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Synthesis of a novel anionic hydride organosiloxane presenting biochemical properties

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Abstract

Synthesis of an anionic hydride from monomeric silsesquioxanes is described. The novel compound, dubbed "silica hydride" is the first of several newly synthesized compounds from an interstitially embedded hydride family. It is a hydride-based compound with H^- ions interstitially embedded in a matrix of caged silica. This compound exhibits profoundly different characteristics than other known compounds in hydride family. Unlike saline hydrides, the silica hydride demonstrates no overt or violent reaction with water or air. However it is capable of generating aqueous reductive potential readings of −750 mV for extended time periods. In vitro biological testing demonstrated no cytotoxicity induced by the compound while demonstrating efficacy as an antioxidant. In vivo studies of the compound have shown that it has a significant ability to reduce lactic acid build up in muscles by one-half after exercise. The synthesis of the silica hydride resulted in an approximately 16.8% w/w hydride content, as determined by density changes, proton NMR spectroscopy and ion beam analyses. Scanning and tunneling electron microscopy, Rutherford backscattering spectroscopy (RBS), forward recoil (FReS) ion beam analyses, in addition to Fourier transform infrared spectroscopy, reduction potential and ^{29}Si CP-MAS solid state NMR were additionally used to characterize the compound.

Keywords: Silica; Hydride; Silsesquioxane; Antioxidant; Anion; NMR; Microcluster

1. Introduction

Silicate and derivative silicate frameworks are the most abundant compounds on the Earth. Their use in science, medicine and engineering has increased drastically in the last decade. Within the last few years, the molecular modeling of silicates has advanced significantly enough to allow rendering of structures of interest [1]. Of all the synthesized and modeled silicate compounds, silsesquioxanes have emerged in the forefront for their numerous applications and potential uses.

Silsesquioxanes are a class of three-dimensional organosiliceous compounds with the general formula $(RSiO_{1.5})_n$, where n is an even number. The R constituent group may be any number of functional groups, although most applications of silsesquioxanes incorporate methyl, halogen, vinyl or phenyl chains [2]. Silsesquioxanes are structures of polyhedral frameworks with varying degrees of symmetry, with silicon atoms at corners and oxygen atoms interspersed between them in a tetrahedral configuration. The tetrahedral coordination forms a three-dimensional framework by a series of Si–O–Si bonds, creating a silica cage as shown in Fig. 1.

Applications of silsesquioxanes have utilized the cage structures to act in several roles, including catalysts [3], metal complexes [4], mimicked-silica surfaces [5] and to synthesize new porous materials [6]. Their potential to mimic silica surfaces arises from the similarity of silsesquioxanes to siliceous clusters that possess the structural and electronic features of hydroxylated silica surfaces. Although the chemistry of silsesquioxanes and their

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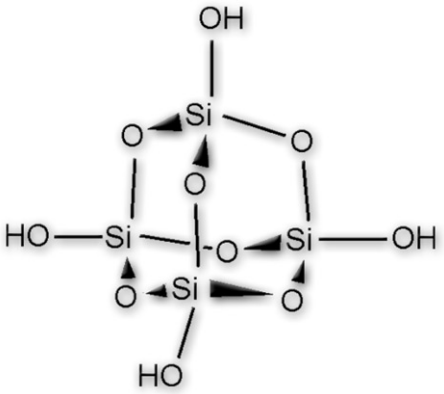

Fig. 1. The functional groups, R, may be any of the numerous varieties including phenyl, methyl, halogen or vinyl groups. Evidence in this analysis suggests the presence of hydroxyl-terminated constituents.

complexes has seen a great evolution, there are still limitations with their possible uses. Their limited use is often due to size constraints, substrate incompatibilities and polymerization problems [7].

Silsesquioxanes combine a hybrid inorganic–organic composition, with nanosized cage structures having dimensions comparable to those of most polymeric segments or coils. The caged nanostructures, with typical sizes of 1–3 nm, have been thought of as the smallest possible particles of silica [8].

Most of the emphasis and work on these compounds has been geared towards the development of polymer-inorganic nanocomposites with properties focusing on materials science and microelectromechanical (MEMS) advances. Possible uses in biotechnology and medicine have received only a partial emphasis as compared to applications in engineering and materials science [9].

Silicon and siliceous compounds such as silica have long been understood to play an active role in an organism's health and development. Silicates do not have a vast set of explicitly defined intricate biochemical mechanisms for their assembly. However, as an organic biomolecule, silicon is known to be involved in cellular development and metabolism [10].

Laboratory experiments on chicks and infant rats demonstrate that silicon is essential for normal skeletal growth [11]. Bone is a uniquely flexible material made of apatite (calcium–phosphorus) crystals imbedded in a protein matrix containing collagen and glycosaminoglycans. Silicon appears to play a role in the initial stages of bone development when the initial protein matrix is constructed. Reports have indicated an increase in the mineralization rate of bone and enhanced calcium deposition, resulting in a faster and stronger bone growth [12].

The absence of siliceous compounds has been related to certain pathologies in biochemistry. Atherosclerosis has been correlated to significantly decreased silicon levels in arterial walls. The decrease in silicon concentrations immediately prior to venule and arterial plaque development appears to indicate that a deficiency of silicon is related to the resultant weakness in blood vessel walls [13].

Silicon has also been linked to other biochemical mechanisms in both plants and animals. In particular, a number of single-celled organisms (i.e.: radiolarians, diatoms) make hydrous glass shell casings of opaline-type silica [14]. Such silica has no crystalline properties, but rather constitutes a framework of tetrahedrally coordinated Si–O–Si bonds in which many vertices are terminated with OH groups. The terminating hydroxyl groups hydrogen bond to nearby opaline structures, forming a pseudo-crystalline cluster of silica. The tiny H-bonding structures of silica precipitate into a regular framework, even though no crystalline ordering is formed. Colloidal silica surfaces have been shown to form strong hydrogen bonds [15].

In addition to key applications in materials science, siliceous compounds, including silsesquioxanes, while mimicking the surface of heterogeneous silica surfaces, have found widespread uses. Such applications include sol–gel polymerization [16], as models of zeolite activity [17], as alternatives for SiO_2 thin films in microfabrication [18], as liquid crystal polymers [19] and in hair fixatives [20].

There are numerous potentials for uses of silsesquioxanes with the implementation of biomolecular-based technologies in many disciplines, including chemical, biological and clinical arenas. Current emphasis focuses on the provision of efficient immobilized biological constructs and bioencapsulated polymers [21]. Current techniques for bioencapsulation are incredibly specific and are individually restrictive in terms of the types of biologicals that can be accommodated with the polymer to effectively carry the targeted compound [22]. The synthesis of such polymers has been more of a hit-and-miss process, rather than a highly theorized method. There is no universal technology or published methodology to develop immobilization or bioencapsulation methods. Thus, testing any new biological agent that is to be immobilized or that is to be novelly bioencapsulated is a difficult, if not impossible, task.

Current technologies in bioencapsulation use biological-polymer composites either in an organic, inorganic and hybrid organic–inorganic composition, where the biological substance is permanently encapsulated as an integral component of a covalently formed framework [23]. Specific examples include sol–gel bioencapsulates, including metal-oxide, silicate and organosiloxane matrices. Decades of work integrating sol–gel chemistry and biological functionality have established the methods for the encapsulation of a diverse group of catalytic and non-catalytic proteins, antibodies, antigens, poly(nucleic acids) and live microbial, plant and animal cells [24,25]. Previous successful encapsulates include the antioxidant superoxide dismutase in a SiO_2/Cu–Zn matrix [26].

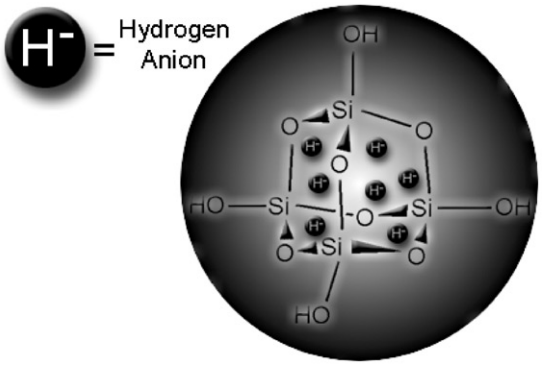

Fig. 2. The Concept of Silica Hydride. Conceptually the hydride embedded organosiliceous silsesquioxane, or silica hydride, is a monomeric silica-based cage with interstitially placed hydride anions. As a bioencapsulated compound, the silica acts as a colloidal carrier for the hydrogen anions in solution.

To our knowledge, all published bioencapsulated compounds have been based on large polymer structures and have been subject to inherent problems of non-specificity to a biological target, low solubility and slow dissolution rates [27]. The steric hindrances of the large polymers with bioencapsulates have been a significant deterrent to their use.

The idea behind synthesis of the novel compound described in this paper is based on the use of a monomer nanocomposite as a carrier in a bioencapsulated compound. The synthesis uses a silica and hydroxyl group terminated silsesquioxane monomer, trademarked Silica Microclusters® (Flantech Group, Soquel, CA), that is interstitially imbedded with hydride anions as conceptually depicted in Fig. 2. The results from the characterization of this compound provide evidence to this claim, including DRIFTS FTIR and NMR data.

Typically, the use of hydrides in chemistry has focused on three types of hydrides: covalent, metallic and saline. In the manufacture and synthesis of most metallic hydrides, hydrogen gas will suffice to fuel the reaction since hydrogen gas catalytically separates into two neutral hydrogen atoms [28]. The synthesis of metallic interstitial hydrides is a perfect representation of the "electron sea" theory, where electrons act as malleable, "free-floating waves" in the metallic lattice, that creating the necessary electron source to form the hydride ions [29]. A covalent hydride, CH_4 for example, as its name may imply, consists of sp^3 hybridized, covalently bonded hydrogen atoms [30]. Saline hydrides, such as LiH, $NaBH_4$ or $LaAlH_4$, are known equally for their robust reducing capabilities and their violent reactivity with water [31].

With the immense potential for bioencapsulates and nanocomposite technologies, it would be very beneficial to create a hydride out of a compound that would involve the combinational reducing effects of a saline hydride compound and the beneficial attributes of the host compound, all without the reactivity of the saline hydrides. Synthesizing a biologically friendly hydride would have immense potential as an antioxidant and radical scavenger as discussed later in this paper.

It is of considerable interest that if monoatomic hydrogen gas is placed upon any arbitrary non-transition metal chemical compound under pressure, little or no hydrogen atoms enter into the matrix [32]. The compounds do not have the activation energy to separate the hydrogen gas into monovalent hydrogen and there are no electron donors in the substrate available to create the necessary hydride ions.

It was discovered in the present work that if a hydride-ionic plasma was placed under pressure, virtually any compound it came in contact with could then absorb its emitted ions. Since the 1920s, creating a hydride gas has been standard practice. One effective way is to add a current to a tungsten filament in a hydrogen gas atmosphere [33]. The filament separates hydrogen gas into a monovalent hydrogen gas while the photoelectric effect on the tungsten filament donates electrons to the H gases forming a H^- plasma. Electric arcs are also used to create H^- plasma in such applications as atomic spectroscopy (ICP-AES and AAS) [34]. Langmuir, in 1927, while using the tungsten filament hydride ion synthesis technique, discovered that moist air prevents hydride ions from recombining back into hydrogen gas [33].

The idea for this synthesis experiment was to then create a hydride plasma under a water vapor atmosphere and expose the plasma to an organosilicate compound, circumventing the fore-mentioned problem of the hydrogen not having the catalysis or the electron availability to combine with the host substrate.

Interestingly, Langmuir noted that the monoatomic ions produced by this process would become embedded in the glass walls of the tubing of his apparatus and that same tubing could later be induced to release the ions. The glass tubing used by Langmuir was a borosilicate glass, an amorphous siliceous compound. In the present study, an apparatus similar to what Langmuir used was constructed to create a plasma of H^- ions. The H^- atmosphere was applied to the pure Microcluster Silica® powder under pressure and in the presence of a water vapor, creating a novel silsesquioxane bioencapsulated-hydride compound, dubbed: silica hydride.

2. Materials and methods

A 1.0 L sealed glass vessel was fabricated containing the items as depicted in Fig. 3. Two 5 cm × 0.6 cm diameter W rods were positioned transversely 2 mm apart in the top of the reaction vessel with two insulated leads connecting the W rods to a 20 A constant-current transformer (Lambda-EMI 102A-1KV, Neptune, NJ). Ten grams of Microcluster® silica (Flantech Group, Soquel, CA) was placed on the stage inside the vessel with 100 ml of distilled

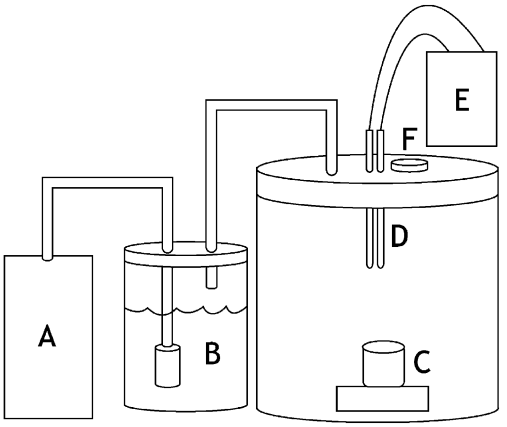

Fig. 3. Synthesis Apparatus. The representation of the apparatus used to synthesize the compound. A hydrogen gas generator (A) provides H_2 gas that is sparged through a filter stone in deionized, distilled water (B), where the hydrogen gas and water vapor are transported into a reaction vessel (C) with the substrate. Two tungsten electrodes (D) create a captive plasma H^- gas via a constant current high-voltage power supply (E). Vessel evacuation, purge and sealing were performed using a mechanical valve (F). The resultant actions interstitially embed the hydride anions created by the plasma into the substrate.

and deionized H_2O added to the basin. A steady stream of hydrogen gas was bubbled through an aquarium stone in water and introduced to the reaction vessel, purging all of the air from the vessel and increasing pressure to 172 kPa at which time the vessel was sealed. A 500 V potential was applied to the W rods. At voltages ranging from 350 to 750 V, a constant arc could be maintained between the electrodes without melting. The potential was applied for 30 s at which time the current was shut off and additional hydrogen was pumped into the vessel creating a captive plasma. The sample was allowed to sit in the plasma for 30 min at which time the silica sample was removed and weighed with an analytical balance.

3. Results

Determination of the mass of the anionic hydride organosiloxane sample showed an increase from 10.0 to 11.70 g upon exposure to the hydride plasma under pressure. The sample was allowed to sit at room temperature with desiccant in a glass vial for 3 weeks at open atmosphere at which time the proceeding analyses were performed.

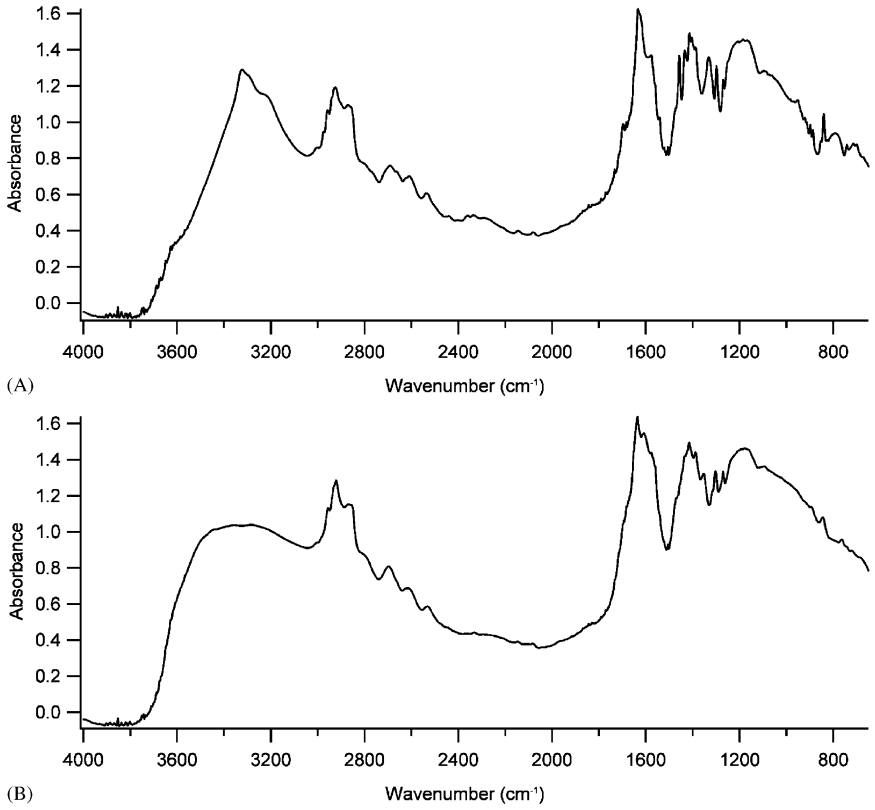

Fig. 4. FTIR DRIFTS spectra of Microcluster Silica® and Silica Hydride. Infrared spectrometry of the Microcluster Silica® starting material (A) and the product (B) suggest a distinct resemblance and similarity to other silsesquioxane monomers.

3.1. FTIR characterization

A FTIR DRIFTS spectrum obtained by illustrates a silsesquioxane monomer with hydroxyl terminating groups exhibiting H-bonding in clusters as depicted in Fig. 4.

FTIR-DRIFTS ν (cm^{-1}): 3350 (br, OH), 2925 (s, Si-OH), 2690 (vw, Si-H), 2600 (vw, Si-H), 2650 (vw, Si-H), 1600 (vs, Si-OH), 1390 (s, Si-OH), 1190 (s, Si-O), 1140-1000 (br, Si-O), 890 (m, Si-O), 870 (m, Si-O-Si), 710 (m, O-Si-O).

3.2. Ion beam analysis

An ion beam analysis was performed with the silica powder being pressed into a pellet (1.66 g/cm^3) compared to a C standard. Rutherford backscattering spectroscopy (RBS) was analyzed with 2 MeV He beam, while 3 MeV He beam was used in a forward-recoil spectrometry (FReS) measurement. RBS suggests that the powder contains elements O and Si. Including H-content by FReS, the powder relative percentage makeup becomes H (78.1%), O (15.6%) and Si (6.2%). Trace amounts of B and W (< 25 ppm) were also observed. Original values from samples of non-reacted Microcluster® silica comparatively illustrate an elemental makeup of H (22.4%), O (55.6%) and Si (21.9%).

3.3. ^{29}Si NMR characterization

An 8-h CP-MAS solid state 400 MHz-^{29}Si NMR analysis resulted in a unique spectra with two peaks, one broad, one sharp, centered at -103.5 ppm relative to a 3-(Trimethylsilyl)-1-propane-sulfonic acid standard, consistent with the organosilicate spectra obtained form other silsesquioxanes.

3.4. ^{1}H-NMR characterization

A Varian Unity Inova 500 NMR spectrometer was used to obtain the following results to be shown in Fig. 5: ^{1}H NMR (500 MHz, D_2O, δ): 4.72 (s, 1H, Solvent), 3.10 (s, 1H, -O–Si–OH), 1.2 (br s, 2H, -SiH_2-), 0 to -1 (q, $J = 86$ Hz, 1H, H^-).

Quantitative analysis with a 0.1 M dimethylsufone (MSM) internal standard (δ 2.8, s, 6H) integrated to 6 arbitrary equivalent units representing the MSM was compared to the integrations of the siliceous multiplet at δ 2.8 and with the hydride quadruplet from δ 0 to -1 ppm. Comparative analysis of the integrations show a 16.8% hydride content.

3.5. Scanning electron microscopy

SEM analysis with a 40 KeV-JEOL 840II microscope illustrated small, $\sim$ 2 μm, spheres consisting of numerous of smaller spheres as shown in Fig. 6.

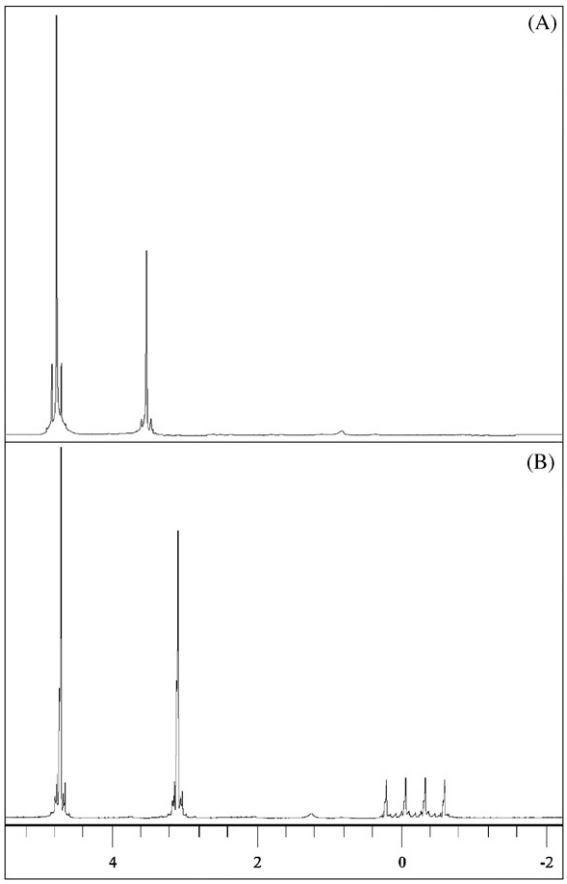

Fig. 5. ^{1}H-NMR spectra of Microcluster Silica® and Silica Hydride. A Varian Inova 500 MHz nuclear magnetic resonance spectrometer was used as one means to characterize the siliceous hydride compounds. The starting material (A) and the product (B) share spectral similarities with the exception of the 86 Hz coupled quadruplet centered at -0.25 ppm. Coupling analysis of the quadruplet signal support the hypothesis of localized stabilization of the hydrogen anions to the silsesqioxane caged structure.

3.6. Transmission electron microscopy

A Philips 300 KeV-CM30 transmission electron microscope allowed the resolution to image very small, spherical compounds that were measured to be about 50 Å also shown in Fig. 7. An EDAX PV9900 energy dispersive X-ray spectrometer qualified an elemental analysis of the compound to contain Si and O.

3.7. Oxidation–reduction potential analysis with pH and rH

The ORP and pH were recorded for 250 ml distilled and deionized H_2O in a Pyrex beaker. 10.0 μg/ml of the siliceous hydride was added to the beaker and allowed to stir for 15 min at which time addition ORP and pH

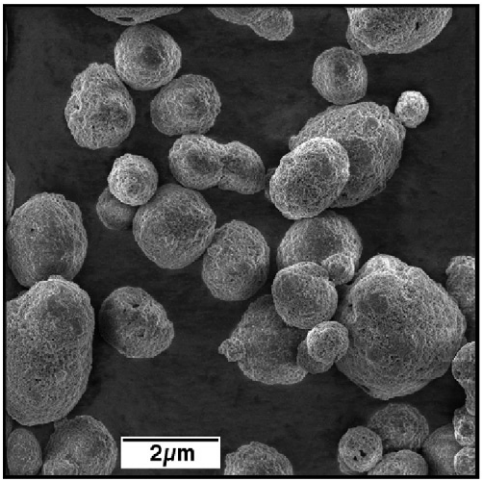

Fig. 6. Scanning Electron Micrograph of Large Clusters. This SEM image taken by a 40 KeV-JEOL 840II microscope shows the aggregate ($\sim$ 2 μm) clusters of the H-bonded silica hydride monomer units. Substructures of smaller clusters form this aggregate.

readings were taken. The initial ORP and pH of the water averaged 341.33 ± 2.5 mV and pH 7.12 ± 0.06, respectively. The readings after 15 min were −436.21 ± 2.1 mV for the ORP and pH 9.13 ± 0.09 for the pH measurements. The hydrogen pressure unbiased reducing potential, rH, was calculated from (1) and (2):

$$E_h = 1.23 - \frac{RT}{F}\,\mathrm{pH} - \frac{RT}{4F}\ln\frac{1}{P_o}, \tag{1}$$

$$rH = -\log P_o, \tag{2}$$

where E_h is the measured oxidation–reduction potential, F is the Faraday constant, R is the universal gas constant and T is absolute temperature. The 1.23 refers to the measured potential under one atmosphere pressure of oxygen is 1.23 V greater than in a solution of the same pH. rH is defined explicitly as the negative logarithm of the oxygen pressure, P_o. The use of rH gives a hydrogen proton-unbiased look at the absolute reducing potential of a compound, eliminating the effects of pH in the ORP measurement.

The measured rH for the compound was 11.02 ± 0.04 indicating a highly reduced environment.

4. Discussion

The result of the synthesis is a bioencapsulated hydride/silica-based structure containing regular repeating, Si–O bonds forming small, 50 Å spherical units with hydroxyl and silica functional groups extending from the siliceous cage. FTIR DRIFTS analysis of the silica hydride are consistent with spectra of other silsesquioxane monomers [2]. TEM analysis visually demonstrates the 50 Å spherical units.

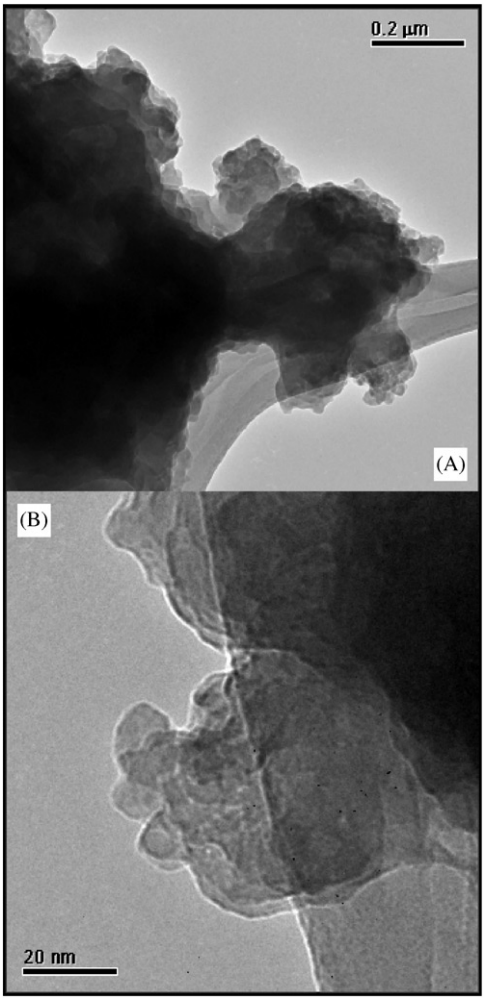

Fig. 7. Transmission Electron Micrograph of Silsesquioxane Sub-Units. Images from a Philips 300 KeV-CM30 microscope show the (A) smaller subunits (up to $\sim$ 500 nm) of the silica clusters. Further magnification (B) displays the small, colloidal ($\sim$ 50 Å) siliceous monomers.

^{1}H-NMR indicates repeating structure of Si–O groups and the distinct presence of the hydride species from 0 to −1 ppm from TMS. The ^{29}Si-CP-MAS confirms the general structure of a silsesquioxane with a chemical shielding of −103.5 ppm. DRIFTS FTIR data are also consistent with the results obtained by the other characterization methods. Both scanning and transmission electron microscopy support the hypothesis of a caged system, however the monomeric units are approximately half the size of currently published silicates. The hydride content, as calculated by density changes

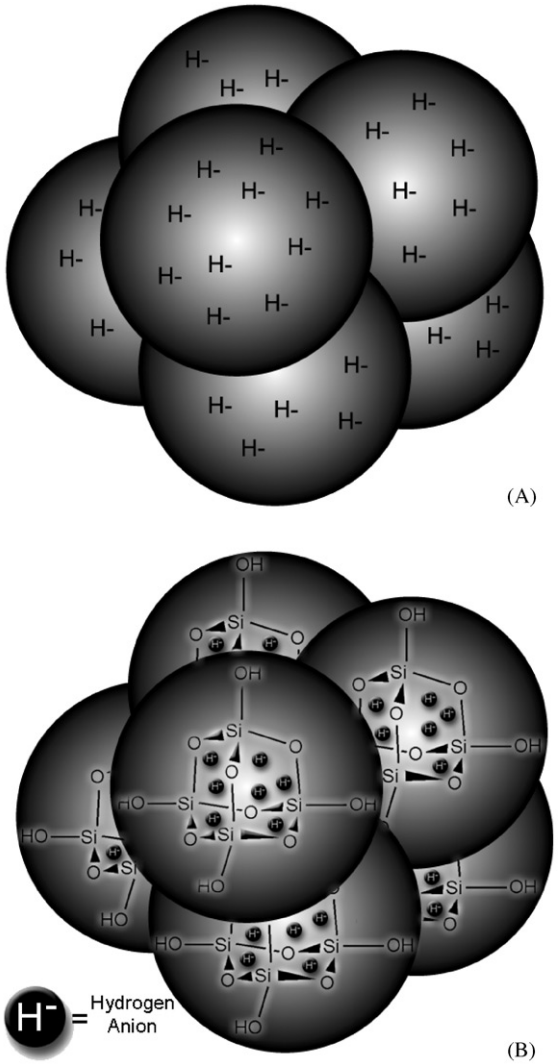

Fig. 8. The Silica Hydride Microclusters. The microclusters of silica act as (A) a colloidal carrier of hydride ions in a matrix of organosilicate, H-bonded clusters. A modeled, more detailed look at the structure (B) illustrates numerous silsesquioxane-based monomers interstitially embedded with hydrogen anions.

and electrochemical analyses are consistent with ^{1}H-NMR and IBA of about 17% w/w of the compound. The weight gain of about 17% appears to be a direct contribution of the hydride versus water due to desiccant drying before analysis, as suggested by comparative extrapolations on before and after FReS and RBS analyses and integrations of ^{1}H-NMR spectra.

The synthesis process appears to cluster the organosilicate subunits into hydrogen-bonded aggregates that further group into approximately 2 μm clusters as shown in Fig. 8. Dissolution in water decreases the cluster size from 2 μm to the smaller subunits of about 500 nm, then into individual cages of about 50 Å (Fig. 9).

This new organosilicate silsesquioxane compound, commonly named silica hydride, has been the subject of numerous tests involving reduction potential (ORP) and pH as well as being analyzed as an effective antioxidant [35]. Adding a few mg to water will drop an ORP reading by −750 mV. A recent publication [36] of a clinical study has illustrated the capability of this compound to significantly reduce lactic acid after exercise by 50%. Viability and cytotoxicity probes show that the silica hydride does not cause any decrease in intracellular esterase activity or otherwise induce a toxic cytoplasmic environment [37]. There are a plethora of uses of a hydride-based compound such as silica hydride since it does not impose a direct negative effect to cellular viability and cytoplasmic health. Particular uses include nutritional supplementation as an antioxidant. The incredible reduction potential of silica hydride adds to the possible uses of this type of compound.

The compound does not react violently or visibly with H_2O. However, it will reduce the ORP reading to −750 mV for a period of at least several weeks. Most antioxidant compounds are relatively large chemical species. Examples of this are vitamins A, K, C, ubiquinone and n-acetyl-cystine. It is hypothesized that steric hindrances may affect the efficacy of antioxidants [38]. The small size and reducing capacity of silica hydride, the silsesquioxane hydride compound, may lead to future development as an antioxidant.

5. Conclusion

The novel siliceous compound acts as a colloidal carrier for the very small hydride anions that are released in an aqueous solution. This nanosized colloidal bioencapsulated compound could be an incredibly effective radical scavenger and aid in the reduction of oxidative stress due to its minimal size and high reduction potential.

This novel compound presented in this paper has demonstrated promising in vitro and in vivo biochemical significance with uses including reducing agents, antioxidants and nutritional supplementation. The synthesis is simple and efficient with consistent results of about 17% w/w hydride content with respect to the starting compound. Biologically friendly compounds that incorporate health-beneficial minerals, such as silica, with the scavenging and reducing capabilities of a hydride provide for numerous possibilities of uses. This technique has proven valid for creating hydrides out of other non-metallic, compounds, such as carbonate. The continuation of studies on this new family of hydride compounds could prove invaluable in biochemical, medicinal and analytical venues.

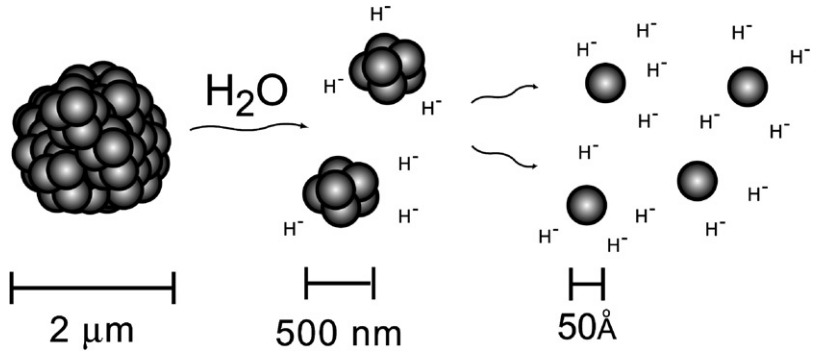

Fig. 9. Dissolution of Silica Hydride in Water. The silica hydride compound does not violently react with water and has been determined by TEM and particle analysis to break down in an aqueous environment from the aggregate clusters to the silicate monomeric structures while releasing the hydride ions into the solution. ORP, *rH* and ^{1}H-NMR measurements indicate significant long-term (on a magnitude of weeks) reduction potentials of −750 mV.

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