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Novel membrane mimetic systems based on amphiphilic oxyethylated calix[4]arene: Aggregative and liquid crystalline behavior

Lucia Ya. Zakharova[a,b,*], Yuliana R. Kudryashova[a], Natalia M. Selivanova[b], Mikhail A. Voronin[a], Alsu R. Ibragimova[a], Svetlana E. Solovieva[a], Aidar T. Gubaidullin[a,b], Alexey I. Litvinov[a], Irek R. Nizameev[a,b], Marsil K. Kadirov[a,b], Yuri G. Galyametdinov[b], Igor S. Antipin[a,c], Alexander I. Konovalov[a]

[a] *A.E.Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Center, Russian Academy of Sciences, 8, ul. Akad. Arbuzov, Kazan 420088, Russia*
[b] *Kazan State Technological University, Kazan, 68, ul. K. Marx 420015, Russia*
[c] *Kazan State University, Kazan, 18, ul. Kremlevskaya 420008, Russia*

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ABSTRACT

Self-organization of amphiphilic calixarenes oxyethylated at a lower rim has been investigated in water and water–organic solutions. In the range of isotropic solutions three types of structural transitions were indicated by a complex of methods. The first critical point indicated by surface tension, dynamic light scattering and atomic force microscopy methods is probably connected with the formation of “infinite” organized structures (of hundreds nanometers in size) through the open association model. This aggregative phenomenon covers the concentration range below 10^{-3} M. In the case of aqueous calixarene solutions these large aggregates co-exist with small micelle-like particles and undergo a rearrangement with an increase in the concentration. The second structural transition occurs beyond 10^{-3} M. It is revealed in aqueous calixarene solutions by surface tension, spine probe, viscosimetry and dynamic light scattering methods. Small aggregates (~10 nm in diameter) are formed in this range through a closed model typical for conventional surfactants. The third transition indicated by viscosimetry and in single case by tensiometry can be connected with an elongation of aggregates. The polarization microscopy and X-ray diffraction studies reveal the anisotropic behavior with the concentration of solutions. Parameters of the existence of liquid crystalline mesophases are found to be influenced by the structure of substituents at both the upper and lower rims, as well as by the nature of solvent.

It is generally recognized that self-organizing systems based on synthetic amphiphilic compounds due to their relative simplicity make it possible to isolate single factors and obtain information on the structural behavior of their prototypes, i.e. natural organized systems, in particular biomembranes [1]. This approach is considered to be a biomimetic way based on the analogy between synthetic and natural amphiphiles. Both exhibit the capacity to form aggregates of different morphology and to interact selectively and reversibly with a diversity of organic and bioorganic guests, thereby controlling their physico-chemical properties. The topic of high importance is that biological amphiphiles and drugs are capable of forming various types of aggregates differing in their size, packing mode, morphology and hence in their functionality. The structural diversity of biosystems is mostly due to the contribution of various non-covalent interactions including van der Waals forces, hydrogen bonds, hydrophobic and stacking effects, etc. Another essential feature is their capacity to associate through different mechanisms. According to Ref. [2] two models of association are typical for amphiphiles depending on their geometry and hydrophilic–lipophilic balance. In particular, the closed packing mode is observed for conventional surfactants with distinctly separated hydrophilic and hydrophobic fragments, while an alternative open model is observed for bio-relevant amphiphiles including drugs. The former usually results in the formation of small micelle-like aggregates with a marked surface curvature, while the latter leads to the formation of “infinite” structures of large size with a small, if any, surface curvature. Such a structural lability of biospecies makes it possible for them to adjust to the microenvironment and participate in metabolic transformations. Structural transitions are known to play a key role in the functioning of biomembranes, in particular, in the transport through lipid bilayers, with the fusion/fission processes involved. For example,

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* Corresponding author at: A.E.Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Center, Russian Academy of Sciences, 8, ul. Akad. Arbuzov, Kazan 420088, Russia. Tel.: +7 8432 732293/629032; fax: +7 8432 732253.
E-mail address: lucia@iopc.ru (L.Ya. Zakharova).

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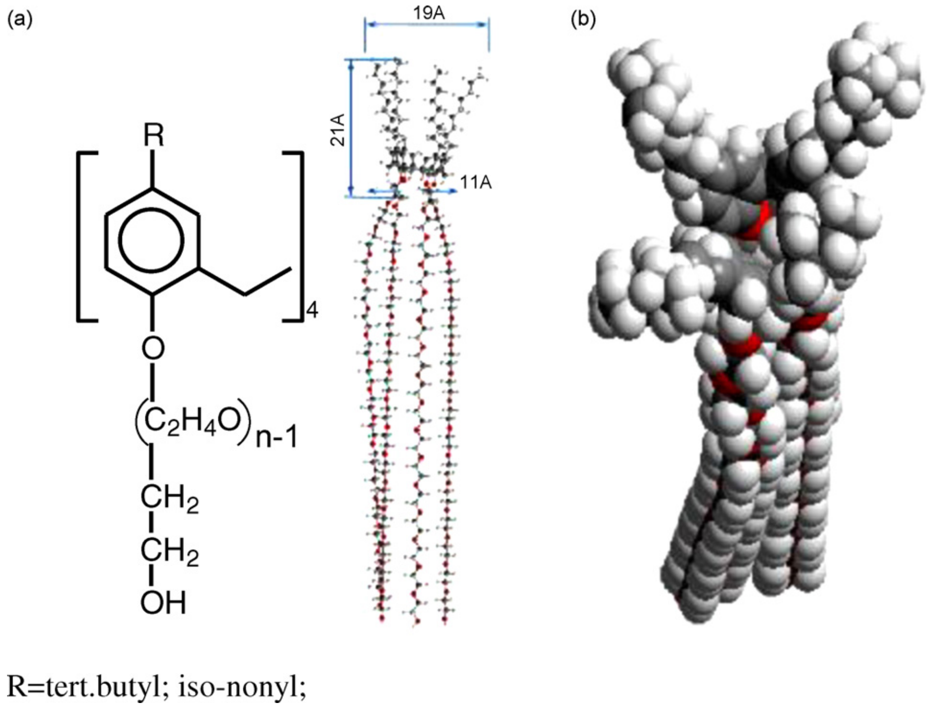

Scheme 1. (a) Chemical structure of amphiphilic oxyethylated calix[4]arene. (Abbreviated form *m*CO*n* will further be used to designate ACO, where *m* is the number of carbon atoms in substitutes in the upper rim of calixarene, while *n* is the number of oxyethylene fragments in the lower rim.); (b) the image of 9CO16; the dimensions are given for the gas phase-minimized structure optimized by MM method with MM2 force field; Chem3D program.

the phase inversion, i.e. the transitions between the positive and negative surface curvature permanently occurs on the merging of the cell membranes and vehicles in the processes of exocytosis and endocytosis.

Besides the above fundamental aspect an obvious practical viewpoint should be taken into account, when biomimetic systems are considered. At present, membrane mimetic chemistry has become a versatile chemical tool. One of the most promising approaches to the design of nanosystems with desirable parameters, i.e. nanocontainers, nanoreactors, sensors, luminescent or magnetic nanoparticles, nonviral vectors, etc. is the self-organization of amphiphilic compounds [3]. Different types of self-organizing matrixes are known to be used, such as amphiphile and polymer micelles, vesicles, gels, liquid crystals, etc. Our long-term investigations show that applications of compartmentalization of reactants in membrane mimetic systems involve altered reaction rates and products [4]. Monolayers and organized multilayers can be profitably employed as molecular electronic devices. Opportunities also exist for using different surfactant aggregates with polymeric membranes for the control and regulation of reverse osmosis and ultrafiltration. Therefore, the design of new amphiphilic building blocks and exploration of their self-organization is of both fundamental and practical importance.

The synthesis of diverse amphiphilic molecules on the basis of macrocyclic platforms results in the development of a new type of amphiphiles, which can be regarded as the intermediate between conventional surfactants and some biological compounds. The specific aggregation mode of cyclophane based amphiphiles is quite different from that of conventional surfactants, which is highlighted in literature [5,6]. We synthesized new amphiphilic calix[4]arenes (Scheme 1) patented as nontoxic building blocks for nanocontainers capable of binding bioactive substrates including drugs [7]. These amphiphilic calixarenes oxyethylated at a lower rim (ACOs or *m*CO*n*, where *m* is the number of carbon atoms in substitutes in the upper rim of calixarene, while *n* is the number of oxyethylene fragments in the lower rim) are of a dual nature. On the one hand, they are structural analogues of nonionic surfactants, in particular oxyethylated aliphatic and aromatic alcohols. Therefore, they may form micelle-like aggregates in aqueous solution due to the hydrophobic effect. On the other hand, cyclophanic platform introduces peculiarity and can direct association on an alternative way, since bulky geometry would favor the formation of layer structures.

Thus, due to the combination of the surfactant-like outline with the cyclophane platform, amphiphilic calixarenes are assumed to be suitable for modeling the multi-type association mechanisms of bio-relevant amphiphiles. In this case different modes of self-organization can occur, which is supported by the following points: (i) the presence of hydrophobic fragments provides grounds for predicting the contribution of the hydrophobic effect; (ii) the occurrence of aromatic rings can provide the possibility of stacking effect; (iii) the existence of a cavity formed by aromatic rings provides the contribution of inclusive interactions, with the calixarene cavity involved. The capability for associating through different modes makes it possible to predict a diverse structural behavior of the systems based on ACOs, including the transition from isotropic to anisotropic solutions. The liquid crystalline behavior of calixarenes is of current importance [8a,6g]. The variety of nanostructures can be enlarged by adding the metal ions. In particular, the approach to the formation of lyotropic liquid crystals (LLC) in the presence of lanthanum salts has been documented in our works [8b–e,4d]. LLC are of particular interest due to the relative simplicity of their synthesis and control of their size and geometry. It is noteworthy, that the structural transitions with the participation of liquid crystals play a key role in functioning biomembranes [9], therefore the examination of conditions for their existence are of importance. Besides, LLCs provide a wide possibility for the design of supramolecular architectures of practical use. In particular, lyotropic mesophases find application in heterogeneous catalysis, biology, pharmacy, optical-communication systems, and organic and molecular electronics [10].