Available online at www.sciencedirect.com

ScienceDirect

*Mendeleev Commun.*, 2024, **34**, 890–892

Mendeleev Communications

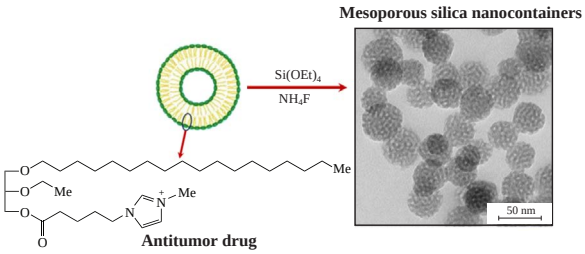
# Cationic glycerolipid as a templating agent for the synthesis of mesoporous silica nanoparticles

**Olga V. Dement'eva,*[a] Elena M. Shishmakova,[a] Anastasia V. Ivchenko,[a] Maxim S. Staltsov,[b] Alina A. Markova[c] and Victor M. Rudoy[a]**

[a] *A. N. Frumkin Institute of Physical Chemistry and Electrochemistry, Russian Academy of Sciences, 119071 Moscow, Russian Federation. E-mail: dema_ol@mail.ru*
[b] *Division of Nuclear Physics and Technologies, National Research Nuclear University MEPHI, 115409 Moscow, Russian Federation*
[c] *N. M. Emanuel Institute of Biochemical Physics, Russian Academy of Sciences, 117334 Moscow, Russian Federation*

DOI: 10.1016/j.mencom.2024.10.038

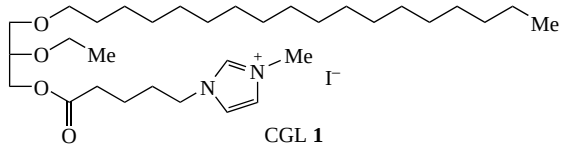
**A new method for encapsulating cationic glycerolipids is proposed, based on their use as templating agents in the sol–gel synthesis of mesoporous silica particles. Using the example of *rac*-*N*-{4-[(2-ethoxy-3-octadecyloxyprop-1-yl)-oxycarbonyl]butyl}-*N'*-methylimidazolium iodide, it is shown that this method results in the formation of high-capacity container particles with a pronounced porous structure and a narrow size distribution.**




*Keywords*: mesoporous silica nanoparticles, sol–gel synthesis, glycerolipids, imidazolium salts, liposomes, template, drug delivery.

Mesoporous silica nanoparticles (MSNs) obtained by the sol–gel method on surfactant micelle templates are of interest for various practical applications.[1–3] In particular, they are among the most promising systems for the targeted delivery and/or controlled release of various functional compounds (primarily drugs).[1,4] In some cases the functional compounds to be loaded into MSNs can themselves act as templating agents in the synthesis of such particles.[4–8] This applies to amphiphilic compounds capable of forming associates of one form or another in aqueous solutions, in particular, various bioactive substances.[4–6,8] The resulting MSNs are characterized by an extremely high content of loaded substance (up to 1 g or more per 1 g of $SiO_2$), the release rate of which can be controlled by changing the pH of the medium.

The described approach can also be applied to the encapsulation of various lipids and lipid-like compounds.[8,9] Thus, according to our data, the use of liposomes of cationic glycerolipid (CGL), *rac*-*N*-{4-[(2-ethoxy-3-octadecyloxyprop-1-yl)oxycarbonyl]butyl}-*N'*-methylimidazolium iodide **1** (its structural formula is shown below),† which has a significant antitumor activity,[11] as a template leads to the formation of silica capsules with a diameter of 0.2 to 1.5 μm.[8] At the same time, the system also contains a certain amount of 'monolithic' particles of a much smaller size (10–50 nm) having an onion-shape structure. This indicates partial destruction of the CGL liposomes in an alkaline medium, apparently due to their interaction with deprotonated silicic acid oligomers. In addition, due to the presence of an ester bond in molecule **1**, its partial hydrolysis under these conditions cannot be ruled out. Such possibility is indicated by the results obtained in the synthesis of MSNs on vesicles of the biologically active gemini-surfactant decamethoxin.[12]




CGL **1**

In this work, we studied the formation of MSNs based on CGL **1** associates in a neutral medium, when both of these mechanisms should be realized to a significantly lesser extent. As already noted, in aqueous solutions with a concentration exceeding the critical association concentration of 0.02 mM CGL **1** forms liposomes with an average diameter of 500 to 1000 nm. The synthesis of MSNs was carried out as follows.‡

The particle size and structure were determined by high-resolution transmission electron microscopy (HRTEM). At the qualitative level, the content of templating compounds in the silica matrix was evaluated by FTIR. Capacity of MSNs was determined by thermogravimetric analysis (TGA).

High-resolution transmission electron microscopy (HRTEM) data indicate that during the synthesis spherical MSNs with a narrow size distribution and a pronounced porous structure are

† Lipid **1** was synthesized in the group of Prof. G. A. Serebrennikova (Lomonosov Institute of Fine Chemical Technologies).[10]

‡ *Synthesis of MSNs based on CGL* **1**. An aqueous solution of $NH_4F$ (25 mg $ml^{-1}$, 2.0 ml) was added to a solution of CGL **1** (1.5 mM, 25 ml) under intensive stirring. To the obtained mixture, tetraethoxysilane solution in absolute ethanol (15%, 1 ml) was added in 50 μl portions at intervals of 5 min. The reaction mixture was stirred overnight at 25 °C. At the end of the synthesis, the MSNs were separated from the other reaction products using a Universal 320R centrifuge (Hettich, Germany), and then redispersed in water or alcohol on an ultrasonic bath.

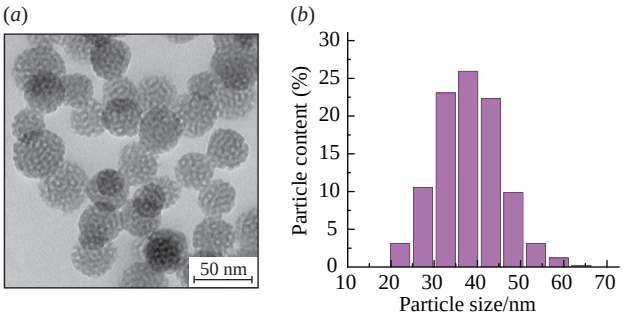



**Figure 1** (*a*) HRTEM image of MSNs obtained using CGL **1** associates. (*b*) A histogram of the size distribution of such particles.

formed (Figure 1).§ Their average diameter is about 38 nm, and the pore diameter is approximately 3–4 nm. This result differs significantly from that obtained previously[8] and indicates a change in the shape of CGL associates during the formation of silica particles. This could be due to several main reasons. Firstly, in this case the concentration of silicic acid oligomers in the system should be noticeably lower than previously[8] due to the fractional introduction of the precursor, as well as due to a decrease in the rate of hydrolytic condensation of $Si(OEt)_4$ in a neutral medium. This difference in the concentration is especially pronounced at the initial stage of the MSN formation. The degree of deprotonation of silicic acid oligomers also turns out to be significantly lower than in an alkaline medium,[13] which leads to a weakening of their electrostatic interaction with CGL cations. Secondly, it should be taken into account that in our case the hydrolysis and polycondensation reaction of $Si(OEt)_4$ are catalyzed by fluoride ions. This implies the formation and subsequent breaking of Si–F bonds.[14,15] The presence of Si–F groups can also affect the nature of the interaction of the template with silicic acid oligomers.

Figure 2 shows FTIR spectra measured in diffuse reflectance mode.§ In the spectra of pure CGL **1** and particles synthesized using it, absorption bands in the range of about 2800–3000 $cm^{-1}$, corresponding to the stretching vibrations of C–H bonds,[16,17] as well as a band near 1730 $cm^{-1}$, due to C=O vibrations, are clearly visible. The formation of the matrix itself is confirmed by the presence of an intense band near 1100 $cm^{-1}$, which corresponds to the vibrations of Si–O–Si bonds. It should be noted that the vibration frequencies of C=N and C=C groups in the range of 1450–1560 $cm^{-1}$ are very close to each other due to the effect of conjugation of these bonds in cyclic systems. Therefore, it is difficult to identify each of these groups separately.

Treatment of MSNs with an ethanolic HCl solution leads to complete removal of templating CGL **1**, as evidenced by the disappearance of characteristic bands in spectrum *3* in Figure 2. At the same time, the bands corresponding to Si–O–Si bonds are preserved, *i.e.*, during etching of the template, no destruction of the silica matrix occurs. A broad absorption band with a maximum near 3500 $cm^{-1}$ in spectra *2* and *3* may be associated with the presence of adsorbed water in the samples.[15]

According to TGA data,§ the synthesized particles are characterized by a high capacity for the glycerolipid **1**. Thus, the

§ HRTEM was performed using a Libra 120 microscope (K. Zeiss, Germany) at an accelerating voltage of 120 kV. The FTIR spectra were recorded on a Nicolet 380 FTIR spectrometer (Thermo Electron Corp., USA) in the diffuse reflectance mode in the range of wavenumbers 400–4000 $cm^{-1}$; the number of scans was 640. The TGA experiments were carried out using a TGA Q500 device (TA Instruments, USA) in open platinum crucibles under argon atmosphere in the temperature range from 25 to 600 °C; the heating rate was 10 °C $min^{-1}$. Before TGA, the samples were dried at room temperature in a vacuum drying oven VD 23 (Binder, Germany).

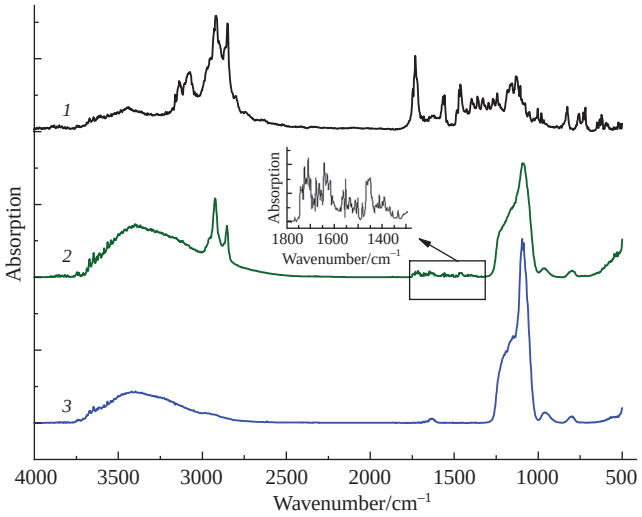



**Figure 2** Fourier transform IR spectra of CGL **1** (*1*) and MSNs synthesized on its associates, before (*2*) and after (*3*) treatment of the particles with HCl/EtOH.

main weight loss of the MSN sample, corresponding to the destruction of encapsulated CGL, is observed in the range of 200–550 °C [curve *1* in Figure 3(*a*)] and amounts to about 25 wt%. This corresponds to the incorporation of about 70 wt% of the CGL **1** introduced into the reaction system. At the same time, the character of thermal destruction of encapsulated CGL **1** is very different from that registered for the free drug which would decompose in a much narrower temperature range (200–350 °C). The main reason for such differences, apparently, is the fact that in the silica matrix the thermal destruction of CGL occurs under conditions of strongly restricted geometry. Moreover, it can be assumed that the head groups of CGL **1** are partially incorporated into the walls of the matrix pores during the formation of MSNs.

Note that the CGL we used herein does not have characteristic absorption bands in the UV or visible region, which significantly complicates the analysis of the kinetics of its release from the MSNs. However, given the results of our experiments performed with other amphiphilic compounds,[4] it can be expected that the rate of this process should depend on the pH of the medium. To confirm this assumption, experiments on cell cultures are necessary, which is one of the goals of our further work.

In conclusion, the data obtained indicate the possibility of using CGL **1** as a templating agent in the synthesis of MSNs. Obviously, other compounds of this family that have antitumor effects can also be tested for this purpose. Given the ability of MSNs to accumulate in tumors by the mechanism of passive delivery, it can be expected that their use may allow for targeted delivery of such drugs and, as a result, reduce the risk of adverse side effects. In our opinion, this approach may in the future become an alternative to liposomal delivery. In this case,

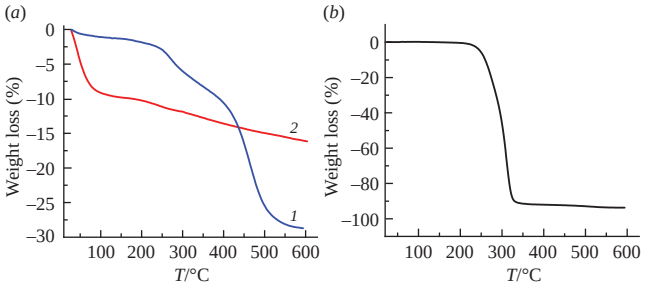



**Figure 3** (*a*) TGA curves for MSN samples synthesized on CGL **1** associates, measured before (*1*) and after (*2*) template removal. (*b*) TGA curve for pure CGL **1**.

liposomes containing various active components (for example, metal nanoparticles[18]) can also serve as a template.

The work was carried out under the assignment of the Ministry of Science and Higher Education of the Russian Federation.

## References

1 K. Zivojević, M. Mladenović, M. Djisalov, M. Mundzic, E. Ruiz-Hernandez, I. Gadjanski and N. Ž. Knežević, *J. Control. Release*, 2021, **337**, 193; https://doi.org/10.1016/j.jconrel.2021.07.029.
2 H. K. Kordasht, M. Pazhuhi, P. Pashazadeh-Panahi, M. Hasanzadeh and N. Shadjou, *Trends Anal. Chem.*, 2020, **124**, 115778; https://doi.org/10.1016/j.trac.2019.115778.
3 B. Singh, J. Na, M. Konarova, T. Wakihara, Y. Yamauchi, C. Salomon and M. B. Gawande, *Bull. Chem. Soc. Jpn.*, 2020, **93**, 1459; https://doi.org/10.1246/bcsj.20200136.
4 O. V. Dement'eva, *Colloid J.*, 2020, **82**, 479; https://doi.org/10.1134/S1061933X20050038.
5 V. Morales, J. McConnell, M. Pérez-Garnes, N. Almendro, R. Sanz and R. A. García-Munoz, *J. Mater. Chem. B*, 2021, **9**, 4178; https://doi.org/10.1039/D1TB00481F.
6 M. Zhang, J. Feng, Y. Zhong, J. Luo, Y. Zhao, Y. Yang, Y. Song, X. Lin, Y. Yang, H. Song and C. Yu, *Chem. Eng. J.*, 2022, **440**, 135837; https://doi.org/10.1016/j.cej.2022.135837.
7 O. V. Dement'eva, A. M. Semiletov, A. A. Chirkunov, V. M. Rudoy and Yu. I. Kuznetsov, *Colloid J.*, 2018, **80**, 474; https://doi.org/10.1134/S1061933X18050058.
8 O. V. Dement'eva, T. B. Roumyantseva and V. M. Rudoy, *Colloid J.*, 2016, **78**, 281; https://doi.org/10.1134/S1061933X16020034.
9 S. Martinez-Erro, F. Navas, E. Romaní-Cubells, P. Fernández-García, V. Morales, R. Sanz and R. A. García-Muñoz, *Int. J. Mol. Sci.*, 2021, **22**, 7968; https://doi.org/10.3390/ijms22157968.
10 A. A. Markova, N. V. Plyavnik, V. V. Tatarskii, A. A. Shtil and G. A. Serebrennikova, *Russ. J. Bioorg. Chem.*, 2010, **36**, 532; https://doi.org/10.1134/S106816201004014X.
11 A. A. Markova, N. V. Plyavnik, N. G. Morozova, M. A. Maslov and A. A. Shtil, *Russ. Chem. Bull.*, 2014, **63**, 1081; https://doi.org/10.1007/s11172-014-0552-4.
12 O. V. Dement'eva, K. A. Naumova, I. N. Senchikhin, T. B. Roumyantseva and V. M. Rudoy, *Colloid J.*, 2017, **79**, 451; https://doi.org/10.1134/S1061933X17040020.
13 R. Iler, *Chemistry of Silica: Solubility, Polymerization, Colloid and Surface Properties, and Biochemistry*, Wiley, New York, 1979.
14 C. J. Brinker, *J. Non.-Cryst. Solids*, 1988, **100**, 31; https://doi.org/10.1016/0022-3093(88)90005-1.
15 E. J. A. Pope and J. D. Mackenzie, *J. Non.-Cryst. Solids*, 1986, **87**, 185; https://doi.org/10.1016/S0022-3093(86)80078-3.
16 M. V. Landau, S. P. Varkey, M. Herskowitz, O. Regev, S. Pevzner, T. Sen and Z. Luz, *Microporous Mesoporous Mater.*, 1999, **33**, 149; https://doi.org/10.1016/S1387-1811(99)00133-X.
17 L. J. Bellamy, *The Infra-Red Spectra of Complex Molecules*, Chapman and Hall, London, 1975.
18 O. V. Zaborova, S. O. Livshitz, M. A. Kirsanova and V. G. Sergeyev, *Mendeleev Commun.*, 2023, **33**, 337; https://doi.org/10.1016/j.mencom.2023.04.013.

*Received: 30th May 2024; Com. 24/7513*