Angewandte Chemie International Edition

DOI: 10.1002/anie.201102011

VIP **Colloidal Spheres**

# Extension of The Stöber Method to the Preparation of Monodisperse Resorcinol–Formaldehyde Resin Polymer and Carbon Spheres**

*Jian Liu, Shi Zhang Qiao,* Hao Liu, Jun Chen, Ajay Orpe, Dongyuan Zhao, and Gao Qing (Max) Lu**

Colloidal spheres are subject to extensive research in chemistry, materials science, and condensed-mater physics because of their widespread applications, such as the fabrication of photonic crystal materials, optical sensing, and drug delivery.[1,2] The Stöber method produces colloidal silica spheres by the hydrolysis and condensation of silicon alkoxides, such as tetraethyl orthosilicate (TEOS), in alcohol solvents (e.g., ethanol) in the presence of water and a base catalyst (e.g., ammonia aqueous solution).[3] By using the Stöber method, it is possible to achieve excellent control of particle size, narrow size distribution, smooth spherical morphology of the resulting silica,[4] microporous silica,[5] and mesoporous silica particles.[6] However, the preparation of non-silica spheres, especially polymer spheres, by the Stöber method has not been reported to date.

Nanostructured polymers, especially phenolic resins, exhibit biocompatibility for biomedical applications, such as cellular delivery vehicles, cell targeting, and imaging.[2,7,8] In addition, nanostructured phenolic resins are also widely used for preparing a variety of nanostructured carbons, which have attracted interest for potential applications as adsorbents, super-capacitors, lithium-ion battery electrodes, drug delivery carriers, as well as supports for catalysts.[2,9,10] The physical and chemical properties of nanostructured phenolic resins, such as their shape, size, porosity and surface charge, influence their functionalities and are important for their applications. A great deal of research has been directed towards the synthesis of nanostructured phenolic resins in the form of nanoparticles and nanoporous structures.[2,10–12] Despite the variety of synthetic methods and products reported, the synthesis of phenolic resin spheres with precisely controlled size has met with only limited success.[12] The synthesis of phenolic resin colloidal materials would open new opportunities for the design and preparation of new smart materials.

According to the hydrolysis polymerization reaction mechanism, the organic sol–gel of resorcinol/formaldehyde (RF) resins is analogous to silicate sol–gel process.[13] Furthermore, RF precursors also have similar structures to silanes, and both can form three-dimensional (3D) networks through the sol–gel process because of their four coordination sites and tetrahedral coordination geometry. RF resins and silicas with similar morphologies and nanostructures have been synthesized under similar conditions. For example, 1) both silica and RF resin aerogels were synthesized by the sol–gel polymerization in the presence of an acid or base;[13,14] 2) by using basic amino acids, such as lysine as a catalyst, RF nanospheres[12] and silica nanospheres[15] were synthesized through polymerization of resorcinol and formaldehyde or TEOS, respectively; 3) using the cationic surfactant as a template and synthesis conditions similar to those used to prepare ordered mesoporous silica MCM-41,[16] Moriguchi et al.[17] synthesized ordered mesoporous RF resin polymers; 4) an organic–organic assembly method[11] has been developed to synthesize ordered mesoporous RF resins, which is analogous to the synthesis of mesoporous silica SBA-15[18] with various morphologies and mesostructures by using triblock copolymer (e.g., Pluronic P123) as a soft template.

We report herein for the first time the extension of the Stöber method for the preparation of monodisperse RF resin polymer spheres with uniform and controllable particle size on the submicrometer scale. The synthesis approach is a very facile and versatile procedure for making polymer beads and is considered to be low cost and suitable for industrial production. We chose RF as a precursor because it can form four-coordinate covalently bonded silica-like frameworks by polymerization. The effect of synthesis parameters on the morphologies and particle size of the resulted RF spheres was investigated in detail. We also demonstrated that these polymeric spheres can be directly transformed to monodisperse carbon spheres with a yield of 62 wt% by a carbonization process. After loading with platinum nanoparticles, the carbon spheres revealed very good electrocatalytic oxygen reduction performance.

---

[*] Dr. J. Liu, Prof. S. Z. Qiao, Dr. H. Liu, A. Orpe, Prof. G. Q. Lu
ARC Centre of Excellence for Functional Nanomaterials
Australian Institute for Bioengineering and Nanotechnology
University of Queensland, QLD 4072 (Australia)
Fax: (+61) 7-3365-6074
E-mail: s.qiao@uq.edu.au
maxlu@uq.edu.au

Prof. D. Y. Zhao
Department of Chemistry, Laboratory of Advanced Materials
Fudan University, Shanghai 200433 (China)

Dr. J. Chen
ARC Centre of Excellence for Electromaterials Science
Intelligent Polymer Research Institute
University of Wollongong, NSW 2522 (Australia)

Prof. D. Y. Zhao
Department of Chemical Engineering, Monash University
Clayton, VIC 3800 (Australia)

[**] This work was financially supported by the Australian Research Council (ARC) through Linkage Project program (LP0882681), Discovery Project program (DP1094070, DP1095861, DP0987969, DP0879769), and the ARC Centre of Excellence for Functional Nanomaterials. J.L. gratefully acknowledges the award of ARC Australian Postdoctoral Fellowship.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201102011.

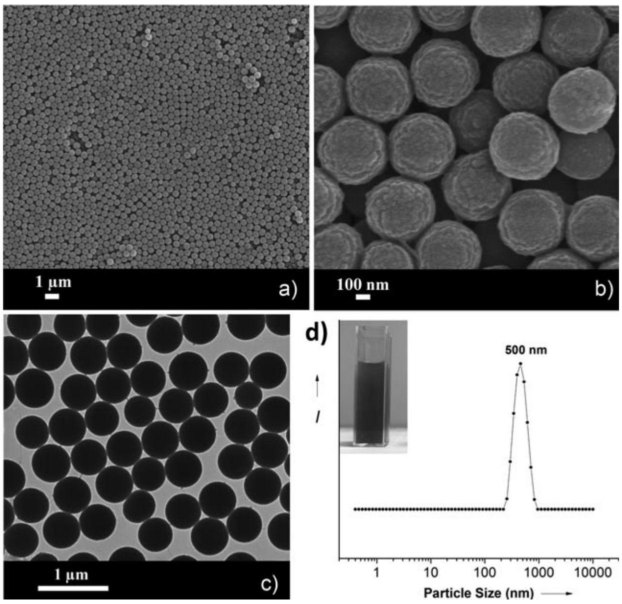
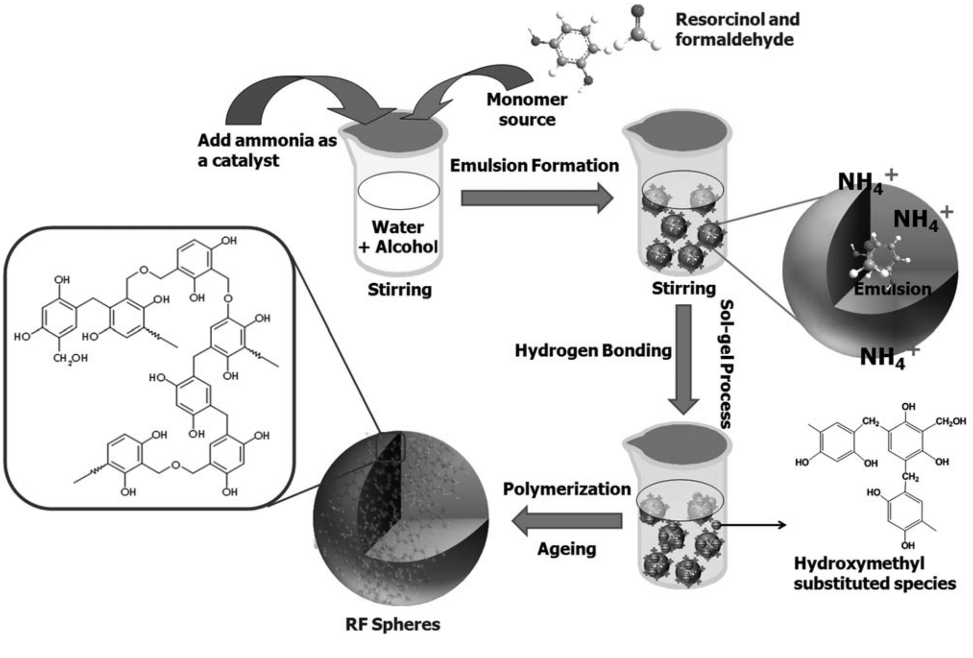


*Figure 1.* a),b) SEM images of RF polymer particles at different magnifications, c) TEM image, and d) DLS plot of the RF resins spheres prepared by the extended Stöber method (Inset: photograph illustrating the dispersivity of the RF resins spheres in ethanol).

In this study, the RF resin colloidal spheres are synthesized by the polymerization of resorcinol/formaldehyde in a mixture of alcohol and aqueous ammonia, a process similar to the synthesis of silica spheres by the Stöber method as illustrated in Scheme 1. Emulsion droplets are first formed through the hydrogen bonding of water, alcohol, resorcinol, and formaldehyde. RF polymerization takes place from the inside of droplets by ammonia catalysis, resulting in uniform colloidal spheres. The detailed synthesis parameters are given in Supporting Information (Table S1). The RF resin polymer colloidal spheres generally have tunable diameters from 200 to 1000 nm, and can be synthesized at a temperature ranging from 10 to 60 °C and with a wide reactant molar ratio ($NH_4OH$/resorcinol/formaldehyde/alcohol/$H_2O = 1\text{–}3/x/2x/y/2311-1.95y$ where $x = 1.4\text{–}2.8$; $y = 0\text{–}1186$). Figure 1 a and b show the scanning electron microscopy (SEM) images of RF polymer particles synthesized at $NH_4OH$ concentration of 0.0529 mol L$^{-1}$, ethanol/water volume ratio of 0.4, resorcinol concentration of 0.0648 mol L$^{-1}$ and at 30 °C, indicating that RF resin polymers have regular spherical particles with a uniform size. The high-magnification SEM image (Figure 1 b) demonstrates that these colloidal spheres have smooth surface and a mean diameter of 520 nm, with a standard deviation of 29 nm. The uniformity of colloidal spheres allows them to form ordered arrays, as seen in Figure 1 a (and Supporting Information, Figure S1). Transmission electron microscopy (TEM) image (Figure 1 c) further confirms the RF polymer particles have spherical morphology, and some of them can self-assemble into 2D hexagonal arrays on the carbon film of grid when the TEM sample is prepared. The dynamic light scattering (DLS) data (Figure 1 d) shows that the RF polymer spheres are well dispersed with particle size around 500 nm.

In the Stöber method, the diameter of silica spheres can be reduced by decreasing the concentration of $NH_4OH$ or TEOS, increasing the content of water, or using an alcohol that has short alkyl chains. To confirm the RF system has similar hydrolysis polymerization reaction kinetics to the silane precursors, the effect of ammonia solution concentration on the synthesis of RF resins was investigated. The particle size increased from 520 to 740 nm with increasing the ammonia concentration from 0.0529 to 0.1587 mol L$^{-1}$ (Figure S2a,b), which was consistent with the results for the synthesis of silica spheres by the Stöber method. In the absence of ammonia, the product had an irregular shape and no spheres could be obtained (Figure S2c,d). Further studies indicated that using other alkaline sources, such as NaOH or KOH, did not produce RF spheres. Thus, ammonia played an important role for the formation of RF spherical particles (Figure S2).



*Scheme 1.* The formation of RF resins spheres using the extended Stöber method.

Not only the ammonia concentration but also the ethanol/water volume ratio can be used to control the size of the RF resin colloidal spheres. By increasing the ethanol/water volume ratio from 0 to 0.75 under an $NH_4OH$ concentration of 0.0529 mol L$^{-1}$ at 30 °C, the particle size increases from 340 to 850 nm (Table S1, Figure S3 and S4). Furthermore, the precursor concentration has a significant effect on the size of these RF resin spheres. When the concentration of resorcinol is changed from 0.0324 to 0.0648 to 0.0996 $\mathrm{mol\,L^{-1}}$, the particle size increases abruptly from 260 to 520 to 1200 nm, respectively (Figure S4 and S5). Further increasing the concentration of resorcinol to 0.388 $\mathrm{mol\,L^{-1}}$, gives RF aerogels with a particle size around 40 nm (Figure S5). Such aerogels are formed because the large number of RF molecules serves to decrease the bending energy and inhibit the formation of emulsion droplets.

The size of the RF resin colloidal spheres can also be adjusted by choosing an alcohol with different alkyl chain (methanol, ethanol, isopropanol). SEM and TEM images confirm that upon introduction of methanol, the RF resins spheres obtained have diameter around 430 nm (Figure S6). When *iso*-propanol is used the size of the colloidal spheres obtained increases to 1100 nm. In addition, by simply changing the reaction temperature, the size and shape of RF resins can be significantly tuned (Figure S7). Colloidal spheres with a large particle size and rough surface can be prepared at a relative low temperature (10 °C), however, aggregated colloidal spheres are obtained at a high temperature (60 °C).

The results shown above reveal that by decreasing the ratio of alcohol/water, amounts of $NH_4OH$ and RF precursor, or using alcohols with short alkyl chains, the particle size of RF resin colloidal spheres can be gradually reduced (Figure S4). These factors have been demonstrated to be applicable for the synthesis of silica spheres as well.[3–5] To our knowledge, this is the first time that the RF resin colloidal spheres with various diameters have been synthesized by a facile and versatile procedure. Note that in our case the particle size of RF resin colloidal spheres can be further tuned by adding triblock copolymer Pluronic F127. Increasing the initial F127 concentration used from 0 to 0.184, 1.107, and 1.476 $\mathrm{mmol\,L^{-1}}$ can systematically decrease the particle size from 520 to 320, 230, and 60 nm, respectively (Table S2, Figure S8).

Ammonia solution plays a critical role in the formation of RF resin polymer nanospheres. Scheme 1 summarizes the formation mechanism: the first step the emulsion formed is stable without a surfactant because of the hydrogen-bonding interactions between ammonia, alcohol, RF precursor, and water; ammonia molecules catalyze the polymerization of RF inside the droplets. The second step in the formation of spheres is initiated by the polymerization of resorcinol with formaldehyde. Resorcinol can react quickly with formaldehyde to form numerous hydroxymethyl substituted species. The growing hydroxymethyl substituted species are positioned at the surface of the emulsion droplets owing to the electrostatic interaction with ammonia molecules, and further cross-linking of these species during the hydrothermal treatment results in uniform colloidal spheres (Scheme 1). As mentioned above, $NH_4^+$ in the emulsion can not only accelerate the polymerization of RF, but also supply the positive charges that adhere to the outer surface of spheres to prevent the aggregation which cannot be provided by any other alkaline sources, such as NaOH. With increasing the concentration of ammonia or precursor, the polymerization rate of RF increases, resulting in emulsion droplets with larger size, and a larger final particle size. By increasing the quotient of water or adding amphiphilic triblock copolymer (F127), the surface tension decreases,[19] smaller sized emulsion droplets are formed, and RF resins colloids spheres with smaller size are obtained. The longer the carbon chains of the higher molecular weight of alcohol are, the higher the viscosity of reaction solution is and the stronger the surface tension is, and thus emulsions of larger size are formed. This increase emulsion size results in the production of RF resin colloidal spheres with large particle size.

Previously, RF with dodecahedral single-crystal morphology was also made in a similar way to the production of dodecahedral single-crystal silica.[20] Our preliminary results show that nanostructured RF with various morphologies, such as mesoporous nanoparticles and hollow nanospheres, can be successfully synthesized by applying the similar method for synthesis of the silica with the same nanostructure.

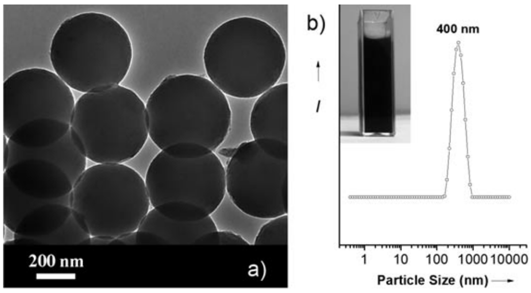


***Figure 2.*** a) TEM images and b) DLS plot of carbon spheres obtained by carbonizing the 520 nm RF colloidal spheres (inset: photograph illustrating the dispersivity of the carbon spheres in ethanol).

RF resins are of interest because of the high yield of carbon conversion that can be obtained from them. Carbon spheres are obtained by carbonizing the RF resins spheres at 600 °C for 4 h under $N_2$ atmosphere (see Experimental Section for full details). TEM images (Figure 2a and Figure S9) show that all the carbon spheres preserve a spherical morphology and have a narrow size distribution. However, the diameter of carbon particles is smaller than of the parent particles, for example, from 520 nm of the RF resin polymer spheres to 410 nm owing to shrinkage (19 %) during the carbonization process (Figure 2a and Figures S9a,b). The DLS data (Figure 2b) further confirms that the carbon spheres have a narrow size distribution with particle sizes around 400 nm. A high yield of carbon spheres with tunable diameters from 150 to 900 nm can be directly produced by carbonization of the RF resins spheres (Figures S9 and S10a). The diameter of the carbon spheres is controlled by choosing RF resin polymer sphere precursors with different particle size. The highly cross-linked RF polymer structures are the principal reason for the retention of spherical morphology under the high-temperature annealing. Nitrogen sorption measurement shows that the BET surface area of the carbon spheres obtained from the 520 nm RF colloidal sphere is 504 $\mathrm{m^2\,g^{-1}}$ and the total pore volume is approximately 0.27 $\mathrm{cm^3\,g^{-1}}$ (Figure S10b). These microporous carbon spheres could be promising materials for catalyst supports, adsorbents, and electrode materials.

To demonstrate the produced microporous carbon spheres as support materials for catalysts, platinum nanoparticles were decorated onto the carbon-sphere surface in a microwave-assisted reduction process performed in a mixture of $H_2PtCl_6$ salt and ethylene glycol. The SEM image and X-ray diffraction (XRD) pattern reveal that Pt nanoparticles are successfully loaded onto the carbon spheres' surface with an average particle size around 6 nm (Figure 3 a,b and Figure S11). These platinum-nanoparticle-modified carbon spheres (nanoPt/cs) were further investigated for the electrocatalytic oxygen reduction reaction in a standard three-electrode electrochemical cell using nanoPt/cs-coated glassy carbon (GC) as a working electrode. The linear sweep voltammograms of the nanoPt/cs-coated GC electrode immersed (and stationary) in a oxygen ($O_2$) saturated 0.5 M $H_2SO_4/H_2O$ solution indicated a substantial catalytic oxygen reduction process with an onset potential of ca. 0.6 V (vs. Ag/AgCl) under an $O_2$ atmosphere (Figure 3 c). No reduction response is observed in this region under an $N_2$ atmosphere. Therefore, the current under the $O_2$ atmosphere was unequivocally the result of electrocatalytic oxygen reduction performance.[21] This result show that these carbon spheres have the potential to become a new kind of catalyst (metal-based) support materials, suitable to be used in energy conversion and other related areas.

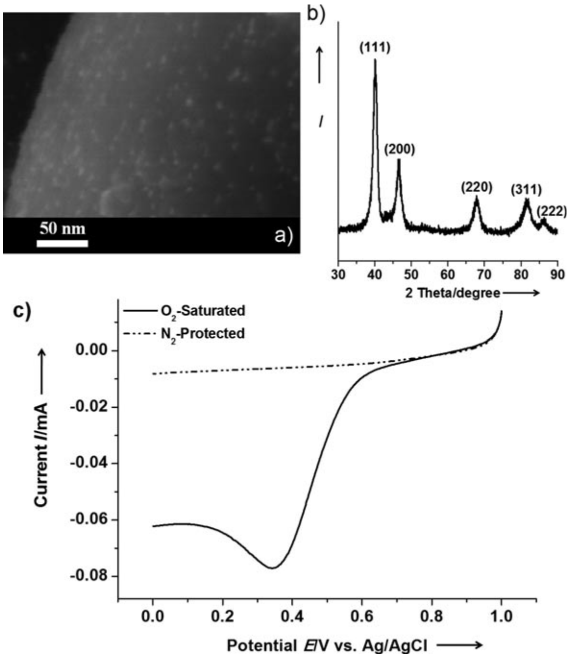


***Figure 3.*** a) SEM image, and b) XRD pattern of Pt/carbon spheres, c) linear-sweep voltammograms of Pt/carbon spheres for the oxygen reduction reaction (ORR) in an $O_2$-saturated and $O_2$-free (under $N_2$ atmosphere) 0.5 M $H_2SO_4$ solution at room temperature at a scan rate of 10 mV$s^{-1}$.

In summary, we have successfully extended the classical Stöber method to conveniently synthesize the monodisperse RF resin polymer colloidal spheres, by a route similar to the synthesis of opal silica spheres. The particle size of the RF resin spheres can be tuned from 200 to 1000 nm by varying the concentration of ammonia or RF precursor, alcohol/water ratio or the alkyl chain of alcohol. Polymerization rate of RF, the surface tension, and hydrogen bonding are the main factors to finely control the size of colloidal spheres. The obtained resin spheres can be carbonized to carbon spheres with a high yield. Our results show that this approach is useful for the large-scale production of RF resin polymer and carbon spheres. It can be speculated that by extending the methods for synthesis of silica nanostructures, more nanostructured RF resins and carbons with different morphologies could be designed and synthesized. These polymer and carbon spheres are potentially important for application in electrode materials, photonics, adsorption and separation, water treatment, and drug delivery.

## Experimental Section

Details on the synthesis parameters of RF resins spheres are described in the Supporting Information in Table S1. Typically, monodisperse RF resins spheres were synthesized by using resorcinol and formaldehyde solution as precursors. In a typical synthesis of the RF resins spheres with 520 nm diameter, ammonia aqueous solution ($NH_4OH$, 0.1 mL, 25 wt %) was mixed with a solution containing absolute ethanol (EtOH, 8 mL) and deionized water ($H_2O$, 20 mL), then stirred for more than 1 h. Subsequently, resorcinol (0.2 g) was added and continually stirred for 30 mins. The formaldehyde solution (0.28 mL) then added to the reaction solution and stirred for 24 h at 30 °C, and subsequently heated for 24 h at 100 °C under a static condition in a Teflon-lined autoclave. The solid product was recovered by centrifugation and air-dried at 100 °C for 48 h. The typical yields of spheres per synthesis are around 72 %. For carbonization, the RF resin spheres were heated under $N_2$ atmosphere to 350 °C with a heating rate of 1 °C$\min^{-1}$, then maintained at 350 °C for 2 h, and subsequently heated to 600 °C with a heating rate of 1 °C$\min^{-1}$ and kept at 600 °C for 4 h.

The samples were investigated using SEM, TEM, X-ray diffraction (XRD), and dynamic light scattering (DLS). SEM images of samples were recorded on a JEOL 6300 and JSM-7500FA microscope. TEM images were obtained by JEM-2100 F microscope (JEOL, Japan). Dynamic light scattering measurements were carried out at 25 °C on a Malvern Zetasizer NanoZS Instrument (detection range: 3–3000 nm). XRD analysis was conducted on a GBC MMA X-ray diffractometer with $2\theta$ ranging from 30° to 90°.

The details on the preparation of nanoPt/cs and nanoPt/cs-coated GC electrode are described in the Supporting Information.

Received: March 22, 2011

**Keywords:** carbon · colloidal spheres · nanoparticles · polymers · Stöber method

---

[1] a) U. Jeong, Y. L. Wang, M. Ibisate, Y. N. Xia, *Adv. Funct. Mater.* **2005**, *15*, 1907; b) F. Li, D. P. Josephson, A. Stein, *Angew. Chem.* **2011**, *123*, 378; *Angew. Chem. Int. Ed.* **2011**, *50*, 360.
[2] a) X. M. Sun, Y. D. Li, *Angew. Chem.* **2004**, *116*, 607; *Angew. Chem. Int. Ed.* **2004**, *43*, 597; b) A. H. Lu, W. C. Li, G. P. Hao, B. Spliethoff, H. J. Bongard, B. B. Schaack, F. Schüth, *Angew. Chem.* **2010**, *122*, 1659; *Angew. Chem. Int. Ed.* **2010**, *49*, 1615; c) S. R. Guo, J. Y. Gong, P. Jiang, M. Wu, Y. Lu, S. H. Yu, *Adv.*

*Funct. Mater.* **2008**, *18*, 872; d) M. Feyen, C. Weidenthaler, F. Schuth, A. H. Lu, *J. Am. Chem. Soc.* **2010**, *132*, 6791; e) K. T. Lee, Y. S. Jung, S. M. Oh, *J. Am. Chem. Soc.* **2003**, *125*, 5652.

[3] W. Stöber, A. Fink, E. J. Bohn, *J. Colloid Interface Sci.* **1968**, *26*, 62.

[4] D. L. Green, J. S. Lin, Y. F. Lam, M. Z. C. Hu, D. W. Schaefer, M. T. J. Harris, *J. Colloid Interface Sci.* **2003**, *266*, 346.

[5] R. Vacassy, R. J. Flatt, H. Hofmann, K. S. Choi, R. K. Singhy, *J. Colloid Interface Sci.* **2000**, *227*, 302.

[6] M. Grün, I. Lauer, K. K. Unger, *Adv. Mater.* **1997**, *9*, 254.

[7] a) X. X. Chen, M. A. Dam, K. Ono, A. Mal, H. B. Shen, S. R. Nutt, K. Sheran, F. Wudl, *Science* **2002**, *295*, 1698; b) M. Oh, C. A. Mirkin, *Nature* **2005**, *438*, 651; c) J. G. Park, J. D. Forster, E. R. Dufresne, *J. Am. Chem. Soc.* **2010**, *132*, 5960.

[8] Y. Fang, D. Gu, Y. Zou, Z. X. Wu, F. Y. Li, R. C. Che, Y. H. Deng, B. Tu, D. Y. Zhao, *Angew. Chem.* **2010**, *122*, 8159; *Angew. Chem. Int. Ed.* **2010**, *49*, 7987.

[9] A. S. Arico, P. Bruce, B. Scrosati, J. M. Tarascon, W. Van Schalkwijk, *Nat. Mater.* **2005**, *4*, 366.

[10] a) C. D. Liang, Z. J. Li, S. Dai, *Angew. Chem.* **2008**, *120*, 3754; *Angew. Chem. Int. Ed.* **2008**, *47*, 3696; b) C. D. Liang, S. Dai, *J. Am. Chem. Soc.* **2006**, *128*, 5316; c) S. Tanaka, N. Nishiyama, Y. Egashira, K. Ueyama, *Chem. Commun.* **2005**, 2125.

[11] a) F. Q. Zhang, Y. Meng, D. Gu, Y. Yan, C. Z. Yu, B. Tu, D. Y. Zhao, *J. Am. Chem. Soc.* **2005**, *127*, 13508; b) Y. Meng, D. Gu, F. Q. Zhang, Y. F. Shi, H. F. Yang, Z. Li, C. Z. Yu, B. Tu, D. Y. Zhao, *Angew. Chem.* **2005**, *117*, 7215; *Angew. Chem. Int. Ed.* **2005**, *44*, 7053.

[12] a) Y. R. Dong, N. Nishiyama, Y. Egashira, K. Ueyama, *Ind. Eng. Chem. Res.* **2008**, *47*, 4712; b) A. H. Lu, B. Spliethoff, F. Schüth, *Chem. Mater.* **2008**, *20*, 5314.

[13] a) C. J. Brinker, G. W. Scherer, *Sol-Gel Science: The Physics and Chemistry of Sol-Gel Processing*, Academic Press, New York, **1990**; b) A. C. Pierre, G. M. Pajonk, *Chem. Rev.* **2002**, *102*, 4243; c) S. A. Al-Muhtaseb, J. A. Ritter, *Adv. Mater.* **2003**, *15*, 101.

[14] R. W. Pekala, *J. Mater. Sci.* **1989**, *24*, 3221.

[15] T. Yokoi, Y. Sakamoto, O. Terasaki, Y. Kubota, T. Okubo, T. Tatsumi, *J. Am. Chem. Soc.* **2006**, *128*, 13664.

[16] C. T. Kresge, M. E. Leonowicz, W. J. Roth, J. C. Vartuli, J. S. Beck, *Nature* **1992**, *359*, 710.

[17] I. Moriguchi, A. Ozono, K. Mikuriya, Y. Teraoka, S. Kagawa, M. Kodama, *Chem. Lett.* **1999**, 1171.

[18] a) D. Y. Zhao, J. L. Feng, Q. S. Huo, N. Melosh, G. H. Fredrickson, B. F. Chmelka, G. D. Stucky, *Science* **1998**, *279*, 548; b) D. Y. Zhao, Q. S. Huo, J. L. Feng, B. F. Chmelka, G. D. Stucky, *J. Am. Chem. Soc.* **1998**, *120*, 6024.

[19] V. K. Lamber, R. H. Dinegar, *J. Am. Chem. Soc.* **1950**, *72*, 4847.

[20] a) C. Z. Yu, B. Z. Tian, J. Fan, G. D. Stucky, D. Y. Zhao, *J. Am. Chem. Soc.* **2002**, *124*, 4556; b) F. Q. Zhang, D. Gu, T. Yu, F. Zhang, S. H. Xie, L. J. Zhang, Y. H. Deng, Y. Wan, B. Tu, D. Y. Zhao, *J. Am. Chem. Soc.* **2007**, *129*, 7746.

[21] a) S. H. Joo, S. J. Choi, I. Oh, J. Kwak, Z. Liu, O. Terasaki, R. Ryoo, *Nature* **2001**, *412*, 169; b) B. Lim, M. J. Jiang, P. H. C. Camargo, E. C. Cho, J. Tao, X. M. Lu, Y. M. Zhu, Y. N. Xia, *Science* **2009**, *324*, 1302.