that of the biomolecules. Applying that knowledge is to key to sustainable silica syntheses using biomolecules.

4.1 Specific biomolecules involved in biomineralisation of silica

The unravelling of the mystery behind the complex and intricate structure formation in diatoms, and other biomineralising creatures, has led to key insights into this process. Specific biomolecules have been shown to have a direct and integral role in the way these creatures shape and utilise silica (Perry 2009; Patwardhan and Staniland 2019). As we shall see, the underlying principle by which silica biomineralisation is conducted is not far removed from that of the Stöber processes. Evolution of the biomineralisation process over millennia has adapted and refined it into an elegant, efficient process. However, there are many lessons that can be learned to improve our own silica production methods.

4.2 Long-chain polyamines

The biomolecules responsible for silica synthesis in species such as diatoms contain moieties that play a crucial role. As discussed earlier, amine-containing surfactants are important for controlling condensation and particle morphology, through their structure-directing activity. The presence of the ammonium cation in the Stöber process is also critical. These amino compounds are so critical in fact, that without them, spherical silica is not formed. It is no coincidence then, that amines also play a critical role in the biomineralisation process (Lechner and Becker 2015; Hyde et al. 2016). The role they play in biomineralisation is comparable to their role in Stöber processes. In order to draw direct parallels with the Stöber processes, the role these amines play in biomineralisation must first be explored.

Belton et al. (2008) studied the effect that different LCPAs had on the polymerisation of silicic acid. They found that longer chain length, higher degree of methylation, and higher number of amines on the LCPAs increased the rate of condensation of the silicic acid. The authors suggest this was due to the ability of the polyamines to form microemulsions while carrying a positive charge, which provides a water-free microenvironment where the removal of water from the condensation reactions provides the driving force for the proton donor/acceptor condensation mechanism (outlined in **Scheme 3**).

The reason for this increase in kinetic activity is related to emulsion-forming ability of the LCPAs. This ability is directly related to how effective the amines are at preventing aggregation of the forming silica by controlling the condensation of the precursors through electrostatic interactions. They investigated the emulsion stability of the LCPAs and found that stability decreased as number of amines and amine spacing along the molecular chain decreased. Resistance to localised charging is greater when the number of amines along the molecular chain increases and their proximity decreases. This enhances the hydrophobic character of the LCPAs, thus increasing their emulsion stability. The silica can them form inside the polyamine microemulsion, which increases the condensation rate due to the hydrophobic environment providing a driving force for water removal.

Kröger et al. (2000) isolated LCPAs from *N. angularis* and studied their morphological control of particles formed upon condensation of silicic acid. They found that LCPAs with longer chain lengths resulted in particles of 800 nm – 1 μm, while shorter chain length resulted in particles of 100 – 200 nm. While no explanation is given by the author for this difference in particle size, it is likely that it is due to the enhanced condensation rates associated with longer chain length polyamines, as described above. An increased condensation rate would favour the formation of larger particles. Thus, silica particle size will increase with increasing chain length. Mizutani et al.

(1998) studied the catalytic effect of amines on the polymerisation of silicic acid. They found that polyamines increased polymerisation rate more so than linear amines, which had a moderate effect. Monoamines had very little effect on the polymerisation rate, while in the absence of an amine catalyst, no polymerisation occurred. The mechanism by which these amines catalyse biogenic silica polymerisation is still not clear. Some studies suggest that the process is driven by electrostatic interactions between the silica precursor and the positively charged amine groups (Sumper and Kröger 2004; Wenzl et al. 2008). Depending on the proximity of amines and their chain length, at near-neutral pH, different degrees of positive charge exist on the amines. These positive charges can then interact electrostatically with the negatively charged oligomeric silicate species, bringing them in close enough contact such that polymerisation takes place. This would explain why the monoamines had little effect on the polymerisation rate. Monoamines can only electrostatically interact with one silicate species at a time, whereas polyamines can interact with multiple, bringing them in closer proximity and facilitating polymerisation.

However, this amine-silicate interaction may proceed by a chemical mechanism also. Delak and Sahai et al. (2005) studied the effect of different length polyamines on the dimerisation of trimethylethoxysilane (TMES) – a silica precursor in which only the ethoxy bond is labile. This is significant because at pH 5.5, as used in the study, close to the pH at which biogenic silica forms, TMES is neutral. Furthermore, the intermediate product tetratmethylsilanol, is also neutral at this pH (pK_a = 12.7). This means that electrostatic interactions cannot form the basis of the catalytic activity of these polyamines in this system. The authors propose instead that the catalytic mechanism proceeds via chemical reaction, in which a pentacoordinate intermediate is formed by nucleophilic attack of TMES by the amine. In this pentacoordinate system, the ethoxy bond of TMES is more labile and thus more susceptible to hydrolysis. Further attack by water with a

transition through a hexacoordinate intermediate, followed by a condensation step proceeding through an S_N2 mechanism leads to dimerisation. While this mechanism is plausible, and under the conditions of this specific system, likely, it is not representative of the conditions of biogenic silica formation. The usual form of naturally occurring silica is silicates, in which the silicon is bonded to oxygen (Fairbridge 1997). Therefore, naturally occurring silica species are likely negatively charged at slightly acidic pH, due to silanol group deprotonation or the facile hydrolysis of labile bonds, and because of this, electrostatic interactions cannot be negated. However, there is no reason to assume that the electrostatic and chemical mechanisms contributing to polyamine catalytic activity in this context are mutually exclusive. Both mechanisms may occur together, though it remains uncertain.

4.3 Amino acids and peptides

Following on from the work with LCPAs, other biomolecules identified in the biomineralisation process were studied. Species-specific proteins, such as silaffins and silacidins, were isolated (Wenzl et al. 2008; Kröger et al. 2014). Owing to the complex nature of interactions present in the natural system, iterative investigations starting from simple molecules were carried out. The amino acids serine, lysine, proline, aspartic acid, and their homopeptides were shown to induce silicic acid polymerisation and condensation (Coradin and Livage 2001). It was shown that the peptides had a more pronounced effect than their corresponding amino acids in the polymerisation process. At low pH (4 – 7), the oligomeric silica species are negatively charged (Coradin et al. 2003). Depending on their pK_a and pK_b values, the amine and carboxylic acid groups of the peptides are likely positively and negatively charged, respectively. Thus, the interaction between the peptides and silica species are predominately through electrostatic interactions via the protonated amine

groups. This is analogous to the Stöber process in which the ammonia plays a morphological catalyst role.

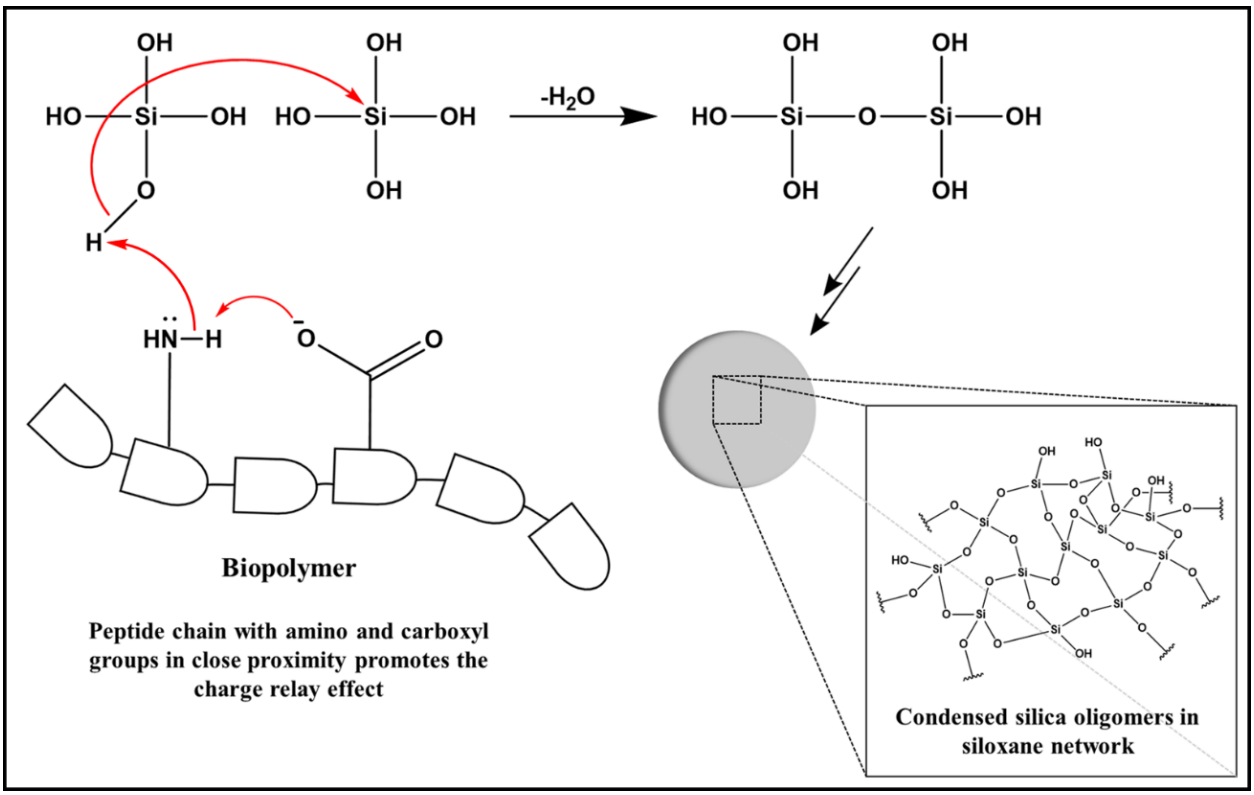
To probe this further, different chain lengths of poly-lysine and poly-arginine were investigated (Coradin et al. 2002). Again, it was shown that the positively charged amine groups of the polypeptides play a key role in the polymerisation and condensation process. Increasing the chain length of the polypeptides increased the rate of precipitation. This suggests that having more positively charged amine groups along a chain allows the negatively charged oligomeric silica precursors to be in close enough proximity for polymerisation to occur. Of course, other interactions such as hydrogen bonding may also play a key role. The overall result is that the electrostatic interactions help anchor the silica species and allow polymerisation and condensation.

It is clear that carboxyl and amino groups play a key role in silica polymerisation by bringing the oligomeric silica species in close enough proximity for condensation to occur. This is similar to mechanism of the Stöber processes discussed in **Sections 2.3** and **2.4**. However, prior to polymerisation, nucleation must occur. Nucleation is the dimerisation of the silica precursor, which begins the process of polymerisation. Wallace et al. (2009) studied the effects of carboxyl-terminated surfaces and amine-terminated surfaces on silica nucleation. They found that carboxyl-terminated surfaces were able to induce silica nucleation under ambient conditions and at slightly acidic pH. In contrast, amine-terminated surfaces failed to induce silica nucleation under identical conditions. This contrasts with the above studies on polymerisation, where the amine groups were more actively involved than the carboxyl groups. However, it seems during nucleation, the amine groups by themselves have little influence. Interestingly, when combining both carboxyl- and amine-terminated surfaces, it was found that the silica nucleation rate was 18× faster than carboxyl-terminated surface alone. This observation can be explained by the charge relay effect

commonly seen in the active site of some enzymes. Many biomolecules such as enzymes and proteins contain what is referred to as a catalytic triad, containing three main components: acid, base, and nucleophile (Brumlik and Buckley 1996). This triad forms the basis of the charge relay effect. In this mechanism, the base residue is activated due to polarisation from the acid residue, which is in close proximity. Once the base residue is polarised, it in turn activates the nucleophile. The activation of the nucleophile is as a result of the catalytic triad acting synergistically to lower the pK_a of the nucleophile (Ekici et al. 2008). As outlined in the next paragraph, this mechanism may explain why peptides and the combined carboxyl- and amine-terminated surfaces have such an influence on the silica nucleation and polymerisation rate.

To investigate the charge relay effect and its influence on silica nucleation and polymerisation, Kuno et al. (2011) synthesised different combinations of polypeptides using lysine (K), histidine (H), and aspartic acid (D). Homopolypeptides (K_{10} and H_{10}), block polypeptides (K_5D_5 and H_5D_5), and alternate polypeptides [$(KD)_5$ and $(HD)_5$] were used to test how individual polypeptide chains and combinations of peptides affect the nucleation and polymerisation of trimethyethoxysilane. The homopolypeptides had the lowest catalytic activity, the block polypeptides showed around 8 – 9 % higher catalytic activity than the homopolypeptides, while the alternate polypeptides showed the highest catalytic activity which was around 11 % higher than the homopolypeptides. These results show strong evidence for the charge relay effect. In the block polypeptides, K_5D_5 and H_5D_5, only one amino acid group is adjacent to one carboxylic acid group, whereas in the alternate polypeptides, $(KD)_5$ and $(HD)_5$, each amino acid group is adjacent to one carboxylic acid group. This increased catalytic activity with neighbouring amino and carboxyl groups is what Wallace et al. also observed in their study. **Scheme 2** shows a simplified mechanism by which this process takes place with silicic acid. The carboxyl groups act as the acid which activates the amine group

by deprotonation, which increases the electron density around the amine. The amine group therefore has more nucleophilic character and promotes the nucleation and polymerisation of silica as shown. Further confirmation of the importance of the charge relay effect on silica polymerisation is provided by Murai et al. (2014) who studied the peptides Ser-His-Glu (SHE) and Val-His-Val-Glu-Val-Ser (VHVEVS) and their influence on the nucleation and polymerisation of trimethylethoxysilane. The secondary structure of SHE was found to be a random coil, while that of VHVEVS was found to be a β-sheet. This β-sheet conformation was found to increase the catalytic activity of VHVEVS by bringing the His and Glu residues into close proximity to enable the charge relay mechanism. Monolithic silica structures were prepared with both peptides, but the surface of the silica prepared with VHVEVS was smooth, while the surface of the silica prepared with SHE was rough. This indicates that the β-sheet conformation of VHVEVS exerts increased morphological control over the polymerisation process. Thus, the presence of LCPAs and peptides, and their conformation, in silica-synthesising organisms has a major influence on the rate at which silica nucleation and polymerisation occurs and the morphology of the final structure.



Scheme 2 Charge relay effect in biosilica synthesis. Here the peptide chain of the biopolymer has amino and carboxyl groups in close proximity, which is the case for many biopolymers. The oxygen of the carboxyl group hydrogen bonds to the hydrogen of the amino acid group. This pulls electron density away from the nitrogen. The lone pair on the nitrogen then activates the nucleophile, in this case a silicic acid molecule. This starts the condensation process. The silicic acid monomers condense to form a siloxane network which results in the formation of silica. The biopolymer can also act as an SDA, which can promote the formation of spherical silica particles, represented here by the grey sphere

4.4 Silaffins

One of the most intensely studied diatom species is C. *fusiformis*. This species, like many other diatoms, uses silica to make elaborate, visually arresting silicate cell walls. Pelagic sediment on the ocean floor, made up of these tiny creatures, provides a large source of bioessential silica in the marine environment and contributes heavily to the oceanic silica cycle. This silica cycle plays an important role in global climate regulation through the carbonate-silicate cycle (Berner 1992), showing that, while these creatures may be tiny, they have a global impact. Another recently solved

mystery is how these diatoms exerts such fine control over the silica biomineralisation process. Silaffin proteins – polycationic peptides – were first discovered upon isolation from *C. fusiformis* (Thamatrakoln et al. 2006). These silaffins are responsible for the intricate and complex silica structures in the cell wall of *C. fusiformis*. Initially, silaffin-1A, silaffin-1B, and silaffin-2 were classified (Kröger et al. 2001). Named for their affinity for silica, these silaffins are highly associated with the cell wall structures of the diatoms. In order to isolate these initially, HF extraction was used. Subsequent extraction with ammonium fluoride, which does not remove amino acid modification, lead to the identification of the native silaffins; natSil-1A and natSil-1B (Kröger et al. 2014). Characterisation of these native silaffin proteins revealed extensive post-translational modification with the serine residues phosphorylated and the lysine residues modified with LCPAs (Kröger et al. 1999; Sumper and Kröger 2004). Other amino acid residues may play a role in silica synthesis via the charge relay effect, mentioned previously. The interaction of post-translationally modified proteins and polypeptides with oligomeric silica species occurs in silica deposition vehicles (SDVs). SDVs are structures present in diatoms, as well as other organisms (Simpson and Volcani 1981), that mediate the growth of biogenic silica by controlling the hydrolysis and condensation of silicic acid, which proceeds in a similar way to the hydrolysis and condensation of TEOS (Belton et al. 2010). A key similarity between silaffins and CTAB, which is used in the modified-Stöber process, is the presence of quaternary ammonium ions. These are well known to be effective structure directing agents in the synthesis of zeolites and spherical silica (Goretsky et al. 1999). where longer chain alkylammonium ions, i.e., more hydrophobic molecules, showed excellent structure directing activity. As mentioned previously, CTAB, a quaternary ammonium surfactant, is used extensively in silica synthesis due to its structure directing activity. **Fig. 5** shows the structure of a silaffin isolated from C. *fusiformis*, which

contains numerous quaternary ammonium groups. These groups are analogous to the structure of CTAB which is the SDA in modified-Stöber syntheses. In fact, silaffins isolated from diatoms have been shown to induce silica polymerisation under acidic conditions *in vitro* (Pamirsky and Golokhvast 2013; Kröger et al. 2014). Thus, this natural biomineralisation process and the Stöber processes are directly analogous. It seems Nature has already evolved molecules capable of creating complex hierarchical silica structures. The challenge now is for materials scientists to capitalise on this knowledge to improve synthesis methods for materials such as silica.

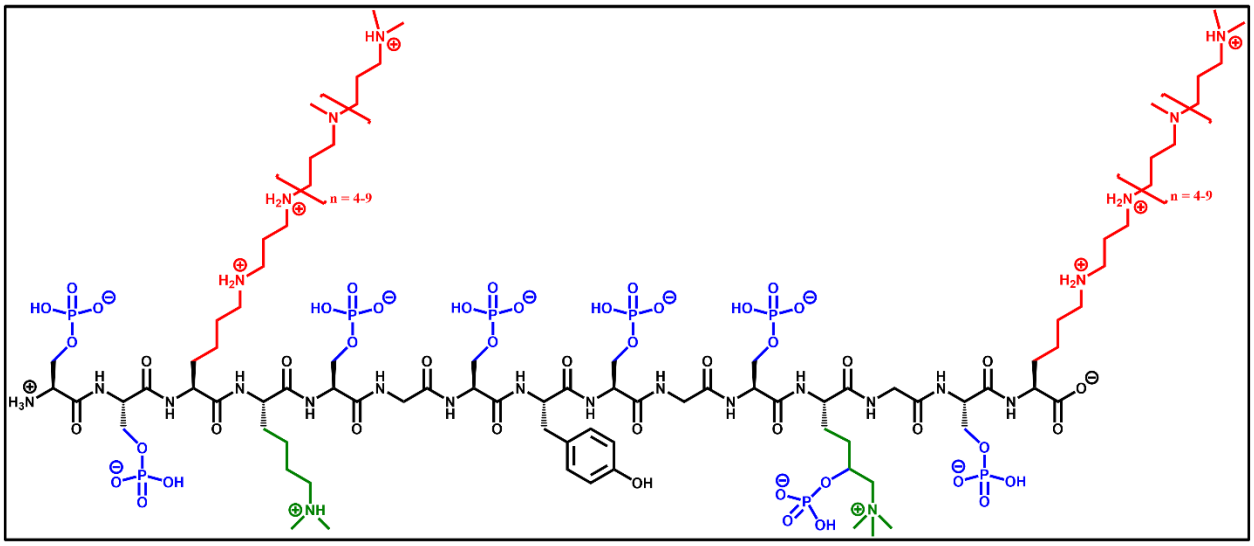


Fig. 5 Chemical structure of native silaffin-$1A_1$ from C. fusiformis. Adapted from Lechner and Becker (2015)

5 Bridging the gap – connecting Stöber to Nature

5.1 Biomolecule physicochemical characteristics key to spherical silica synthesis

We have seen how the extraordinary creatures like diatoms are able to create complex silica structures using specific biomolecules under ambient temperature and pH and how it relates

closely to Stöber processes. The key features of these biomolecules responsible for silica biomineralisation, such as the presence of LCPAs and peptides (Lechner and Becker 2015; Kamalov et al. 2018), the charge relay effect (Kuno et al. 2011; Murai et al. 2014), and electrostatic interactions (Kotzsch et al. 2017; Kolbe et al. 2020) are strikingly similar to how spherical silica particles are formed in Stöber processes. Long-chain quaternary ammonium surfactants, like CTAB, promote the polymerisation and condensation of silica precursors through similar interactions. The following sections will look more closely at biomolecules that are not specific to the *in vivo* biomineralisation process, but contain physicochemical characteristics akin to them, and so could be used in the formation of spherical silica particles. Thus, even though the way in which traditional silica (Stöber and modified-Stöber) and biogenic silica is made is different, the underlying processes of hydrolysis and condensation, and particle growth are very similar.

5.1.1 Amphiphilicity

An important property of many SDAs is their amphiphilicity. Surfactants like CTAB contain a hydrophilic headgroup in the form of a quaternary ammonium cation and a hydrophobic tail group in the form of a long carbon chain. These physical characteristics allow CTAB to form micelles in solution which play a crucial role in forming spherical silica (see **Sections 2.3** and **2.4**). Any biopolymer replacement for CTAB should also have this structure-directing facility.

In food technology, water-in-oil (w/o) and oil-in-water (o/w) emulsions are routinely stabilised by biopolymers to create new foods and drinks. Emulsifiers are a specific class of surfactants and what makes emulsifiers effective is that they are amphiphilic, which helps to lower the interfacial tension and facilitate smaller droplet sizes (Ghasemi et al. 2017). Commonly used emulsifiers include soy lecithin and sodium caseinate. Amphiphilic biopolymers typically contain large hydrocarbon chains and ionic moieties such as carboxylates and ammoniums. As discussed earlier

in **Sections 2.3** and **2.4**, CTAB, which is also amphiphilic, helps control particle morphogenesis through electrostatic interactions. This electrostatic interaction is the key to forming spherical particles when using surfactants such as CTAB. Electrostatic interactions between CTAB and the oligomeric silica species form the basis of the morphological control that is achieved. The amphiphilic nature of certain biopolymers should also provide this control, provided the other physicochemical characteristics, discussed next, are present.

5.1.2 Charge relay effect

As we have seen from the studies discussed earlier, the presence of a catalytic triad, enabling the charge relay effect, has a great effect on the silica nucleation and polymerisation rate. The presence of adjacent carboxyl and amino groups along a peptide chain of a biopolymer, together with the presence of a silica precursor, can activate and promote the nucleation and polymerisation of silica. In fact, the charge relay effect has been exploited in biocatalysis due to this catalytic behaviour (Gruber and Kratky 2004; Anobom et al. 2014; Amrein et al. 2015; Nothling et al. 2017). Biopolymers which contain polypeptide chains are ideal candidates to act as SDAs in silica synthesis due to the presence of adjacent carboxyl and amino groups.

5.1.3 Polyamines

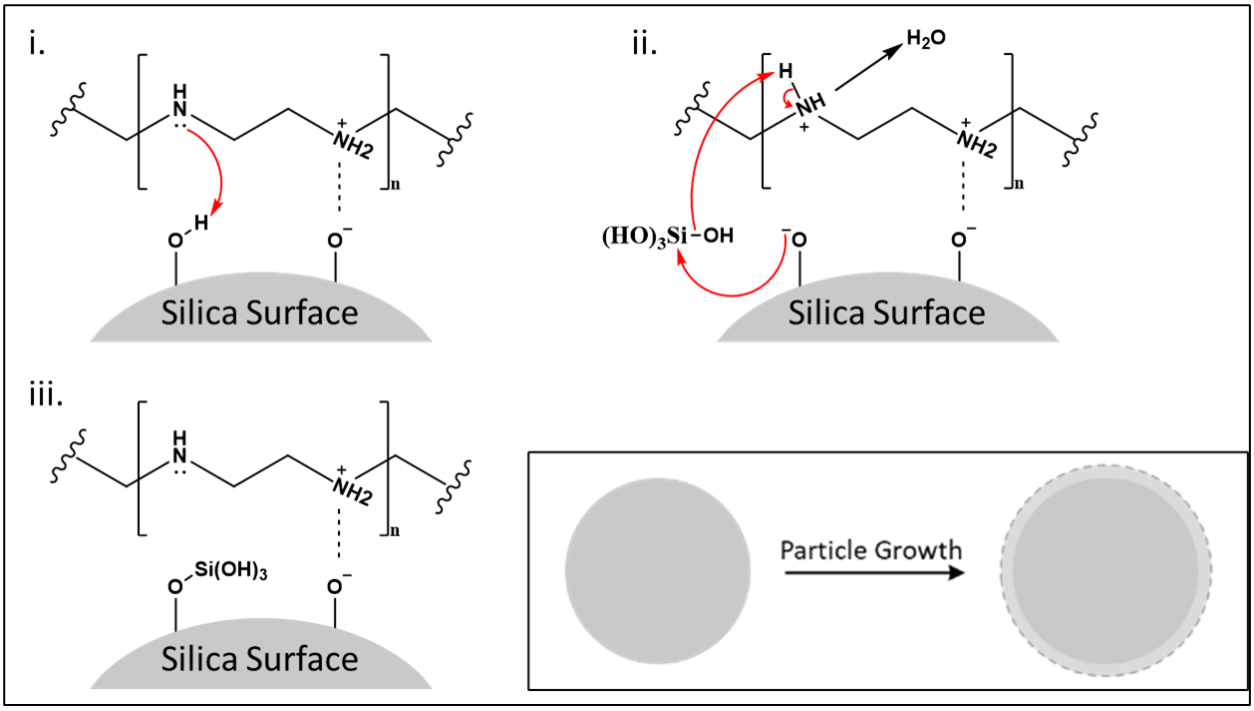
While the presence of LCPAs found in diatoms have been shown to play an integral role in silica biomineralisation, studies have shown that shorter chain polyamines can provide morphological control over silica polymerisation. Some of the LCPAs isolated from diatoms have complex molecular structures which can make *in vitro* replication difficult. Thus, if shorter chain polyamines are shown to behave in a similar way to LCPAs, it would simplify biomimetic silica production. The studies mentioned previously isolated biomolecules from diatoms which were

subsequently shown to play a key role in the polymerisation and condensation of silicic acid. Since then, there have been a few limited studies trying to replicate this process biomimetically.

Menzel et al. (2003) studied the effects polyamines with different lengths and branching had on silicic acid condensation. They found that diaminoethane and 1,3-diaminopropane accelerated the condensation of silicic acid the most. As the chain length of the polyamine increases the accelerating effect decreases. Linear polypropylene imine (PPI) had less of an effect on accelerating the condensation reaction that linear polyethylene imine (PEI). The methylated (branched) variants, PMPI and PMEI, both showed similar effects and did not accelerate the reaction as much as the non-branched variants. In the absence of any amine, the condensation reaction was the slowest.

It is clear from this study that polyamines speed up the condensation of silicic acid, with shorter, unbranched polyamines accelerating the reaction more than longer, branched polyamines. A faster condensation rate could promote particle growth (Yokoi et al. 2009; Greasley et al. 2016). Other work probing whether this is the case was done by Belton et al. (2005), who studied naturally occurring polyamines – spermidine and spermine – along with a series of linear ethyleneamine homologues. The chain length and number of amines on the homologues increased stepwise, from ethylenediamine up to pentaethylenehexamine. They found that the smaller chain length polyamines showed no distinct spherical silica structures. However, as the chain length and number of amines increased, somewhat more spherical and distinct particles were produced. Interestingly though, spermidine produced larger particles than spermine, which has a longer chain length and an extra amine. The aggregation rate of the particles was also found to generally increase with increasing chain length and number of amines, with more pronounced increases for tetraethylenpentamine and pentaethylenehexamine.

As mentioned previously, the interaction of amines, for example quaternary ammonium groups, is important for the controlled condensation and growth of spherical silica. The authors point out that at near neutral pH about 50% of the silanol groups on the surface of the forming particles are deprotonated, i.e., every second silanol is negatively charged. Therefore, the atomic distance between these deprotonated silanols is ca. 5.4 Å. The inter-amine distance of ethylenediamine is 3.9 Å. Thus, ethylenediamine is unable to bridge the gap between two deprotonated silanols, which would shield and stabilise the surface to prevent uncontrolled aggregation. As chain length and the distance between, and amount of, amines increase, this gap is easily bridged, and the amines form a surface layer on the nascent silica particles. However, at near neutral pH, not all the amines on the polyamines are charged due to their close proximity, which increases the resistance of neighbouring amines to become charged. This can provide a mechanism for controlled growth of the silica particles. These amines are still weakly basic and can promote silica condensation. **Scheme 3** shows a simplified mechanism by which this takes place. The polyamine, which is representative of those found in biomineralisation proteins (see **Fig. 5**), electrostatically interacts with the silica surface through its quaternary ammonium groups. This brings the polyamine molecule close enough to the surface to allow the uncharged amines to deprotonate a silanol, which then attacks free silicic acid via an Sn2 mechanism. This process continues, adding more silicate to the surface, and the particles grow in a controlled manner. The parallels between this mechanism and the mechanism of action of surfactants like CTAB in the modified-Stöber process is striking. Both processes are heavily reliant on the length of the SDA – polyamine or CTAB – and the electrostatic interaction between them and the silica surface.



Scheme 3 Simplified mechanism of silica particle growth in the presence of polyamines. Polyamine is attracted to the silica surface electrostatically (represented by dashed line). (i) Lone pair of electrons on uncharged amine deprotonates a silanol in close proximity. (ii) This deprotonated silanol attacks a free silicic acid molecule via Sn2 mechanism, with OH^- as the leaving group. The OH^- then attacks the protonated amine group, releasing water and reforming the uncharged amine. (iii.) Silicic acid derivative is attached to the surface. The process repeats, adding more silicate to the surface and the particle grows. Image on lower right represents this surface growth. Dark grey is the original particle, light grey is additional silica added by growth process. Dashed line around particle illustrates an increased diameter

This mediation of particle growth is key to forming spherical silica particles. The strong parallel between the natural biomineralisation process and the Stöber silica processes can enable the use of naturally occurring biomolecules that possess the physicochemical properties described above. This provides the possibility of designing a more sustainable process for synthesising silica at an industrial scale – one which uses environmentally benign, non-toxic, and renewable reagents. Biomolecules fulfil the sustainability aspect, and certain biomolecules possess the physicochemical properties required to control silica condensation and growth. Some limited work has been done investigating the effect of such proteins on silica condensation and growth.

5.2 Biomolecule sources

As discussed previously, the physicochemical characteristics of certain biomolecules can promote the polymerisation, and control the condensation, of spherical silica. The presence of polyamine and carboxylic acid groups in biomolecules can increase the nucleation and polymerisation rate of silica through the charge relay effect. Their amphiphilicity can prevent aggregation of nanomaterials by absorbing onto their surface during growth. These properties can bring together the advantages of Stöber processes – facile production of spherical silica – and biomineralisation processes, which provide a sustainable way to produce spherical silica. One of the key advantages of using biomolecules as SDAs over petrochemical surfactants like CTAB is that they are renewable, biodegradable, and readily available from sustainable sources.

Biomolecules originate in living organisms and are a key class of molecules which fulfil the criteria described by the Green Chemistry concept. Biomolecules are also renewable. By contrast, most current industrial polymers are petrochemicals, i.e., they are derived from an infamously finite, environmentally damaging source – crude oil. The vast majority biomolecules are available from a variety of natural, renewable sources, and a small but growing percentage are produced through various biotechnological methods. An attractive feature of many biomolecules is their biodegradability (Niaounakis 2016). This is preferable because it mitigates, or completely solves, the issue of persistence of plastic waste in the environment (Thompson et al. 2009; Thompson 2015).

Many of the sources of biomolecules are forms of biomass like sugars and starch. But first-generation sources are associated with increased food costs and deforestation because they compete with food production resources (Niaounakis 2013). As such, these biomolecule sources cannot realistically be recommended as a solution to industrial production sustainability issues.

However, there are some first-generation sources, such as algae, that do not require arable land or freshwater for cultivation and are not currently a major food source. Algae are already a promising source of biofuels for the same reasons (Tabassum et al. 2017). Second-generation biomolecule sources are typically waste streams. These are an immediately superior candidate source of biomolecules as the use of wastes is an inherently more sustainable practice. For example, chicken feathers, a by-product of the poultry industry, can be used as a source of highly utilitarian keratins (Sinkiewicz et al. 2017). Casein, a major component of waste streams from milk production and spoilage, can be extracted and used in food technology and textiles (Rasmussen and Petersen 1991; Huppertz et al. 2018). This valorisation of waste streams greatly improves the sustainability, economically and environmentally, of these sources compared to first generation feedstocks. The next sections look at the limited work that has been done utilising such sustainable biomolecules with the aim of synthesising silica in a biomimetic way.

5.3 Synthesising spherical silica particles with biomolecules

The knowledge garnered from studying silica biomineralising creatures such as diatoms has provided opportunities to synthesise new and advanced biomimetic silica materials (Chen et al. 2019; Lei et al. 2020; Abdelhamid and Pack 2021). The key physicochemical characteristics that have been shown to be crucial for controlling silica nucleation and polymerisation in biomineralisation can be adapted and used to improve the Stöber processes. The presence of adjacent amino and carboxyl groups to promote the charge relay effect, the presence of quaternary ammonium groups and their electrostatic interaction with oligomeric silica species, and amphiphilicity, are all key physicochemical attributes that are needed if a biopolymer is to promote and control silica nucleation and polymerisation. Furthermore, synthesis of biomimetic silica with

these biomolecules under ambient conditions of temperature and pH can vastly increase the sustainability of the process compared to the traditional Stöber processes (Patwardhan et al. 2018).

5.3.1 Biomolecules as SDAs for spherical silica

There is evidence in the literature that biomolecules can be used to effectively direct the formation of spherical particles in nucleation and growth processes. Biomolecule SDAs have been successfully used to control the morphogenesis of iron oxide, silver, and gold nanoparticles. For example, iron oxide nanoparticles have been synthesised with a variety of different biomolecules. The polysaccharide dextran has been used to control the morphology and size of the iron oxide particles (Hradil et al. 2007; Predescu et al. 2018; Naha et al. 2019). Dextran interacts with the iron oxide surface through chelation and hydrogen bonding, with the strength of the hydrogen bonding increasing with chain length of dextran (Laurent et al. 2008). Alginate has also been used to synthesise iron oxide particles (Finotelli et al. 2008; Wu et al. 2015). Alginate has many carboxyl groups which complex to the iron ions enabling mediation of particle growth (Shears et al. 2007). Silver nanoparticles have also been produced using biomolecules such as starch as stabilising, and structure-control, agents (Yakout and Mostafa 2015; Salaheldin 2018; Kumar et al. 2018). Starch contains many hydroxyl groups which have good metal complexation properties and enable the morphological and size control of the silver nanoparticles (Raghavendra et al. 2016). Gold nanoparticles have been prepared using chitosan as the stabilising agent (Huang and Yang 2004; Adlim and Bakar 2010; Sun et al. 2017). The polyelectrolyte properties of chitosan stabilise the gold nanoparticles through electrostatic interactions (Mohan et al. 2019). It is clear from these studies that biomolecules can readily control and stabilise the growth of nanomaterials. However, using biomolecules to synthesise monodisperse spherical silica nanoparticles has scarcely been explored. Applying the knowledge of the physicochemical properties required for

biomineralisation and the structure-directing ability of some biomolecules in producing nanomaterials can bridge the gap between these similar processes.

There is some evidence that biomolecules can also act as an SDA in the synthesis of spherical silica. Coradin et al. (2003) studied the effects of bovine serum albumin (BSA) and lysozyme on sodium silicate solutions. Lysozyme, a small enzyme, and BSA, a large protein, contain high percentages of acidic and basic groups such as lysine and aspartic acid. The ratio of amino acids-to-silica was used to compare the reactivity of both proteins. They found that under different respective pH, lysozyme and BSA were able to induce silica condensation. The formed solids were shown to have an interspersed network of protein and silica. This suggests that the interaction of protein and silicate is important for condensation. At pH 7.2, lysozyme is positively charged and interacts electrostatically with the negatively charged silicate species to induce condensation. At this pH, BSA is negatively charged, and no silica was formed, highlighting the importance of electrostatic interactions in silica formation. At pH 4.7, where BSA is positively charged, silica formation occurred. Surprisingly, even though lysozyme is also positively charged at this pH, no silica formation occurred. At this pH, the lysine groups of lysozyme are fully protonated, reducing its net positive charge. Further, at this acidic pH, the oligomeric silicate species are less negatively charged. Thus, the overall result is a weaker electrostatic interaction between lysozyme and the silicate species. This further highlights the importance of electrostatic interactions between biopolymers and silica precursors in silica formation. This becomes a key consideration when using biopolymers to form spherical silica particles. It can be argued that the charge relay effect is, at least partially, responsible for this influence.

Another study by Coradin et al. (2004a) looked at the influence of gelatin on silica formation. Different concentrations of gelatin and sodium silicate were tested, and the morphology of the

silica was characterised. They found that at the concentrations studied, silica precipitation occurred. However, at higher gelatin concentration, silica nanoparticles became embedded in the polymer network. The influence of gelatin on the size and shape of these nanoparticles was studied at pH 5 and pH 7. At pH 7, highly agglomerated silica particles were observed. At pH 5, less agglomerated, slightly spherical silica particles were observed. As mentioned previously, at pH 7, the oligomeric silicate species bear high negative charges, which increases the electrostatic interaction between them and the gelatin. In fact, this study showed via thermogravimetric analysis that at pH 7, the silicate species bind twice as much gelatin as at pH 5. In this case though, this means that the gelatin lost its structure-directing ability and a composite precipitate with highly agglomerated silica particles is produced. The presence of more well-defined silica nanoparticles at pH 5 however is explained by the authors in terms of a stabilising effect of gelatin. They posit that negative charges on the carboxylate groups in the side chain of gelatin allow particle growth to proceed without aggregation of the particles. Sodium ions could prevent particle growth by stabilising surface charge. It is suggested that the carboxylate groups of the gelatin interact with the sodium ions preventing this. The fact that larger, less agglomerated particles are produced at pH 5, while smaller, aggregated particles are produced at pH 7 suggests this theory might be correct. In any case the electrostatic interactions between the biopolymer and silicate species are crucial in determining the final size and morphology of the final silica particles.

Probing the use of biopolymers to catalyse and control silica polymerisation, Demadis et al. (2009) studied the influence of chitosan-based biopolymers phosphonomethylated chitosan (PCH), polyethyleneimine (PEI), and carboxymethylinulin (CMI) on solutions of sodium silicate at neutral pH. In this case, the biopolymers were chosen due to their physicochemical similarities to silaffins. The cationic polyamine and anionic phosphate groups are the main similarities, and as discussed

earlier have been shown to be highly influential on the silica polymerisation process. However, the focus of this study was to understand the inhibitory effects these biopolymers have on the condensation process. For diatoms to form their hierarchical silica structures, a supply of dissolved silicon must be present. In the waters of Earth's oceans and rivers, there are vanishingly small quantities of dissolved silicon – far lower than the levels needed by diatoms to make their ornate siliceous cell walls. To solve this issue, diatoms have evolved a means of supersaturating silica within themselves, ensuring adequate supply for biomineralisation (Wallace et al. 2009). The diatoms achieve this by inhibiting the condensation of silicic acid prior to its use in silica deposition vehicles to form the silica structures (Kotzsch et al. 2017). This inhibitory effect is achieved by electrostatic and/or H-bonding interactions between biopolymers and silicic acid.

In the above study, PCH contains protonated amines, PEI contains protonated polyamines, while CMI is anionic. The inhibitory effect of these biopolymers was tested over 72 hrs at various concentrations. While PEI and PCH individually, and together, showed good inhibitory effects towards silica condensation, CMI had less of an effect due to its anionic nature. However, in all cases, the inhibitory effects of the biopolymers could not prevent the condensation of silicic acid, instead the differing degrees of retardation resulted in structural differences in the silica precipitates. At 40 ppm and 150 ppm PCH, the morphology of the particles is quasi-spherical with size ranging between 300 – 500 nm after 72 hrs of growth, eventually forming aggregates ca. 2 µm after 4 weeks. At 20 ppm PEI, which showed comparable inhibitory effects to 40 ppm PCH, the particles were larger. PEI contains polyamine chains, which can mediate particle growth as shown in **Scheme 3**. PCH does not contain these polyamine chains, which may explain the difference in particle size. A combination of 20 ppm PEI and 40 ppm PCH resulted in particles of 150 – 200 nm in size.

Although the authors point out that no synergistic effect between PCH and PEI occurs in relation to the inhibition of silicic acid polymerisation, it seems there is one for particle growth. Smaller more spherical particles are formed with PEI and PCH in combination, as opposed to quasi-spherical with PCH alone, or larger particles with PEI alone. A combination of PCH and CMI results in the formation of aggregated spherical particles, while increasing the concentration of CMI results in even larger aggregates.

Further evidence for the importance of electrostatic interactions between biopolymers and silicate is given by Gautier et al. (2008), who studied the effects of cationic gelatin and anionic alginic acid on sodium silicate polymerisation at pH 5. They found that with only alginate present, no silica is formed unless left for an extended period. In which case, a composite is formed with a small amount of alginate incorporated into the silica network. However, sodium silicate is known to polymerise in acidic solution and the small amount of alginate incorporated into the silica network could be explained by very weak interactions between the anionic alginate and anionic silicate species. When cationic gelatin is added along with alginate, silica polymerisation occurs rapidly. The electrostatic interaction between gelatin and the silicate species brings the polypeptide chain of the gelatin in close enough proximity to induce silica polymerisation. As discussed earlier, the studies by Wallace et al. (2009) and Kuno et al. (2011) show that having carboxyl and amine groups in close proximity, as they are in peptides, along with alternating groups of polypeptides, greatly increases catalytic activity of the biopolymer.

While these studies are excellent examples of using the knowledge gleaned from the biomineralisation process to synthesise silica *in vitro*, the resulting silica is not comparable to that produced in Stöber processes. Aggregation and lack of sphericity, parameters easily controlled in Stöber processes, means there is still some way to go until biomimetic silica achieves parity with

Stöber processes. **Table 1** shows a comparison of the silica formed when using various complex biomolecules in a biomimetic synthesis. In all cases, silica was formed, however, the morphology was mostly either non-spherical, agglomerated, or both.

Table 1 Comparison of different biopolymer SDAs and their influence on silica morphology

SDA[a]	Particle Size (nm)	Morphology	References
BSA/PEI	180 – 320	Spherical	(Jackson et al. 2015)
BSA/lysozyme	50 – 200/ non-spherical	Non-spherical	(Coradin et al. 2003)
Lysine/arginine	< 100	Non-spherical/ agglomerated	(Coradin et al. 2002)
Gelatin	50 - 300	Non-spherical	(Coradin et al. 2004a)
PCH PEI CMI	300 - 2000	Non-spherical	(Demadis et al. 2009)
Gelatin/alginic acid	10 – 50	Non-spherical/ agglomerated	(Gautier et al. 2008)
Gelatin	Non-spherical	Non-spherical	(Jia et al. 2004)

[a]SDA, structure-directing agent; BSA, bovine serum albumin; PEI, polyethyleneimine; PCH, phosphonomethylated chitosan; CMI, carboxymethylinulin

It is clear from the above studies that the physicochemical properties of the biopolymers play an important role in the formation of spherical silica particles. Depending on the functionality present in a given biopolymer, condensation rate can be affected (inhibition or promoted), as can the morphological control exerted on the forming particles. Therefore, it is imperative that biopolymers with potential to act as an SDA in spherical silica syntheses have physicochemical properties which promote condensation while also maximising morphological control.

5.3.2 Ideal biomolecule SDA candidates

Here we highlight some biomolecule candidates which, based on the physicochemical characteristics described previously, show potential to be used as SDAs in the synthesis of spherical silica. The studies described in the previous section, which used biopolymers as an SDA

to produce silica, produced non-spherical or agglomerated particles. To compete with the established Stöber processes, a biomolecule SDA needs to be able to create discrete spherical particles with acceptable size-monodispersity. Ideal biomolecule SDA candidates need to meet all the criteria described in the previous sections in order to achieve this goal. We have identified three candidates that fulfil these criteria – lysozyme, casein, and lecithin. Lysozyme has some potential to act as an SDA in spherical silica synthesis, while casein and lecithin are more promising.

Lysozyme

Lysozyme is a small cationic protein consisting of 129 amino acids, including 6 lysine and 11 arginine residues exposed on the surface (van den Heuvel et al. 2018). Lysozyme has been shown to interact electrostatically with negatively charged oligomeric silica species, mediating particle aggregation to form nanocomposites (Coradin et al. 2003; Ramanathan et al. 2009; Cardoso et al. 2010). Su et al. (1998) used neutron reflectometry to study the adsorption of lysozyme on the surface of silica. They found that at low concentrations, lysozyme adsorbs sideways-on, forming a monolayer on the silica surface. Molecular dynamics simulations by Hildebrand et al. (2015) also suggest that this sideways-on orientation provides a strong electrostatic attraction between lysozyme and the silica surface. Small-angle X-ray scattering (SAXS) suggests that for small silica nanoparticles, lysozyme-silica aggregates are near stoichiometric (Stawski et al. 2019). The binding of the lysozyme to the silica surface occurs primarily through the amino acid groups on the protein. Initially, the lysozyme deforms slightly, allowing it to bridge the nanoparticles, allowing for aggregation into larger structures. This bridging by the lysozyme is similar to the mechanism of LCPA-mediated particle growth described in **Scheme 3**. The electrostatic interactions bring the oligomeric silicate species in close enough proximity to the surface of

already-formed seed particles for reaction, and thus growth, to take place. The role of lysozyme in nanocomposite formation is quite similar. Indeed, the aggregation-inducing effect that lysozyme has on silica nanoparticles is a useful application, for example, in removing silica from aqueous solutions (Szewczuk-Karpisz and Wiśniewska 2018). However, because the lysozyme binds so strongly to silica and becomes embedded into the silica network (nanocomposites), synthesis of discrete silica particles is difficult. Lysozyme already bears the physicochemical characteristics of an ideal SDA for spherical silica production. If reaction conditions (pH, ionic strength, concentration, etc.) can be found to alter and reduce the strength of the interaction between lysozyme and silica, such that instead of the lysozyme becoming embedded in the silica, it mediates the growth of spherical silica particles, then lysozyme will be an ideal candidate to replace CTAB in the Stöber processes. Furthermore, lysozyme can be purified in an eco-friendly and inexpensive way from chicken egg white (Cheng et al. 2020), permitting a greater improvement in sustainability.

Casein

The majority protein component of milk is a family of phosphoproteins called casein. Differing primary structure and degrees of phosphorylation give rise to four distinct types, α_{s1}-, α_{s2}-, β-, and κ-casein. The caseins contain relatively high levels of the amino acid proline and as such generally lack secondary structure and tertiary structures, which results in high surface hydrophobicity, owing to their hydrophobic residues being exposed (Fox 2003). The caseins adopt an association complex in milk often termed casein micelles. These casein micelles are not fully analogous to traditional surfactant micelles which form reversible and ordered aggregates. Early spectroscopic data suggested casein had a random coil structure (Ono et al. 1987). Later, Holt and Sawyer (1993) performed sequence alignment procedures on casein and described the protein as having a dynamic

structure and called it a rheomorphic protein. It is well know that casein is a transporter of calcium and phosphate (De Kruif and Holt 2003). Calcium phosphate nanoclusters interact with the casein micelle and bind primarily to the phosphoryl residues of the proteins. McMahon and Oommen (2008) showed that these calcium phosphate nanoclusters play an integral part in the casein micelle formation and subsequent stabilisation. Another contributing factor to the stability of the casein micelle is the presence of κ-casein on the surface. According to Holt and Horne (1996), the C-terminal macropeptides of some of the κ-casein molecules form a negatively charged diffuse outer layer on the surface. This makes the surface hydrophilic and also prevents micelle aggregation, while the interior of the casein micelle is hydrated (McMahon and Oommen 2013). Caseins structure is made up of a variety of amino acid residues, with many carboxyl and amino groups adjacent to each other (Huppertz et al. 2018). The amphiphilic nature of casein along with its adjacent carboxyl and amino groups, which enable the charge relay effect detailed earlier, make casein an ideal candidate to function as an SDA in silica polymerisation. Sodium caseinate is a common form of casein which is often used in food manufacturing as an additive for its high protein content. It is produced by acid precipitation and resuspension under alkaline conditions. During this process the calcium phosphate is removed, which leads to the destabilisation of the casein micelles, resulting in individual caseinate molecules or small aggregates (Smialowska et al. 2017). However, reintroduction of calcium can reform and stabilise the casein micelle (McMahon and Oommen 2013). Another, more promising, source of casein is from milk wastes generated dairy and milk processing (Ryder et al. 2017; Gopinatha Kurup et al. 2019). This casein-containing waste is a more sustainable source of casein. Valorisation of waste-streams is a key tenet of the circular economy and use of such casein in spherical silica synthesis fulfils the requirements for sustainable SDAs detailed earlier.

A lot of the work involving sodium caseinate/casein has focused on its emulsifying properties. This surfactant-type property of proteins is due to their amphiphilic nature and it enables the stabilising of oil-in-water system which are common in many food products. Aside from this, casein is an ideal candidate to act as an SDA in the synthesis of spherical silica due to its micelle-forming ability and the presence of amino and carboxyl groups in its peptide chain, all key properties that have been deemed essential in creating spherical silica.

The literature provides some examples of casein being used in somewhat of an SDA role in synthesising nanocomposite particles. Xu et al. (2013) produced core-shell casein-silica nanocomposites using caprolactam-modified casein, polyacrylate, and TEOS. The emulsifying properties of casein were exploited to solvate and stabilise the hydrophobic acrylate monomers. Addition of an initiator, which starts the polymerisation of the acrylate, and TEOS allows for a double in situ preparation of the core-shell casein silica nanocomposite particles. The resultant particles had a spherical morphology, meaning that the polymerisation of the acrylate and TEOS occurred in a controlled manner. The FTIR spectrum of the casein showed large intensity peaks for both amine and carboxyl groups, which as we have seen is essential for SDA activity.

Further evidence for the potential of casein to act as an SDA in silica synthesis is provided by Ma et al. (2013), who also prepared core-shell casein silica nanocomposites. The procedure was similar to that of Xu et al. where the casein was modified with caprolactam followed by subsequent in situ polymerisation of TEOS and acrylate, resulting in the formation of spherical nanocomposite particles. Again, the polymerisation was controlled by the action of casein. Thus, the micelle-forming ability, along with the presence of amino and carboxyl groups, of casein can be used to direct and control the polymerisation of silica. In fact, there is evidence to support the specific interaction of the peptide chains of casein with silica. Tiberg et al. (2001) used neutron

reflectometry to study the adsorption of β-casein on the surface of silica and suggested that a positive charge surplus in the hydrophobic domain of β-casein may electrostatically interact with the negatively charged silica surface, facilitating adsorption. They also note that hydrophobic and hydrogen bonding may also play a role in this adsorption behaviour. This coupled with the micelle-forming ability of casein, and the charge relay effect promoted by the presence of adjacent amino and carboxyl groups on the peptide chain, make casein an ideal candidate for use as an SDA in spherical silica synthesis. Recent work by our group has shown that spherical silica particles can be synthesised using sodium caseinate as the SDA (Curley et al. 2021a). Sodium silicate added to sodium caseinate in acetate buffer (pH 5.94) produced polydisperse spherical particles. Addition of calcium chloride to the same system produced monodisperse spherical silica particles. DLS data showed that the calcium chloride stabilised the casein micelles, which allowed for the production of monodisperse particles. Factorial analysis showed that the interaction between sodium caseinate and calcium chloride had a statistically significant effect on particle size. Furthermore, in the absence of sodium caseinate, no spherical silica particles are formed. This suggests that the micelle structure of casein has a significant role in producing spherical silica particles.

Lecithin

Lecithin is a mixture of acetone insoluble phospholipids, containing mainly phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylinositol (PI), minor compounds such as phosphatidic acid (PA) and other substances (triglycerides, carbohydrates, etc.) (Cabezas et al. 2009). Many of these phospholipids exhibit good emulsifying properties due to their amphiphilic nature. Lecithin is a waste product generated from soybean oil production. It can be obtained from this crude waste by a process called degumming (Ceci et al. 2008). Lecithin can also be obtained from egg yolks, and with hundreds of millions of eggs thrown away every year in the UK alone

(Smithers 2019), this represents another example of a robust supply. Therefore, lecithin, like casein, can be obtained through valorisation of waste-streams, which increases their inherent sustainability.

Fig. 6 shows the structures of the main components of lecithin (and CTAB for reference). In fact, the major application of lecithin is in the food industry as emulsifying agents, which is analogous to the surfactant role of CTAB. Some more advanced uses of lecithin that have exploited this inherent nature have been in drug delivery. Lecithin organogels form when lecithin is dissolved in an organic medium and small amounts of water are added. Upon addition of water, the lecithin molecules form reverse micelles with further water addition converting these to three-dimensional, long, tubular networks (Raut et al. 2012). Lecithin can also form bilayers in aqueous solution. Lecithin and PC contain long-chain fatty acid residues and quaternary ammonium headgroups, which are structurally similar to the head and tail groups of CTAB. The formation of spherical silica particles is highly role of CTAB, as discussed in **Sections 2.3** and **2.4**.

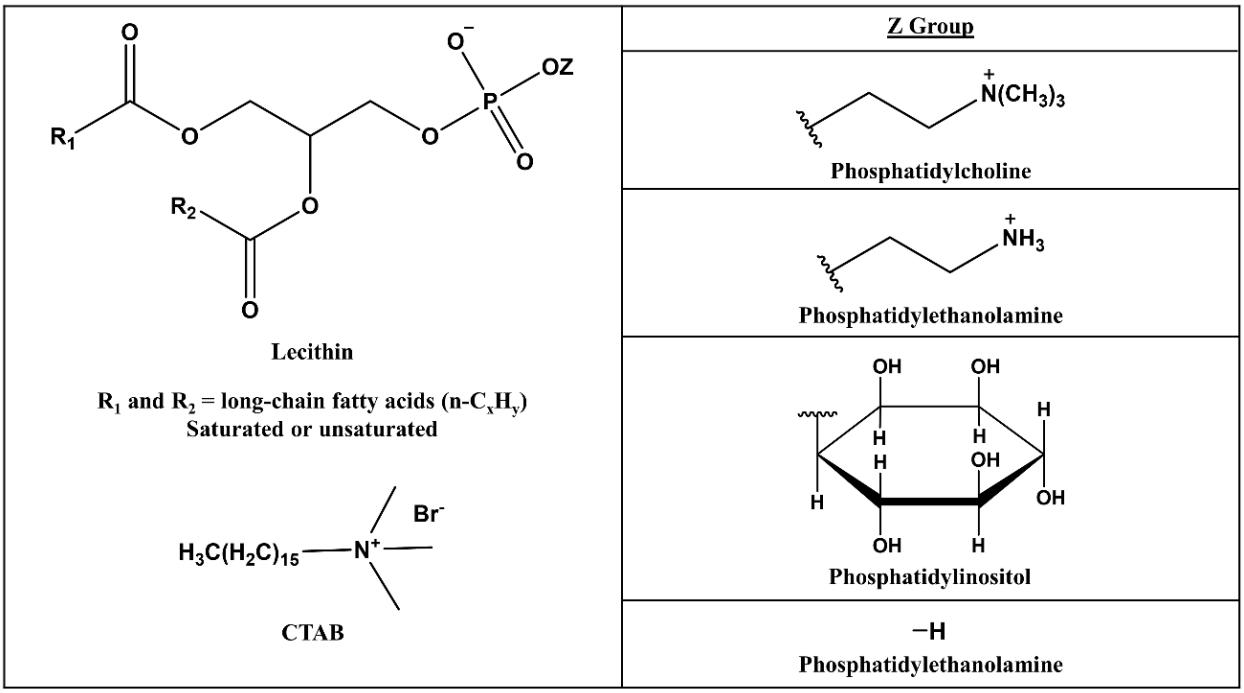


Fig. 6 General structure of lecithin (top left) and the major components of soy lecithin (right column). R_1 and R_2 = fatty acid residues. CTAB is shown (bottom left) for structural comparison. Notice the similarities between the quaternary ammonium headgroups of phosphatidylcholine and phosphatidylethanolamine and that of CTAB. The long-chain fatty acid residues of lecithin are also structurally and chemically similar to the long carbon tail of CTAB

Phospholipids are an important component of the cellular membrane in both plants and animals and are highly abundant and renewable. The hydrophobic tails are the R_1 and R_2 groups (see **Fig. 6** above), which are long-chain fatty acid residues with varying chain length and degree of saturation. The phosphate head is the hydrophilic part of the phospholipid, with the Z group varying depending on the derivative. These zwitterionic phospholipids have surfactant properties just like CTAB, which allow them to stabilise emulsions. This property has made lecithin useful in the food industry, but lecithin has also found limited use in controlling the morphology of silica. This propensity could allow lecithin to replace CTAB in spherical silica synthesis.

The literature shows some limited investigations on the use of lecithin as a means to control silica polymerisation. Galarneau et al. (2007) exploited the surface active agency of lecithin to form sponge mesoporous silica using lecithin/dodecylamine mixed-micelles in ethanol/water. Han et al. (2016) used calcium phosphate to coat the surface of lecithin micelles. These micelles were used to encapsulate perflurocarbon, which is used as an artificial oxygen carrier. The calcium phosphate coated lecithin micelles showed enhanced stability.

These studies show the ability and facility of lecithin to form micelles/bilayer structures. This is important when it is used to mimic biosilica formation. Surfactants like CTAB, which are used in Stöber processes, form micelles, and their ability to function as SDAs has a significant influence on the size and morphology of the resulting silica particles. Recent research by our group has shown that soy lecithin, and one of its major constituents, phosphatidylcholine, can function as an SDA in the synthesis of spherical silica (Curley et al. 2021b). DLS data of phosphatidylcholine and soy lecithin in acetate buffer (pH 5.92) showed that both biomolecules formed bilayer structures. In the presence of phosphatidylcholine, polydisperse spherical silica particles were formed. In the presence of soy lecithin, spherical silica particles with moderate monodispersity were formed. In the absence of either biomolecule, unstructured monolithic silica was formed, showing that phosphatidylcholine and soy lecithin act as SDAs to control the morphology of the silica. While the quality of the silica particles synthesised using phosphatidylcholine and soy lecithin is still below that of those produced using traditional Stöber syntheses, to the best of our knowledge, it is the first reported study using these biomolecules to produce discrete spherical silica particles of moderate monodispersity in a simple biomolecule-templated synthesis. The notably similar physicochemical properties of lecithin and CTAB – bilayer structure and quaternary ammonium headgroups – make lecithin an ideal candidate as an SDA. Thus far, many

of the attempts to use biomolecules as SDAs in the synthesis of spherical silica particles has not yielded much success. Finding biomolecules, such as lecithin and casein, which closely match the physicochemical characteristics detailed previously would finally bridge the gap between Stöber processes and Nature.

5.3.3 Comparison of experimental conditions of biopolymer-based silica synthesis versus Stöber processes

As we have seen, Nature has evolved the biomineralisation process to be a highly sustainable and efficient process. The synthesis of silica in diatoms and other creatures occurs under ambient conditions of temperature and pH in aqueous media. *In vitro* replication of this biomineralisation process can be conducted under similar ambient conditions (Coradin et al. 2002, 2003, 2004a; Jia et al. 2004; Gautier et al. 2008; Demadis et al. 2009). Contrast this to the typical synthesis conditions in the Stöber and modified-Stöber process outlined in **Table 2**. A typical Stöber synthesis is conducted at temperatures between 10 – 80 °C, but to get smaller particles which are more desirable, higher temperatures are needed (Stöber et al. 1968; Bogush et al. 1988; Harris et al. 1990; Nozawa et al. 2005; Wang et al. 2016; Qi et al. 2017; Meier et al. 2018). The Stöber process also needs ethanol as a solvent because TEOS is insoluble in water, therefore, ethanol acts as a mutual solvent for these. Post-processing of the particles typically involves washing with water and acetone. A typical modified-Stöber synthesis using CTAB is run at temperatures between 10 – 40 °C (Slowing et al. 2008; Alothman 2012; Stovpiaga et al. 2015; Yi et al. 2015; Zhao et al. 2016; Möller and Bein 2016; Luo et al. 2017). Again, smaller particles are achieved at higher temperatures. The modified-Stöber process also uses ethanol for the same reason as the Stöber process. Post-processing of the particles synthesised using the modified-Stöber process

requires calcination at very high temperatures to remove the CTAB. Chemical extraction of the CTAB is also possible but requires the use of acid/alcohol mixtures which also require heating.

Table 2 Comparison of experimental conditions of biopolymer-based silica synthesis with Stöber and modified-Stöber processes

Production Process	Precursor	Temperature (°C)	Solvent	Post-processing	References
Biopolymer-based	Sodium silicate	Ambient	Water	Washing	(Coradin et al. 2002, 2003, 2004a; Jia et al. 2004; Gautier et al. 2008; Demadis et al. 2009)
Stöber	TEOS	10 – 80	Ethanol/ water	Washing	(Stöber et al. 1968; Bogush et al. 1988; Harris et al. 1990; Nozawa et al. 2005; Wang et al. 2016; Qi et al. 2017; Meier et al. 2018)
Modified-Stöber	TEOS	10 – 40	Ethanol/ water	Calcination > 500 °C or chemical extraction	(Slowing et al. 2008; Alothman 2012; Stovpiaga et al. 2015; Yi et al. 2015; Zhao et al. 2016; Möller and Bein 2016; Luo et al. 2017)

The above table provides a simple yet effective outline of the advantages of a biopolymer-based silica synthesis over the traditional Stöber processes. Compared to the biopolymer-based silica syntheses, which use biodegradable and sustainable SDAs, water-based chemistries, minimal post-processing, and ambient experimental conditions, the Stöber processes are unsustainable and highly energy-intensive.

6 Conclusions and outlook

The outlook on the use of biomolecules to synthesise spherical silica is bright. The use of sustainable and renewable reagents, ambient reaction conditions, and environmentally friendly methods, offers significant advantages over the traditional, established methods. However, the one area which has perhaps hindered the adoption of such biomolecule-based silica syntheses is their failure to produce monodisperse silica particles thus far. The widespread use of Stöber and modified-Stöber processes is due to the ease, and consistency, with which they can produce discrete and monodisperse silica particles. Various applications, such as chromatography and drug-delivery, require monodisperse silica particles, and as such, it is an essential physical property to control. However, there has been decades of work and refinement since Stöber first reported the synthesis of monodisperse particles. Synthesising such particles using biomimetic methods is much more recent. It has already been shown that using Nature as an inspiration, biomimetic silica can successfully be synthesised *in vitro*. Further optimisation of this process, to control monodispersity, would lead to parity between the Stöber and biomolecule-based processes. These optimisations should focus on the physicochemical characteristics discussed previously – amphiphilicity, adjacent carboxyl and amino groups (charge relay effect), polyamines, and quaternary amines – and the reaction conditions which are conducive to such biopolymers acting as an SDA, because the structure-directing role of a biomolecule is crucial to forming discrete monodisperse spherical silica. Another important physical characteristic that follows on from making monodisperse particles is porosity. Introducing porosity to silica particles enhances their utility and opens up a greater number of potential applications. The extant literature provides some examples of biomolecules being used as porogens for a variety of materials. Whether a biomolecule SDA can be used to both produce monodisperse spherical particles and create well-

defined pore structures remains to be seen. The former, as this review has shown, is progressing, and the latter may follow as a corollary.

Ideally, any biomolecule SDA should come from a renewable source, such that its use constitutes an actual improvement in sustainability. Source variety is also important, as over-reliance on a single biomolecule can lead to maintenance of damaging industries that would otherwise fail economically without valorisation of its waste streams. Using valorised waste streams of more than one process for products of increasing demand also removes the need to compete for arable land to grow crops to meet biomolecule demand. This means that no additional embedded environmental costs from fertilisers, pesticides, etc., are incurred. Further, this prevents the wastes from which the biomolecules are obtained from entering landfills or being down-cycled into agricultural feeds where they break down and release methane gas, which has a potent greenhouse effect, far greater than that of CO_2. Yet another benefit is that the use of biomolecules from valorised waste streams and the general reduction of organic reagents in industrial processes reduces the embedded costs associated with petrochemical production and refinement. This is not to say that there are no greenhouse gas emissions embedded in the production of biomolecules – of course there are. These will arise particularly from processes needed to isolate them from waste streams, and from the use of water-based chemistries, which currently requires far more energy to purify the primary solvent – water – than organic solvents do. Part of the issue here is the lack of development of industrial water purification infrastructures, which could lead to greater efficiencies in this area. The highest priority problem to be solved for the planet right now is that of human driven climate change and that means first and foremost we must reduce greenhouse gas emissions. Producing spherical and monodisperse silica particles using biomolecule-based syntheses and water-based chemistries is a small step towards achieving that.

7 References

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