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Structure–Activity Relationship of the Thiacalix[4]arenes Family with Sulfobetaine Fragments: Self-Assembly and Cytotoxic Effect against Cancer Cell Lines

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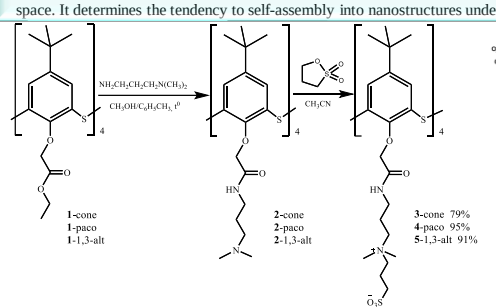
Introduction

The development of new approaches of supramolecular chemistry and the identification of the structure–activity relationship is an important and promising problem. Macrocyclic platforms - thiacalix[4]arenes, can be used for the synthesis of compounds with a regulated ability to self-assembly. Due to the ability to fix the macrocyclic ring in several conformations and the relative ease of its functionalization, functional groups can be arranged in a predetermined manner in space. It determines the tendency to self-assembly into nanostructures under the influence of the substrate (ions, molecules).



In this work, we synthesize sulfobetaine derivatives of thiacalix[4]arene in three conformations. In the presence of Ag+, these derivatives are capable to self-assemble into associates with different architectures (shapes) and, as a consequence, with cytotoxic selectivity for the cervical carcinoma cell line.

Table 1. Size of aggregates formed during association of compound **3** in water in the presence / absence of Ag (I) (hydrodynamic diameters d, nm and PDI).

C,	3		3+Ag+ 1:1		3+Ag+ 1:4		3+Ag+ 1:10	
моль/л	PDI	d, nm	PDI	d, nm	PDI	d, nm	PDI	d, nm
1·× 10-4	0.82±0.15	421±74	**0.17±0.02**	**168±7**	**0.18±0.01**	**243±13**	0.30±0.05	817±48
1·× 10-5	0.54±0.17	335±47	0.31±0.06	152±27	0.27±0.03	756±93	0.75±0.16	446±92
1·× 10-6	0.48±0.33	317±203	0.52±0.12	193±32	0.35±0.09	234±50	-	-

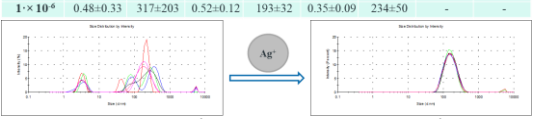


Fig. 1. Size distribution of **3**(*cone*) in the absence/presence of Ag (I) in water (1×10^{-4} M), (1:1)

Table 2. Size of aggregates formed during association of compound **4** in water in the presence / absence of Ag (I) (hydrodynamic diameters d, nm and PDI).

C,	4		4+Ag+ 1:1		4+Ag+ 1:4		4+Ag+ 1:10	
моль/л	PDI	d, nm	PDI	d, nm	PDI	d, nm	PDI	d, nm
1·× 10-4	0.38±0.12	201±32	**0.21±0.01**	**182±11**	**0.19±0.01**	**123±6**	**0.27±0.02**	**147±7**
1·× 10-5	0.31±0.15	143±96	0.34±0.11	285±60	0.35±0.11	249±58	0.36±0.06	235±37
1·× 10-6	-	-	-	-	-	-	-	-

The dynamic light scattering method showed that the synthesized macrocycles in cone, partial cone and 1,3-alternate conformations form submicron-sized particles with Ag+ in water, but the particle size and polydispersity of the systems studied depend on the macrocycle conformation.

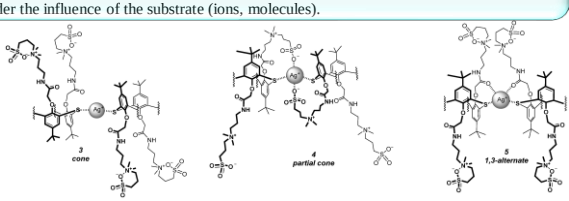


Fig. 2. Coordination of the metals by the isomers of thiacalix[4]arenes **3**–**5** proposed for various conformations.

The type of coordination determines the different shapes of the associates. Cytotoxic properties are shown to be controlled by the shape of associates, with the highest activity demonstrated by thiacalix[4]arenes in partial cone conformation.

Table 3. In vitro cytotoxic effects (μM) of sulfobetaine derivatives **3**–**5** and their aggregates with Ag^+

Test compounds	IC_{50} (μM)			
	M-HeLa	HuTu 80	MCF-7	Chang Liver
3	>5000	>5000	>5000	>5000
3/Ag^+	>5000	>5000	>5000	>5000
4	>500	>500	>500	>500
4/Ag^+	**38.9 ± 2.6**	>500	>500	**85.1 ± 6.4**
5	>500	>500	>500	>500
Imatinib mesylate	84.7 ± 6.3	288 ± 23	207 ± 17	102 ± 7.9

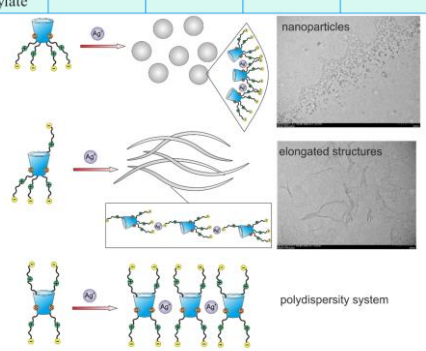


Fig. 3. The possible structures of *p-tert*-butyltiacalix[4]arenes **3**-**5** aggregated with Ag^+ cations.

Conclusions

Thus, for the first time, we have synthesized a series of water-soluble sulfobetaine derivatives of *p-tert*-butylthiacalix[4]arene in *cone*, *partial cone*, and *1,3-alternate* conformation. The association of macrocycles **3**–**5** with Ag^+ was confirmed by DLS methods. The particle size and polydispersity of systems depend on the conformation of macrocycle and are determined by the spatial structure of the sulfobetaine fragments. In the case of **4**/Ag^+ aggregates, extended nanostructures are formed. The cytotoxic effects are shown to be controlled by the shape of the associates. Among the tested compounds, only the **4**/Ag^+ aggregates act selectively on the cervical carcinoma cell line (M-HeLa). In terms of cytotoxic activity, this complex is two times higher than the reference drug imatinib mesylate. The selective activity against tumor cells in combination with low toxicity toward normal cells allow the consideration of **4**/Ag^+ aggregates as effective novel antitumor agents. We hope that the results of our work will make it possible to develop fundamentally new approaches to the synthesis of nanostructures without a drug to solve the problem of multidrug resistance. This work may become the basis for the creation of a new class of anticancer systems: "nano anticancer drugs".

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