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Mendeleev Commun., 2019, **29**, 86–88

Mendeleev Communications

Sulfobetaine derivatives of thiacalix[4]arene: synthesis and supramolecular self-assembly of submicron aggregates with Ag^I cations

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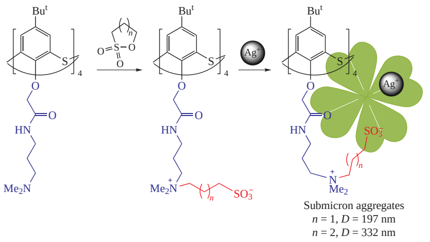
DOI: 10.1016/j.mencom.2019.01.029

Sulfobetaine derivatives of *p-tert*-butylthiacalix[4]arene in cone conformation have been synthesized for the first time. It has been shown by dynamic light scattering that the compounds form submicron-sized particles with silver cation in water, and the particle size depends on the length of a linker in the sulfobetaine moiety.



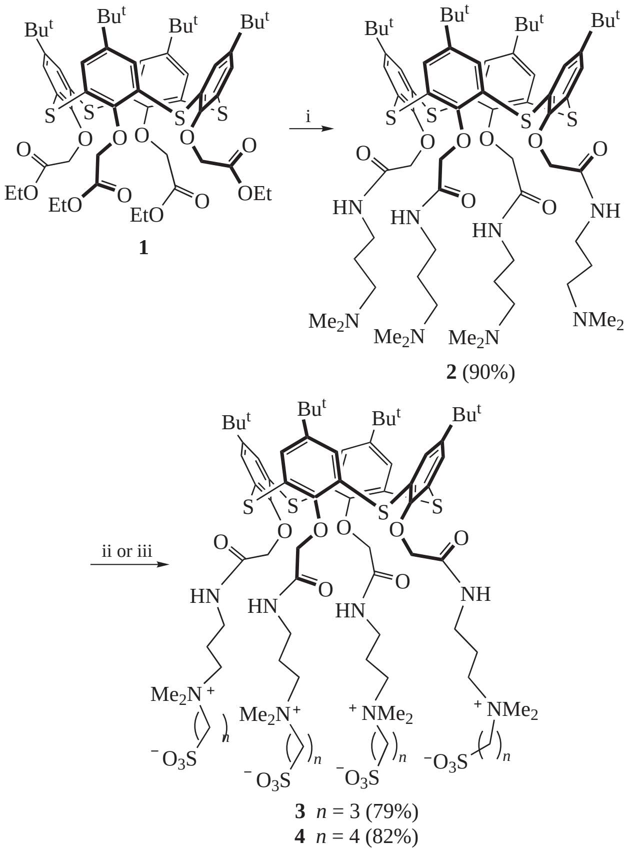
Sulfobetaine neutral surfactants containing both positively and negatively charged ion centers are known to have low toxicity, good water solubility, wide isoelectric range, high foam stability and resistance to hard water.[1–3] Betaines find application as catalysts,[4] some polymers with sulfobetaine moieties have good biocompatibility,[5] are effective in reduction of bacterial adhesion,[6] and find potential application in gene delivery[7] as well as in the treatment of wounds.[8] The structure of the zwitterion moiety of sulfobetaines practically does not depend on pH value.

Despite the wide commercial use of betaine surfactants, their macrocyclic analogues, including thiacalix[4]arenes, are not appropriately presented in the literature. At the same time, it is possible to obtain a series of (thia)calixarene-based amphiphilic compounds with various aggregation properties and with different values of the critical micelle concentration by changing the nature of their polar parts, upper to lower rim position switch of the polar parts, by changing the macrocycle size or the length of the alkyl linkers for hydrophilic moieties. Compared to non-macrocyclic surfactants, the amphiphilic (thia)calixarenes have lower values of the critical micelle concentration.[9]

At present much attention is paid to the investigation of non-covalent self-assembly in solution for nanoscale metal–supramolecular aggregates.[9–12] In general, at nanoscale level materials exhibit new properties, for example, nanoscale silver particles have a bactericidal effect. Aggregates obtained by assembly of various compounds with Ag^I cations are used for the development of materials with antibacterial properties.[13] Silver ions also exhibit a potential antiviral effect on the smallpox as well as on influenza A-1 and B viruses.[14] The antiviral effect of Ag-based associates depends on their size, concentration and dispersion stability.[15] Therefore, the synthesis of stable, mono-disperse, water-soluble aggregates based on Ag^I assembly with molecular building blocks such as (thia)calix[4]arenes,[9,16–18] pillar[5]arenes,[19–21] or cyclodextrins[22] with multiple recognition capacity,[23] attracts growing attention.

In this work, we synthesized a derivatives of *p-tert*-butylthiacalix[4]arene with sulfobetaine moieties on the lower rim and studied their capability of self-assembling in the presence of Ag^I. Tetrasubstituted thiacalix[4]arene derivative **2** was synthesized previously[24] by aminolysis of *p-tert*-butylthiacalix[4]arene **1**. Compound **2** with tertiary amino groups is the precursor for the synthesis of sulfobetaine macrocyclic compounds **3** and **4** (Scheme 1).

Next, the reaction of compound **2** in acetonitrile with 1,3-propanesultone and 1,4-butanesultone was attempted for



Scheme 1 *Reagents and conditions*: i, *N,N*-dimethylpropane-1,3-diamine, PhMe, MeOH, reflux; ii, 1,3-propanesultone, MeCN, reflux; iii, 1,4-butanesultone, DMF, reflux.

Table 1 Size of aggregates formed due to association of compounds **3** and **4** in water in the presence or absence of Ag^I.[a]

c/mol dm^{-3}	**3**		**3** + Ag^I		**4**		**4** + Ag^I	
	Đ	*d*/nm	*Đ*	*d*/nm	*Đ*	*d*/nm	*Đ*	*d*/nm
3×10^{-4}	0.82±0.15	421±74	0.18±0.05	197±5	0.73±0.13	756±93	0.55±0.06	332±23
3×10^{-5}	0.54±0.17	335±47	0.48±0.12	347±121	0.81±0.22	530±270	0.50±0.10	389±83
3×10^{-6}	0.48±0.33	317±203	0.51±0.09	435±153	0.62±0.54	235±206	0.50±0.08	377±62

[a] *Đ* is dispersity, *d* is hydrodynamic diameter.

72 h.[†] However, only the reaction with 1,3-propanesultone gave product **3** in a yield of 79%. ^{1}H NMR spectrum of compound **3** has proton signals of *tert*-butyl groups as one singlet at 1.11 ppm, which confirms the formation of the tetrasubstituted product. The complete set of ^{1}H NMR spectroscopy and MALDI-TOF mass spectrometry (m/z 911.8 $[M + 2Na]^{2+}$) data confirm the structure of product **3**.

The failure of macrocycle **2** reaction with 1,4-butanesultone may be explained by the lower reactivity of the latter compared to 1,3-propanesultone. Therefore, more rigorous conditions were tested for this reaction utilizing DMF as the solvent that has a higher boiling point. Under these conditions the product **4** was isolated in 82% yield.

With the sulfobetaine macrocycles **3** and **4** in hand we investigated their aggregation in aqueous solution in the presence or absence of silver nitrate by dynamic light scattering.[‡] Measurement of hydrodynamic particle size and dispersity of the system was carried out at 20 °C. In the absence of silver nitrate the aqueous solution of macrocycle **3** was characterized by a high value of dispersity (*Đ* = 0.48–0.82) and particle size from 317 to 421 nm (Table 1).

Note that in the range of concentrations studied for compound **3**, aggregate size decreases (421–317 nm) with lowering concentration, while the dispersity also diminishes (Table 1). After addition of Ag^I, nanosized particles with hydrodynamic diameter of about 197 nm and a low dispersity of 0.18 were formed. At the same time, with a decrease in the concentration of **3**, an opposite tendency is observed: the aggregate size and dispersity increase simultaneously (Table 1). Obviously, with a higher macrocycle concentration some charge compensation occurs, which causes higher monodispersity.

A more complicated picture was observed for macrocycle **4**. In the concentration range studied (3×10^{-4}–3×10^{-6} mol dm^{-3}), there is no definite trend in the dispersity change, while the aggregate size decreases (756–235 nm) with lowering concentration (Table 1). The addition of Ag^I to the solution of **4** in a stoichiometric ratio (1:1) led to the formation of aggregates with a size of 300–390 nm and dispersity about 0.50. Therefore, both the aggregate size formed by macrocycle **4** and their dispersity depend weakly on the concentration.

To explain this difference in behavior during the assembly of macrocycles **3** and **4** with Ag^I, we suggested that the silver ion makes different contributions to the self-assembly. The molecules of *p*-*tert*-butylthiacalix[4]arenes **3** and **4** contain several sites which potentially bind metal cations to further create supramolecular associates, namely, bridged sulfur atoms and negatively charged sulfo groups. We supposed that these centers participate in different degree for the two macrocycles in the self-assembly process. To confirm this hypothesis, the 2D ^{1}H–^{1}H NOESY NMR spectra for **3** and **4** were recorded and the possible structure of the associates was established from the corresponding proton cross-peaks (see Online Supplementary Materials). In the ^{1}H–^{1}H NOESY NMR spectrum of compound **3** a cross-peak between the methylene group of $CH_2SO_3^-$ and the methyl groups of Me_2N^+ was revealed, which indicated the convergence of these groups in space with potential formation of an intramolecular ionic bond between them. A similar cross-peak in the 2D ^{1}H–^{1}H NOESY NMR spectrum of **4** was not observed. In the case of **3**, a six-membered ring is formed which is more stable than the seven-membered one for **4**. Therefore, in **3** the charge in the sulfobetaine moiety is compensated, and the coordination of Ag^I is possible only with bridging sulfur atoms, which leads to the formation of stable submicron associates with a low dispersity value.

Thus, using dynamic light scattering in water, we have established that both *p*-*tert*-butylthiacalix[4]arenes **3** and **4** containing sulfobetaine moieties form submicron-sized particles with Ag^I under the experimental conditions. The particle size depends on the length of the alkyl linker between the ammonium and the sulfonate moieties: for the macrocycle **3** with the trimethylene linker, aggregates size and dispersity in the presence of silver nitrate have lower values than those for aggregates formed by the macrocycle **4**. The results obtained open new prospects for design of stable monodisperse colloid systems exhibiting a

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[†] *General procedure for the synthesis of macrocycles* **3** *and* **4**. The mixture of tetrathiacalix[4]arene **2** (0.20 g, 0.16 mmol) and 1,3-propanesultone or 1,4-butanesultone (0.64 mmol) in 15 ml of solvent (MeCN or DMF, respectively) was refluxed for 72 h. After cooling the solvent was evaporated under reduced pressure.

*5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrakis{*N*-[3',3'-dimethyl-3'-(3''-sulfonatopropyl)ammoniopropyl]carbamoylmethoxy}-2,8,14,20-tetrathiacalix[4]arene (cone)* **3**. Yield 0.19 g (79 %), mp 258 °C. ^{1}H NMR (DMSO-d_6) δ: 1.07 (s, 36 H, Bu^t), 2.01 (m, 8 H, $NCH_2C\mathit{H}_2CH_2NH$), 1.95 (m, 8 H, $NCH_2C\mathit{H}_2CH_2SO_3^-$), 2.01 (m, 8 H, $NCH_2C\mathit{H}_2CH_2NH$), 2.52 (m, 8 H, $NCH_2CH_2C\mathit{H}_2SO_3^-$), 3.04 (s, 24 H, Me_2N^+), 3.26 (m, 8 H, $NC\mathit{H}_2CH_2CH_2NH$), 3.36 (m, 8 H, $NC\mathit{H}_2CH_2CH_2SO_3^-$), 3.44 (m, 8 H, $NCH_2CH_2C\mathit{H}_2NH$), 4.84 (s, 8 H, OCH_2CO), 7.40 (s, 8 H, ArH), 8.52 (br. s, 4 H, CONH). ^{13}C NMR (DMSO-d_6) δ: 168.24, 157.82, 146.70, 134.51, 128.15, 74.11, 61.98, 60.73, 50.30, 47.74, 35.50, 33.97, 30.76, 22.44, 18.89. MS (ESI), m/z: 911.8 $[M + 2Na]^+$ (calc., m/z: 1776.7 $[M]^+$). Found (%): C, 54.50; H, 7.18; N, 6.59; S, 14.45. Calc. for $C_{80}H_{128}N_8O_{20}S_8$ (%): C, 54.03; H, 7.25; N, 6.30; S, 14.42.

*5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrakis{*N*-[3',3'-dimethyl-3'-(4''-sulfonatobutyl)ammoniopropyl]carbamoylmethoxy}-2,8,14,20-tetrathiacalix[4]arene (cone)* **4**. Yield 0.18 g (82%), mp 290 °C. ^{1}H NMR (DMSO-d_6) δ: 1.07 (s, 36 H, Bu^t), 1.63 (m, 8 H, $NCH_2CH_2C\mathit{H}_2CH_2SO_3^-$), 1.78 (m, 8 H, $NCH_2C\mathit{H}_2CH_2CH_2SO_3^-$), 1.92 (m, 8 H, $NCH_2C\mathit{H}_2CH_2NH$), 2.52 (m, 8 H, $NCH_2CH_2CH_2C\mathit{H}_2SO_3^-$), 3.02 (s, 24H, Me_2N^+), 3.29–3.31 (m, 24 H, $NC\mathit{H}_2CH_2CH_2NH$, $NC\mathit{H}_2CH_2CH_2CH_2SO_3^-$, $NCH_2CH_2C\mathit{H}_2NH$), 4.84 (s, 8 H, OCH_2CO), 7.40 (s, 8 H, ArH), 8.50 (br. s, 4 H, CONH). ^{13}C NMR (DMSO-d_6) δ: 168.84, 158.26, 147.27, 134.97, 128.58, 74.43, 62.84, 61.28, 50.74, 50.67, 36.05, 34.45, 31.20, 22.86, 22.64, 21.20. MS (ESI), m/z: 1833.7 $[M + H]^+$ (calc., m/z: 1832.8 $[M]^+$). Found (%): C, 54.90; H, 7.38; N, 6.23; S, 14.03. Calc. for $C_{84}H_{136}N_8O_{20}S_8$ (%): C, 54.99; H, 7.47; N, 6.11; S, 13.98.

[‡] *Dynamic light scattering (DLS)*. The particle size was determined using a Zetasizer Nano ZS instrument at 20 °C. The instrument contained 4 mW He–Ne laser operating at a wavelength of 633 nm and incorporated noninvasive backscatter optics (NIBS). The measurements were performed at the detection angle of 173° and the software automatically determined the measurement position within the quartz cuvette. The 0.01–1 mM aqueous solutions of the macrocycles **3** and **4** were prepared. The molar ratio macrocycle : Ag^+ was 1:1. The solutions were held for 15 min, then the particle size was measured. To assess the kinetic stability of the systems, the measurements were carried out once more after 1 h under similar conditions. The experiments were performed for each solution in triplicate.

synergistic effect of biocompatibility and antiviral as well as antibacterial effects, promising for new catalytic and biomedical applications.

This work was supported by Kazan Federal University and the Russian Foundation for Basic Research (grant no. 16-33-60141 mol_a_dk). Study of the spatial structure of compounds by NMR spectroscopy was funded by the Russian Government to support the Program of Competitive Growth of Kazan Federal University among World's Leading Academic Centers.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.01.029.

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Received: 19th July 2018; Com. 18/5647