

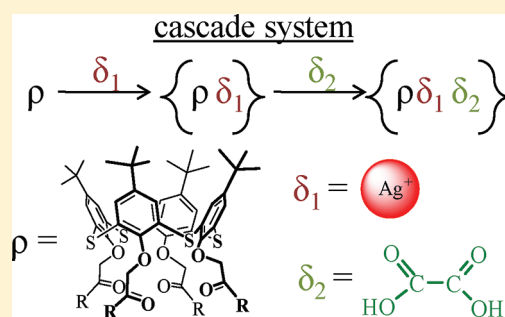
# Cascade and Commutative Self-Assembles of Nanoscale Three-Component Systems Controlled by the Conformation of Thiacalix[4]arene

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Supporting Information

**ABSTRACT:** In this work, the formation of two- and three-component supramolecular systems based on cone, partial cone, 1,3-alternate stereoisomers of heteroditopic “hosts”: *p*-tert-butylthiacalix[4]arene containing 4-amidopyridine fragments with silver(I) cations and dicarboxylic acids in liquid and solid phases were studied by UV spectroscopy, dynamic light scattering, and atomic force microscopy methods. It has been shown that these macrocycles are coreceptors, capable of simultaneously binding silver(I) cations, dicarboxylic acids (oxalic, malonic, succinic, maleic, fumaric acids), and hydroxyl acids (glycol, tartaric acids). For the first time, by the dynamic light scattering method, it has been shown that the conformation of *p*-tert-butyl thiacalix[4]arenes significantly affects the type of three-component system formed: cone is characterized by the formation of cascade systems; for partial cone, intermediate systems; and for the 1,3-alternate stereoisomers, three types of three-component systems (cascade, intermediate, and commutative) were observed.



## INTRODUCTION

Over the past decade, the development of supramolecular chemistry methods as a tool for the design of nanoparticles and nanomaterials with desired properties using programmable self-assembly of supramolecular systems has attracted the attention of researchers.<sup>1–7</sup> Such systems can be formed by noncovalent self-assembly of molecular building blocks, which are characterized by strictly defined sizes, shapes, and their ability of multiple recognition.<sup>8</sup> Polyfunctional compounds capable of forming cooperative associates with several “guests” or multivalent bonds with individual polyfunctional substrates are generally used as prospective molecular building blocks.<sup>9–12</sup>

The main factors to consider in the development of a synthetic receptor preorganized for substrate binding are the spatial orientation of the binding sites, substrate structure complementarity, and the type of binding sites.<sup>13–15</sup> The different combinations of electron donor, electron acceptor, proton donor, and proton acceptor binding sites within a single macrocyclic system and the development of heteroditopic receptors which can recognize and selectively bind cationic, anionic, and neutral substrates at the same time are of great interest, and are nowadays considered as one of the prospective fields of research in supramolecular chemistry. Depending on the nature and how the substrate is coordinated, as well as on the receptor structure, complexes may form as “guest–host”, and also as multicomponent supramolecular aggregates with specific properties.

Metal ions involved in the formation of multicomponent supramolecular systems can act as coordination centers that directionally position the ligands in specific spatial orientations. Also, depending on external conditions, metal ions allow the reversible assembly and disassembly of supramolecular aggregates and thus act as switching centers of the interaction.<sup>16</sup> The possibility of an additional interaction between receptor molecules and carboxyl groups of neutral “guests” is essential in the development of multicomponent supramolecular systems. Multicomponent nanoparticles may be employed in the construction of sensors, in biomimetic and drug delivery systems, as catalysts, as selective extractants, and in programmable materials.

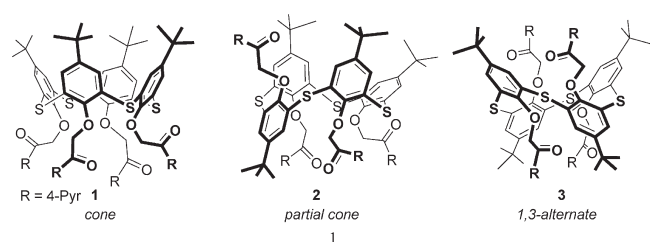
One of the popular molecular platforms for the design of molecular receptors is calix[*n*]arene.<sup>17–21</sup> The advantages of these host molecules includes the possibility of modifying the upper (replacement of *tert*-butyl group by the other fragments) and lower (hydroxyl groups) rim of the appropriate macrocyclic platform and the replacement of original methylene bridges between the aromatic units in calixarenes by sulfur atoms thus allowing for variations in receptor properties. This makes it possible to use them in the development of polytopic coreceptor molecules. The use of metal ions or neutral “guests” as noncovalent bridges allows regulation of

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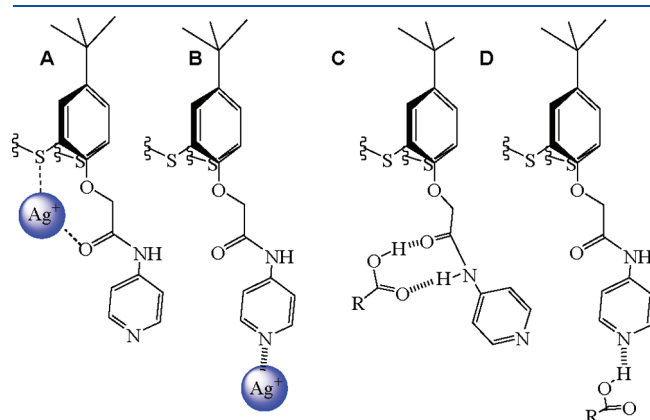
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the structure of self-assembling nanoscale components and materials.<sup>8,10,16</sup>



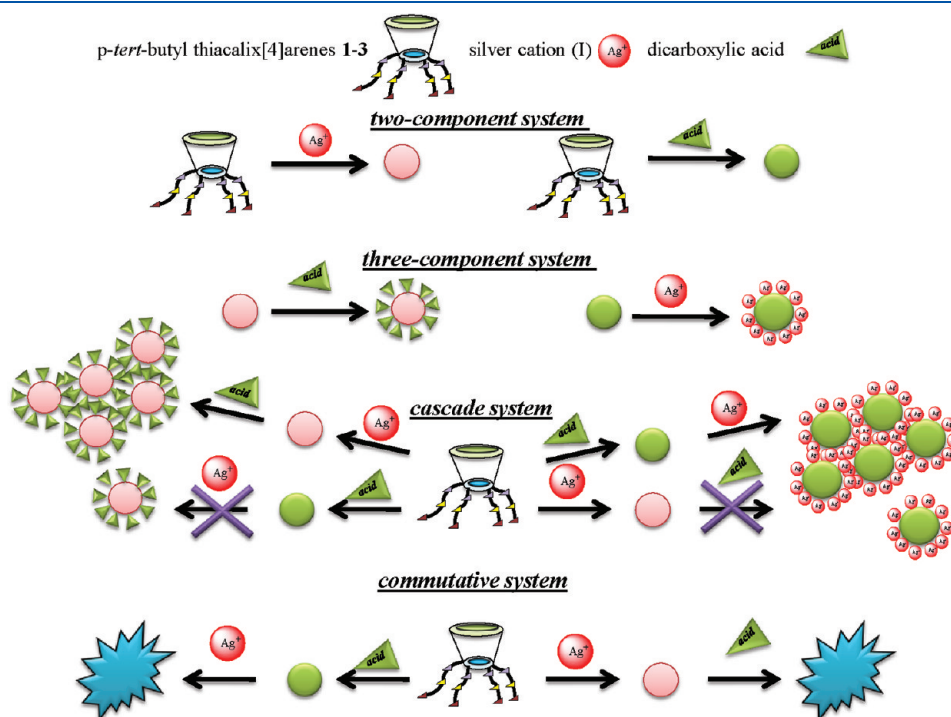
For the development of two- and three-component supramolecular systems based on the stereoisomers in cone, partial cone, and 1,3-alternate conformations of heteroditopic “host” molecules of *p*-*tert*-butyl thiacalix[4]arenes with metal cations and dicarboxylic acids, the use of macrocycles 1–3 was proposed.<sup>22</sup>



**Figure 1.** Possible coordination patterns of the cation (A, B) and acids (C, D) with conformational isomers of thiacalix[4]arenes 1–3.

These thiacalix[4]arene molecules are of great interest in that their structure contains potential coordination centers for both metal cations (bridging sulfur atoms, amide groups and nitrogen atoms of pyridine rings,<sup>23–29</sup> and carboxylic acids), amide functions, and heterocyclic fragments<sup>22,30–32</sup> (Figure 1). In the case of the formation of supramolecular aggregates based on thiacalix[4]arene molecules and silver nitrate, the type A (Figure 1) is more possible. Recently, it was shown<sup>24–27</sup> that thiacalix[4]arenes containing alkoxy, secondary, and tertiary amide fragments are able to form self-assemblies just like type A (Figure 1). Type B (Figure 1) is realized when no free coordination centers are available for further interacting with silver nitrate. The coordination patterns of carboxylic acids with thiacalix[4]arene molecules depend on the proton acceptor ability of receptor binding centers. In the case of thiacalix[4]arenes tetrasubstituted by amidopyridine fragment, the coordination of carboxylic acids by the nitrogen atom of heterocyclic fragments is the most preferred, like type D (Figure 1).

We suggested that the receptors 1–3 are capable of forming not only two-component systems (*p*-*tert*-butyl thiacalix[4]arene + metal cation/carboxylic acid) but also three-component systems ([*p*-*tert*-butyl thiacalix[4]arene + metal cation] + carboxylic acid, or [*p*-*tert*-butyl thiacalix[4]arene + carboxylic acid] + metal cation). The possibility of forming inter- or intramolecular coordination bonds between the receptor and substrate enables simple complexes as well as complex supramolecular systems—associates to be achieved. Depending on the sequence of substrate binding, three-component systems may be classified as commutative; it does not matter which of the substrates will bind in the first place, or cascade; the binding of multiple substrates must occur in a specific order (Figure 2). Obviously, the competition between the silver cation (I) and dicarboxylic acid for the binding sites (amidopyridine fragment) of thiacalix[4]arenes 1–3



**Figure 2.** Two- and three-component systems based on derivatives of *p*-*tert*-butyl thiacalix[4]arene.

can lead to cascade or commutative self-assemblies of nanoscale associates.

In this work, we describe the design of two- and three-component self-assembled supramolecular nanoparticles based on *p*-*tert*-butylthiacalix[4]arenes tetrasubstituted by amidopyridine fragment at the lower rim with silver nitrate and/or dicarboxylic acids. The study of the formation of such supramolecular systems was carried out by UV-titration, dynamic light scattering and atomic force microscopy.

## THE MOLECULAR RECOGNITION OF DICARBOXYLIC ACIDS AND SILVER CATION (I) BY *P*-*TERT*-BUTYL THIALIX[4]ARENE DERIVATIVES

To quantitatively determine the ability of the *p*-*tert*-butylthiacalix[4]arene derivatives to recognize silver ions, dicarboxylic and hydroxy acids, the stability constants, and the stoichiometry of the substrate/*p*-*tert*-butylthiacalix[4]arene complexes formed in the organic system methanol/dichloromethane (1:1) have been determined by UV spectroscopy (Table S1 in the Supporting Information).

Figure S1 in the Supporting Information shows the typical pattern of changes in the electronic spectra during the photometric titration of compound **3** with silver nitrate (I) (Figure S1A in the Supporting Information) and macrocycle **1** with oxalic acid (Figure S1B in the Supporting Information). By UV spectroscopy, it has been established that the interaction of *p*-*tert*-butylthiacalix[4]arene with AgNO<sub>3</sub> leads to a hyperchromic effect. During the titration of macrocycle **1** with oxalic acid, the absorption curves intersect each other at the isosbestic point at 254 nm. Thus, hyperchromic effect at 245 nm and hypochromic effect at 270 nm were observed during the titration.

As was expected, the stoichiometry of the formed associates, thiacalix[4]arene **1–3**, with “guests” (two-component system) depends on the macrocycle conformation which allows the “host” molecule to bind several substrates (Table S1 in the Supporting Information). Thus, in the case of cone stereoisomer, the interaction with silver cations is only possible on one side of the macrocyclic platform with the formation of 1:1 complexes. A similar stoichiometry with this substrate was also obtained for the partial cone stereoisomer, despite the fact that the binding fragments are located on both sides of the macrocyclic platform. The ratio (1:1) of substrate/*p*-*tert*-butylthiacalix[4]arene indicates that the single amidopyridine fragment located on one side of the macrocyclic platform cannot adequately bind to silver cations. However, in the case of 1,3-alternate stereoisomer, with two binding fragments located on both sides of the macrocycle, one receptor molecule is capable of binding two cations with a 2:1 stoichiometry.

Changing from the spherical silver cation (I) to dicarboxylic acid, the picture of molecular recognition by *p*-*tert*-butylthiacalix[4]arenes **1–3** significantly changes. The determining factor in the formation of such complexes is the possibility of hydrogen bond formation between proton donor or proton acceptor fragments of “guest” and “host”. The study of the interaction between dicarboxylic (oxalic, malonic, succinic, maleic, fumaric) and hydroxy acids (glycolic, tartaric acid) with stereoisomers **1–3** by UV spectroscopy showed that the efficiency of binding depends on the nature of substrates and receptor conformation. Thus, it has been shown that, for most of the complexes, the stoichiometry is 1:1 (Table S1 in the Supporting Information). However, different values of stoichiometric

coefficients 2:1 and 1:2 were obtained for a group of acids (Table S1 in the Supporting Information).

In the case of the cone stereoisomer (Table S1 in the Supporting Information), the 1:1 stoichiometry is exclusively characteristic of small dicarboxylic acids (oxalic, malonic, fumaric acid). The stability of the thiacalix[4]arene **1**/acid associates decreases in the series of acids: fumaric ( $\log K = 5.5$ ) > oxalic ( $\log K = 4.0$ ) > malonic ( $\log K = 3.0$ ). It should be noted that only in the case of maleic acid (fumaric acid isomer) is macrocycle **1** able to bind to two molecules of a “guest” (2:1 stoichiometry,  $\log K = 8.9$ ). Thiacalix[4]arene in cone conformation is able to form 1:2 associates with large-sized succinic and tartaric acids.

In the case of glycolic acid, the stoichiometry of thiacalix[4]arenes **1–3**/acid associates does not depend on the conformation of the macrocycle and equals 1:2. However, such low efficiency of interaction with glycolic acid containing one carboxyl group with the formation of dimers is also characteristic of the stereoisomers in partial cone **2** and 1,3-alternate **3** conformations.

It turned out that only the partial cone stereoisomer **2** is characterized to a great extent by the formation of 1:1 associates with the studied substrates. In the case of compound **2** (Table S1 in the Supporting Information), the stability of the 1:1 associates decreases with increasing the bridging alkylidene fragments in the series of acids: oxalic, malonic, succinic, and tartaric acid. During the transition to unsaturated dicarboxylic acids, the efficiency of interaction between “guests” and macrocycle **2** in partial cone conformation also decreases with increasing distance between the carboxyl groups of acids, from maleic acid to fumaric acid (Table S1 in the Supporting Information).

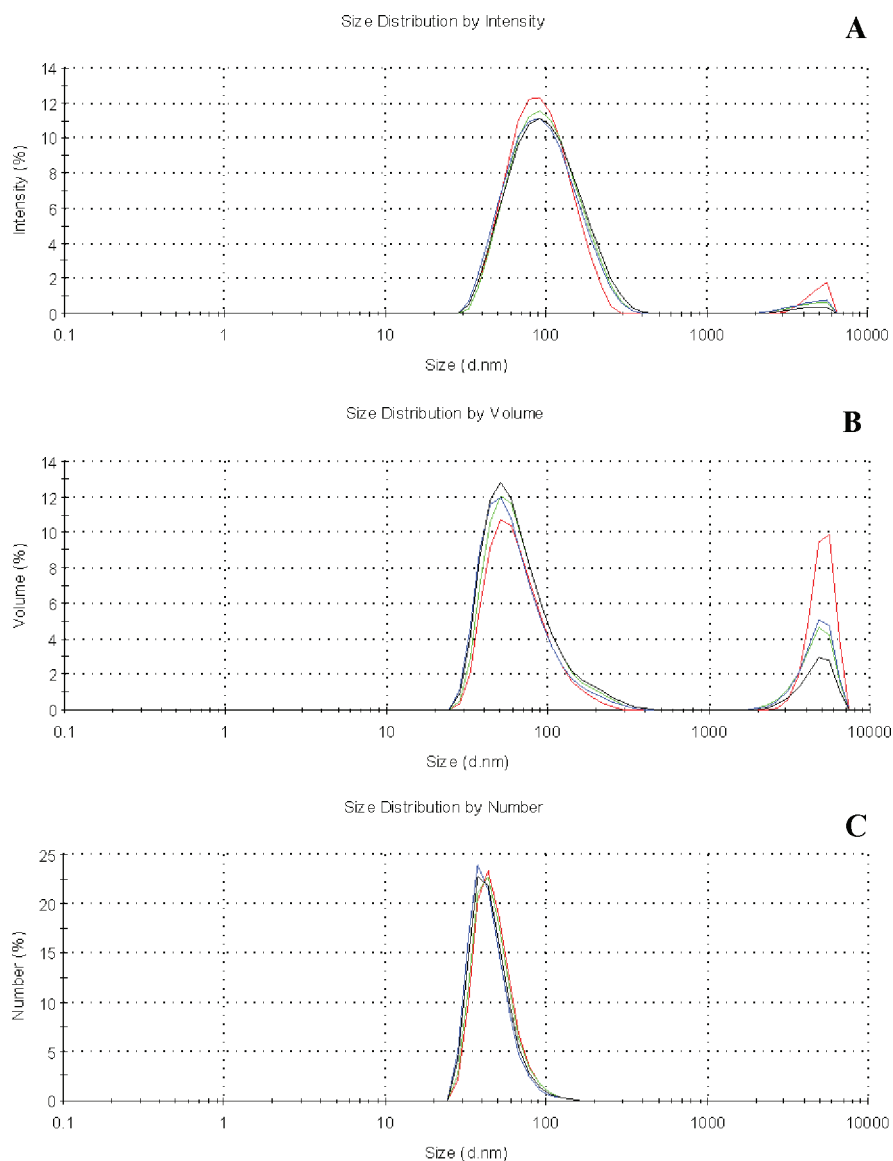
For 1,3-alternate stereoisomer **3** (Table S1 in the Supporting Information) as opposed to cone **1** and partial cone **2**, the constants of association with oxalic, tartaric, maleic, and fumaric acids are similar ( $\log K \approx 3.7$ , 1:1 stoichiometry).

The conformation of thiacalix[4]arenes significantly affects the efficiency of interaction with dicarboxylic acids. For associates with tartaric acid, the association constant increases in the range from partial cone to 1,3-alternate. The opposite tendency is observed for systems containing unsaturated dicarboxylic acids; for example, for maleic acid, the efficiency of binding decreases in the range from partial cone to 1,3-alternate, and for fumaric acid, from cone to partial cone and 1,3-alternate.

Thus, in some cases as shown in Table S1 in the Supporting Information, the obtained values of the association constants of *p*-*tert*-butylthiacalix[4]arenes **1–3** with Ag<sup>+</sup> and dicarboxylic acids are close to 4. The obtained results confirm that the macrocycles **1–3** are potentially capable of simultaneously interacting with silver ions (I) and the studied dicarboxylic acids.

## SELF-ASSEMBLY OF AGGREGATES CONSISTING OF *P*-*TERT*-BUTYL THIALIX[4]ARENES DERIVATIVES WITH SILVER NITRATE (I) AND DICARBOXYLIC ACIDS IN SOLUTION AND SOLID PHASE

Dynamic light scattering (DLS) is one of the methods used in the determination of particle size of supramolecular associates in solution.<sup>25–29</sup> Because the use of binary solvent mixtures of dichloromethane/methanol, as in the case of UV-titration, to determine the size of aggregates by DLS is not desirable,<sup>27</sup> the aggregation of thiacalix[4]arenes with silver cations and dicarboxylic and hydroxy acids was studied in dichloromethane. The measurement of hydrodynamic particle size and polydispersity index of the system was carried out 3 h after the solution was



**Figure 3.** Size distribution by intensity (A), volume (B), and number (C) for the system consisting of thiacalix[4]arene **1** in cone conformation and oxalic acid in CH<sub>2</sub>Cl<sub>2</sub>.

prepared at 20 °C. The kinetic stability of the systems was determined in repeated measurements under similar conditions after 3 and 78 h.<sup>25</sup>

For instances where nanoscale associates based on derivatives of *p*-*tert*-butyl thiacalix[4]arenes **1–3** and silver cations and also dicarboxylic acids were noted, a general tendency of increasing kinetic stability and, as a result, a decreasing polydispersity index of these systems were observed at different time intervals (Table S2 in the Supporting Information). The opposite dependence has been established for self-associates of macrocycle **1** in the cone conformation (Table S2 in the Supporting Information).

It is interesting to note that most systems are able to form several types of nanosized aggregates (Table S2 in the Supporting Information). Thus, a bimodal size distribution in intensity units is shown in Figure S1A in the Supporting Information for the two-component system. However, the transformation of the above distribution from intensity into volume and quantity distributions by Mie theory<sup>33</sup> showed unimodal distribution with

the mode being less than the smallest value of the hydrodynamic diameter (Figure 3B, C). Hence, nanoscale aggregates dominate (Figure 3B, C). However, the most significant is the analysis of particle size for all systems in intensity units, measured after 78 h (Table S2 in the Supporting Information).

Previously, self-association of macrocycles **1–3** was studied. It was shown that only macrocycle **1** in cone conformation, containing four ligating groups located on the same side of the macrocycle platform, formed aggregates with a hydrodynamic diameter of about 69 nm (Table S2 in the Supporting Information).

The aggregation of stereoisomers of *p*-*tert*-butyl thiacalix[4]arenes with silver cations and dicarboxylic and hydroxy acids has been studied in CH<sub>2</sub>Cl<sub>2</sub> by dynamic light scattering.

It has been shown that *p*-*tert*-butyl thiacalix[4]arenes **1–3** containing 4-amidopyridine fragments are able to form nanosized particles with silver cations and acids, except the following systems: cone **1** and tartaric acid, partial cone **2** and succinic acid, 1,3-alternate **3** and tartaric acid, maleic acid. Thus, aggregation

was impossible for systems containing larger size acids (Table S2 in the Supporting Information). This corresponds well with the values of the association constants of *p*-*tert*-butyl thiacalix[4]arenes **1**–**3** with dicarboxylic acids (Table S1 in the Supporting Information).

In the case of macrocycle **1** in cone conformation with silver cations and fumaric acid, besides the 59–378 nm particles, aggregates with hydrodynamic diameters of 7.8 and 9.1 nm, respectively, were also found (Table S2 in the Supporting Information). Furthermore, only in this case does increasing acid size lead to an increase in hydrodynamic diameter in the series of acids: glycolic acid, oxalic acid, succinic acid, maleic acid, fumaric (second type of particle, 378 nm) except for malic acid, which is able to form particles of about 186 nm with macrocycle **1**.

For partial cone **2** stereoisomer, aggregates with the smallest size were formed by the interaction with silver cations, 63 nm

**Table 1. Structural Fragment Quantity (*N*), Molecular Weight (MW, kDa), and Second Virial Coefficient (*A*<sub>2</sub>, mL mol/g<sup>2</sup>) of the Aggregates in the System Consisting of *p*-*tert*-Butyl Thiacalix[4]arene derivatives **1**–**3**, Silver Cations (I), and Oxalic and Succinic Acids<sup>a</sup>**

system	MW, kDa	<i>A</i> <sub>2</sub> , mL mol/g <sup>2</sup>	<i>N</i>
cone <b>1</b>	40.65 ± 9.56	0.550 ± 0.640	32.3
cone <b>1</b> + AgNO <sub>3</sub>	4225.00 ± 260.50	0.003 ± 0.001	
cone <b>1</b> + oxalic acid	41.30 ± 38.30	4.050 ± 22.80	30.6
cone <b>1</b> + succinic acid	33.65 ± 2.70	−0.503 ± 0.272	24.2
partial cone <b>2</b> + AgNO <sub>3</sub>	510.50 ± 33.60	0.014 ± 0.009	
partial cone <b>2</b> + oxalic acid	1405.00 ± 382.00	0.080 ± 0.020	1042.6
partial cone <b>2</b> + tartaric acid	9.77 ± 2.26	−2.26 ± 2.31	6.9
1,3-alternate <b>3</b> + AgNO <sub>3</sub>	2080.00 ± 522.50	0.144 ± 0.023	
1,3-alternate <b>3</b> + oxalic acid	3335.00 ± 116.75	0.010 ± 0.001	2474.7
1,3-alternate <b>3</b> + succinic acid	19.65 ± 3.48	−3.190 ± 1.160	14.1

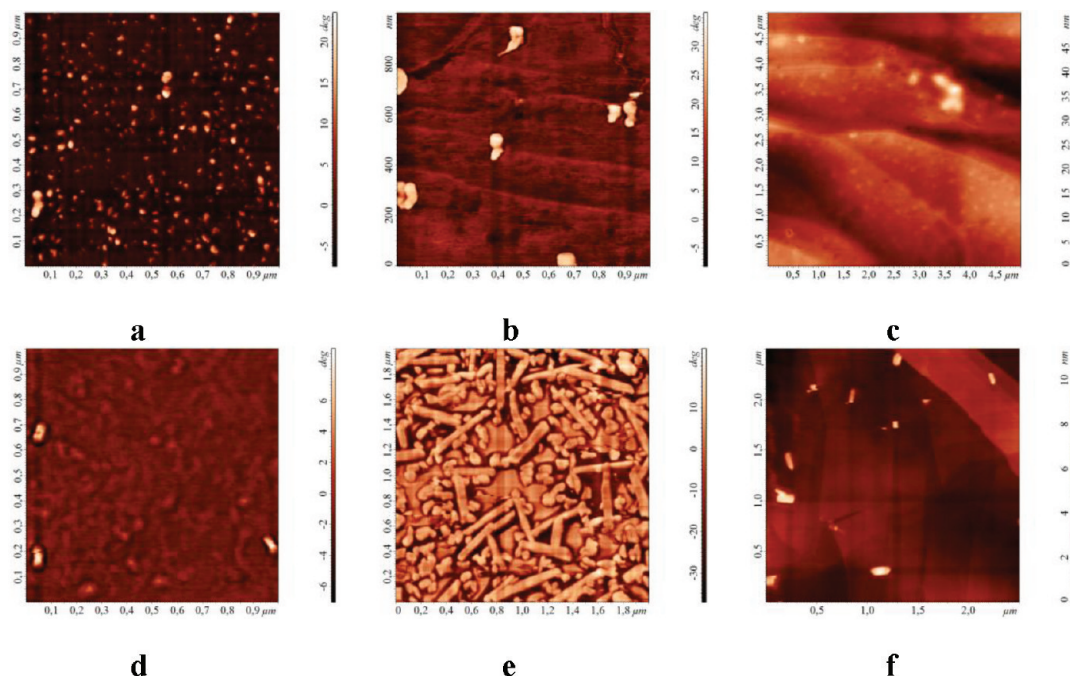
<sup>a</sup> ±, standard deviation of experiments.

and with oxalic acid, 100 nm (Table S2 in the Supporting Information). It should be noted that, as in the case of the macrocycle in cone conformation, the size of the associates based on partial cone **2** stereoisomer increases with the increase in acid size in the range oxalic, maleic, tartaric, and fumaric acids, and for the macrocycle in 1,3-alternate **3** conformation, in the range oxalic, succinic, and fumaric acids (Table S2 in the Supporting Information).

It is interesting to note that in the series of stereoisomers 1,3-alternate **3**, partial cone **2**, and cone **1**, the formation of nanosized particles with only silver cations and fumaric acid leads to decreasing aggregate size (Table S2 in the Supporting Information).

Molecular weights of aggregates formed by macrocycles **1**–**3** with silver nitrate (I) and oxalic, succinic, and tartaric acids were determined by static light scattering (Table 1). From Table S2 in the Supporting Information (hydrodynamic size) and Table 1 (molecular weight), the formation of supramolecular aggregates with a more dense packing occurs only in the case of silver nitrate (I) and oxalic acid. The stoichiometric ratio (*n* (“guest”/“host”)) equals 1:1,<sup>22</sup> and the molecular weights of nanoscale particles (Table 1) allows the estimation of the number of receptor and substrate molecules involved in the formation of the supramolecular associate. It has been shown that the number of molecules of *p*-*tert*-butyl thiacalix[4]arenes, involved in the formation of supramolecular aggregates, decreases in the range from oxalic to succinic and tartaric acids. The negative values of the second virial coefficient (*A*<sub>2</sub>, mL mol/g<sup>2</sup>) indicating the ability to form aggregates for systems containing macrocycles **1**, **3** and succinic acid and also compounds **2** and tartaric acid were determined (Table 1).

The shape of nanoscale particles based on *p*-*tert*-butyl thiacalix[4]arenes **1**–**3** with silver nitrate (I) and oxalic acid has been determined by atomic force microscopy (Figure 4). It has been shown that the formation of particles with different shapes depends on the conformation of macrocycles. It should be noted that the particles formed by silver nitrate (I) and macrocycle **1**–**3**

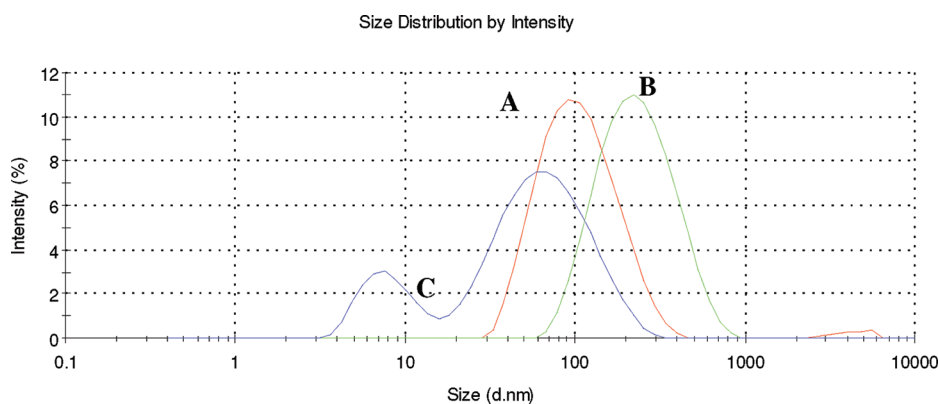


**Figure 4.** AFM images of *p*-*tert*-butyl thiacalix[4]arenes **1** (a), **2** (b), **3** (c) with silver nitrate(I), and **1** (d), **2** (e), **3** (f) with oxalic acid.

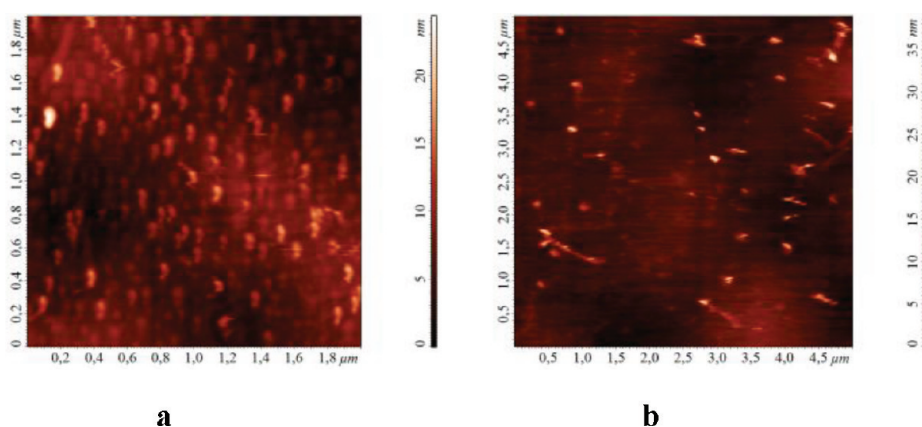
**Table 2. Size of Aggregates (Average Hydrodynamic Diameters,  $d_1$ ,  $d_2$ ,  $d_3$  (nm)), Peak Area Intensity,  $S_1$ ,  $S_2$ ,  $S_3$  (%), for Peaks 1, 2, 3, Respectively, Obtained with p-tert-Butyl Thiacalix[4]arene Derivatives 1–3 and Silver Cations, Dicarboxylic Acids in  $\text{CH}_2\text{Cl}_2$  (HPLC), and Polydispersity Index (PDI) Measured 3 and 78 h after Solution Preparation<sup>a</sup>**

systems	$d_1$ , nm/ $S_1$ , %		$d_2$ , nm/ $S_2$ , %		$d_3$ , nm/ $S_3$ , %		PDI	
	3 h	78 h	3 h	78 h	3 h	78 h	3 h	78 h
[1+AgNO <sub>3</sub> ] <sub>agr.</sub> + oxalic acid	11.3 ± 2.4/ 16.5 ± 2.4	14.7 ± 4.2/ 14.3 ± 7.9	75.9 ± 18.1/ 83.5 ± 2.4	82.2 ± 6.8/ 85.8 ± 7.9	—	—	0.34 ± 0.25	0.36 ± 0.07
[1+AgNO <sub>3</sub> ] <sub>agr.</sub> + succinic acid	12.1 ± 2.2/ 10.9 ± 2.2	13.1 ± 2.0/ 12.9 ± 4.6	89.2 ± 26.6/ 86.8 ± 5.2	88.8 ± 15.0/ 87.1 ± 4.6	4237.5 ± 2115.5/ 2.3 ± 4.6	—	0.33 ± 0.19	0.39 ± 0.20
[3+ fumaric acid] <sub>agr.</sub> + AgNO <sub>3</sub>	—	8.6 ± 2.7/ 19.2 ± 6.9	104.7 ± 15.8/ 100	77.0 ± 4.3/ 80.8 ± 6.9	—	—	0.25 ± 0.03	0.47 ± 0.02
[2+AgNO <sub>3</sub> ] <sub>agr.</sub> + malonic acid	—	10.8 ± 6.4/ 5.3 ± 6.6	109.0 ± 3.5/ 100	107.8 ± 43.8/ 93.9 ± 7.0	—	4934.0 ± 369.5/ 0.8 ± 1.3	0.10 ± 0.01	0.32 ± 0.14
[2+ malonic acid] <sub>agr.</sub> + AgNO <sub>3</sub>	—	—	170.9 ± 3.5/ 100	168.3 ± 13.5/ 100	—	—	0.06 ± 0.02	0.11 ± 0.03
[3+AgNO <sub>3</sub> ] <sub>agr.</sub> + oxalic acid	—	4.1 ± 2.7/ 11.2 ± 11.1	93.8 ± 54.3/ 92.3 ± 5.9	72.1 ± 9.8/ 87.1 ± 10.4	4724.0 ± 937.2/ 7.7 ± 5.9	4186.7 ± 708.9/ 1.7 ± 2.3	0.34 ± 0.17	0.43 ± 0.07
[3+ oxalic acid] <sub>agr.</sub> + AgNO <sub>3</sub>	—	—	99.5 ± 8.6/ 100	125.7 ± 3.9/ 100	—	—	0.09 ± 0.04	0.13 ± 0.03
[3+AgNO <sub>3</sub> ] <sub>agr.</sub> + malonic acid	—	—	168.9 ± 4.4/ 100	185.1 ± 14.8/ 100	—	—	0.13 ± 0.02	0.13 ± 0.03
[3+ malonic acid] <sub>agr.</sub> + AgNO <sub>3</sub>	—	—	178.9 ± 7.3/ 100	184.2 ± 11.2/ 100	—	—	0.05 ± 0.01	0.13 ± 0.03

<sup>a</sup> ±, standard deviation; —, no aggregates are formed.



**Figure 5.** Size distribution by intensity for the system formed by (A) macrocycle **3** and silver nitrate (I), (B) macrocycle **3** and fumaric acid, and (C) supramolecular associates (compound **3** and fumaric acid) and silver nitrate (I) in  $\text{CH}_2\text{Cl}_2$ .



**Figure 6.** AFM images of three-component systems: (a) obtained due to interaction of nanoscale particles based on macrocycle **3** and silver nitrate (I) with oxalic acid, and (b) due to the interaction of aggregates based on macrocycle **3** and oxalic acid with silver nitrate (I).

are spherical or ellipsoidal, and supramolecular associates based on compounds **1–3** with oxalic acid are elongated particles.

Thus, it has been shown that *p-tert*-butyl thiacalix[4]arenes **1–3**, containing substituents with different coordination centers, are able to form nanoscale aggregates with silver nitrate (I) and dicarboxylic acids. Obviously, compounds **1–3** are prospective supramolecular building blocks for the development of cascade or commutative three-component systems.

### 3. THREE-COMPONENT SYSTEMS BASED ON NANOSCALE AGGREGATES FORMED BY *P-tert*-BUTYL THIALIX[4]ARENES TETRASUBSTITUTED AT THE LOWER RIM WITH DICARBOXYLIC ACIDS AND SILVER NITRATE (I)

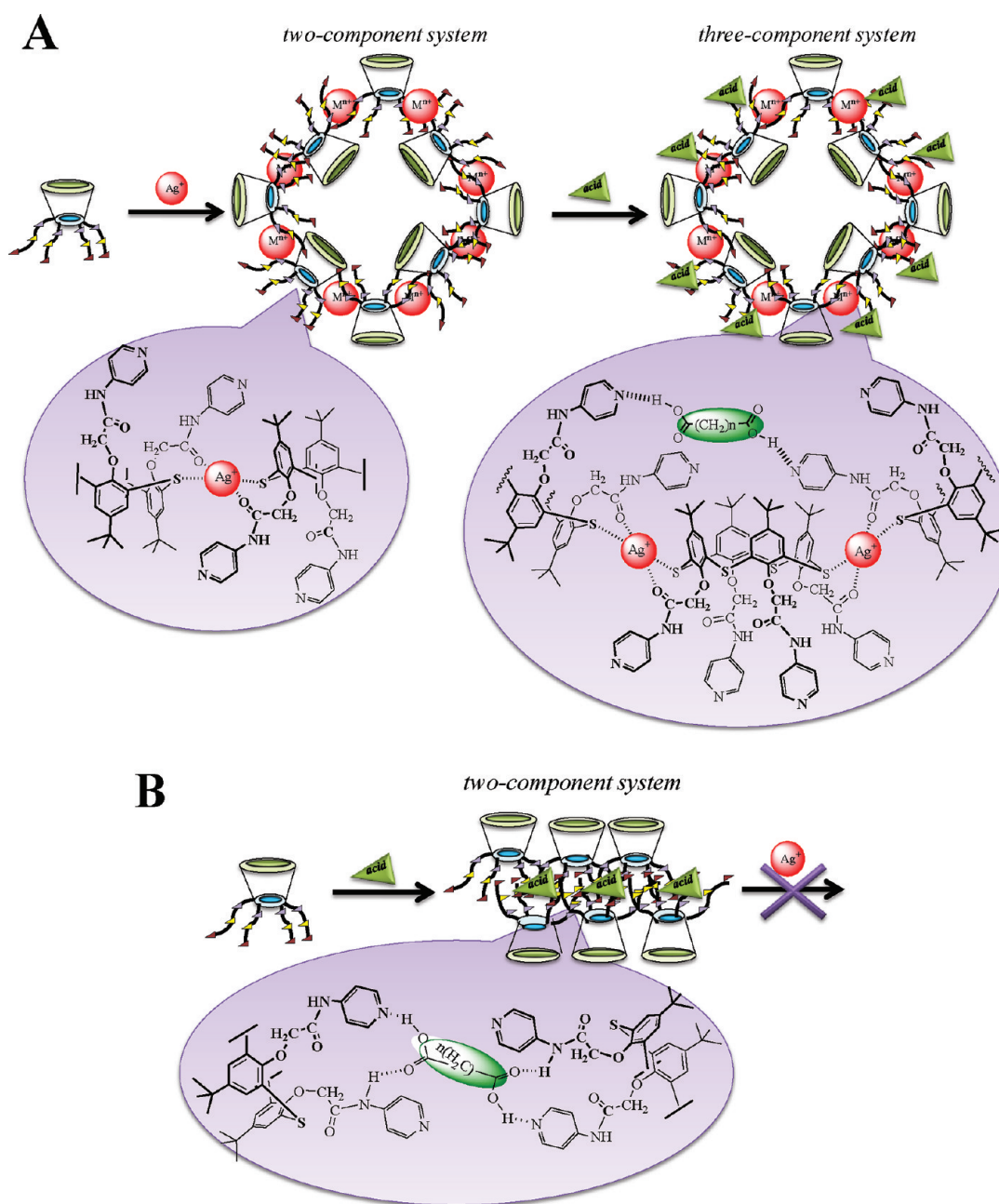
The ability of nanoscale particles (two-component systems) to interact with a third component (silver nitrate or carboxylic acid) for the development of three-component cascade or commutative systems was studied. The change in the hydrodynamic particle size due to the introduction of a third component into the supramolecular assemblies (*p-tert*-butyl thiacalix[4]arenes +  $\text{AgNO}_3$  or carboxylic acid) has been demonstrated by dynamic light scattering. It confirms the formation of three-component systems.

By the change in the hydrodynamic size of particles resulting from the interaction of two-component systems with a third component, the type of three-component system (cascade or

commutative) can be determined. For example, during the interaction of macrocycle **3** with silver nitrate (I) and fumaric acid in dichloromethane, nanoscale particles with hydrodynamic size of about 108.9 and 261.7 nm, respectively, are formed (Table 2, Figure 5). The interaction of supramolecular associates (compound **3** and fumaric acid) with silver nitrate (I) leads to a decrease in the particle size to 77.0 nm (Table 2, Figure 5). However, during the interaction of supramolecular assemblies (compound **3** and silver nitrate (I)) with fumaric acid, a change in the hydrodynamic diameter of nanoparticles is not observed (Table 2). Thus, this is a cascade system.

For commutative systems, the interaction of supramolecular assemblies (*p-tert*-butyl thiacalix[4]arenes and silver nitrate (I) or *p-tert*-butyl thiacalix[4]arenes and dicarboxylic acid) with their respective substrates leads to the formation of three-component nanoscale particles with the same size (Table 2). For example, the hydrodynamic diameter of supramolecular assemblies ([macrocycle **3** + malonic acid] +  $\text{AgNO}_3$ ) and ([macrocycle **3** +  $\text{AgNO}_3$ ] + malic acid) does not depend on the sequence of binding of substrates and is about 185 nm.

In addition to the cascade and commutative systems, intermediate systems exist, in which during the interaction of nanoscale particles (*p-tert*-butyl thiacalix[4]arenes and silver nitrate (I) or *p-tert*-butyl thiacalix[4]arenes and carboxylic acid) with their respective substrates two three-component systems of nanoscale aggregates with various sizes are formed (Table 2). For example,



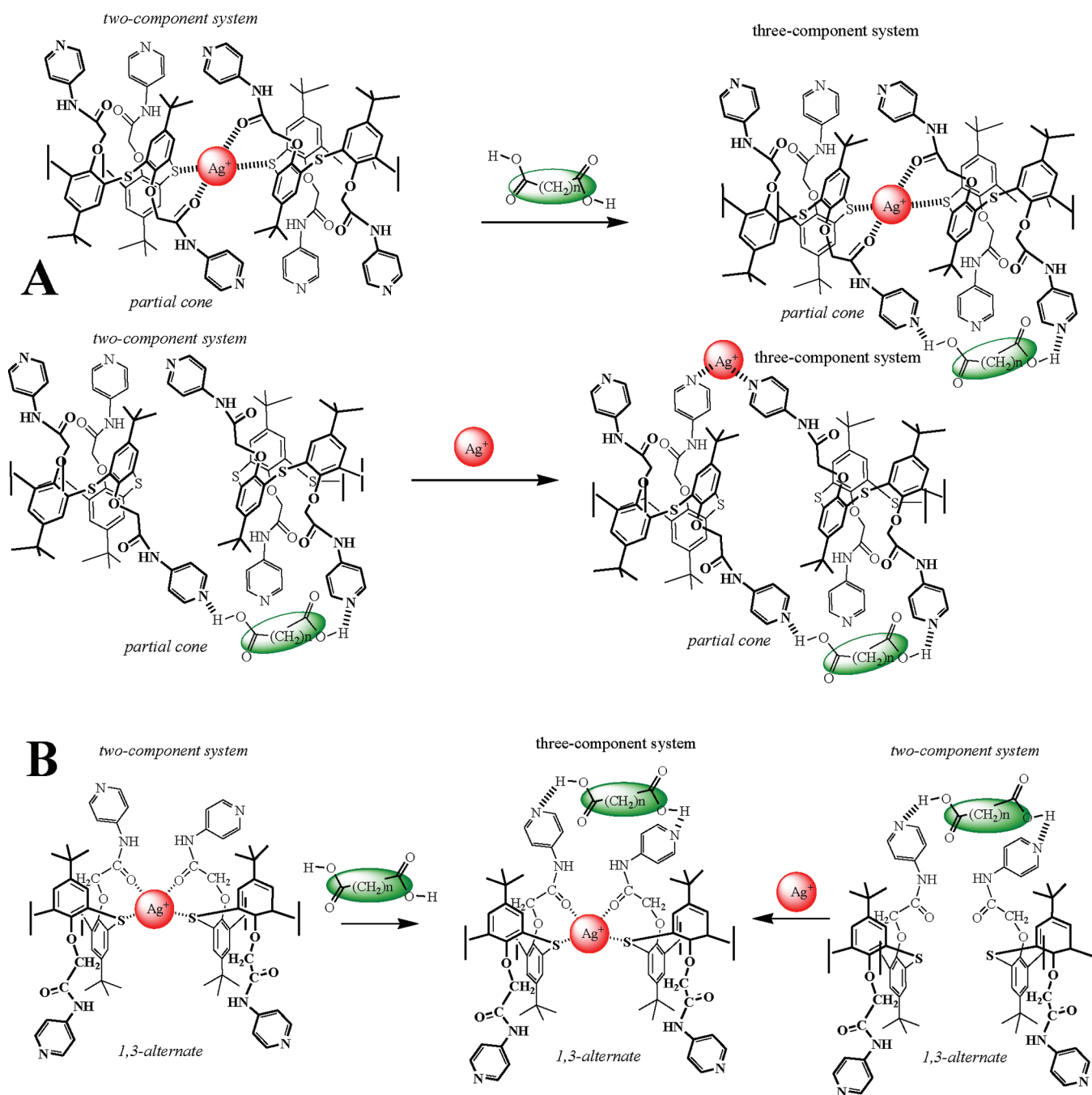
**Figure 7.** Possible ways of forming two- and three-component systems: (A) obtained due to interaction of nanoscale particles based on macrocycle 1 and silver nitrate (I) with dicarboxylic acids, and (B) due to the interaction of macrocycle 1 with dicarboxylic acids.

the hydrodynamic diameter of particles ([macrocycle 2 + malonic acid] + AgNO<sub>3</sub>) is 168.3 nm, and in the case of system ([macrocycle 2 + AgNO<sub>3</sub>] + malic acid) the particle size equal to 107.8 nm.

By atomic force microscopy, it has been shown that the formed intermediate systems based on macrocycle 3 differ not only in size but also in shape (Figure 6). Thus, the first three-component system obtained by the interaction of nanoscale particles based on *p*-*tert*-butyl thiacalix[4]arenes 3 and silver nitrate (I) with oxalic acid is an oval nanoscale aggregate (Figure 6a), while the other three-component systems obtained by the interaction of aggregates based on *p*-*tert*-butyl thiacalix[4]arenes 3 and oxalic acid with silver nitrate (I) are elongated rodlike particles (Figure 6b).

It should be noted that the conformation of the macrocycle has significant influence on the type of three-component system formed: cone is characterized by the formation of cascade systems; for partial cone, intermediate systems; and for 1,3-alternate stereoisomers, three types of three-component systems (cascade, intermediate, and commutative) were observed. We assume that as a result of the formation of two-component systems involving silver nitrate and cone-1 which has been tetrasubstituted by 4-amidopyridine fragments located on the same side of the macrocyclic platform, heterocyclic fragments capable of further interacting with dicarboxylic acids are present on the surface of the assemblies (Figure 7A). In the case of formation of two-component systems based on dicarboxylic acids





**Figure 8.** Possible ways of forming (A) intermediate three-component system based on macrocycle 2, silver nitrate (I), and dicarboxylic acids and (B) commutative system based on macrocycle 3, silver nitrate (I), and dicarboxylic acids.

and cone-1, the surface of nanoparticles has no coordination centers capable of interacting with silver nitrate and hence the formation of three-component systems does not occur (Figure 7B).

For partial cone-2 and 1,3-alternate-3 stereoisomers, 4-amidopyridine fragments are located on both sides of the macrocyclic platform; hence, irrespective of the mode of coordination and nature of substrate, the formation of two-component systems with additional coordination centers on the surface of nanoparticles is observed (Figure 8). Thus, it is possible to form three-component supramolecular assemblies (Figure 8). However, depending on the nature of the substrate (dicarboxylic acid) and the mode of coordination, it is possible to form cascade,

intermediate, and commutative systems. It should be noted that the interaction of nanoparticles with a third component in most cases leads to changes in structure (packing) of the aggregates, and hence, a change in size and shape is observed. If during the formation of three-component systems different coordination nodes are formed, then the aggregates will have varying structures, as it happens in the case of intermediate systems (Figure 8A).

To determine positive or negative allosteric effect during the formation of three-component systems in the complex solvent dichloromethane/methanol (1:1), the effectiveness of interaction of nanoscale aggregates (two-component systems) with appropriate

**Table 3. Logarithms of the Association Constants ( $\log K_{\text{ass}}$ ) and Stoichiometry of ( $n$  ("guest"/"host")) Nanoscale Aggregates Based on Compounds 1–3 and Silver Ions (I), Dicarboxylic Acids<sup>a</sup>**

systems	$n$	$\log K_{\text{ass}}$
[1+AgNO <sub>3</sub> ] <sub>agr.</sub> + oxalic acid <sup>a</sup>	0.5 ± 0.1	1.03 ± 0.30
[1+AgNO <sub>3</sub> ] <sub>agr.</sub> + succinic acid <sup>a</sup>	1.8 ± 0.04	6.99 ± 0.19
[2+AgNO <sub>3</sub> ] <sub>agr.</sub> + malonic acid <sup>c</sup>	1.0 ± 0.1	3.58 ± 0.43
[2+ malonic acid] <sub>agr.</sub> +AgNO <sub>3</sub> <sup>c</sup>	1.1 ± 0.1	4.05 ± 0.59
[3+ fumaric acid] <sub>agr.</sub> +AgNO <sub>3</sub> <sup>a</sup>	2.1 ± 0.1	9.64 ± 0.53
[3+AgNO <sub>3</sub> ] <sub>agr.</sub> + oxalic acid <sup>c</sup>	1.2 ± 0.04	5.03 ± 0.21
[3+ oxalic acid] <sub>agr.</sub> +AgNO <sub>3</sub> <sup>c</sup>	0.5 ± 0.1	2.10 ± 0.23
[3+AgNO <sub>3</sub> ] <sub>agr.</sub> + malonic acid <sup>b</sup>	1.2 ± 0.1	5.24 ± 0.39
[3+ malonic acid] <sub>agr.</sub> +AgNO <sub>3</sub> <sup>b</sup>	1.1 ± 0.2	3.74 ± 0.75

<sup>a</sup> Cascade systems. <sup>b</sup> Commutative systems. <sup>c</sup> Intermediate systems.

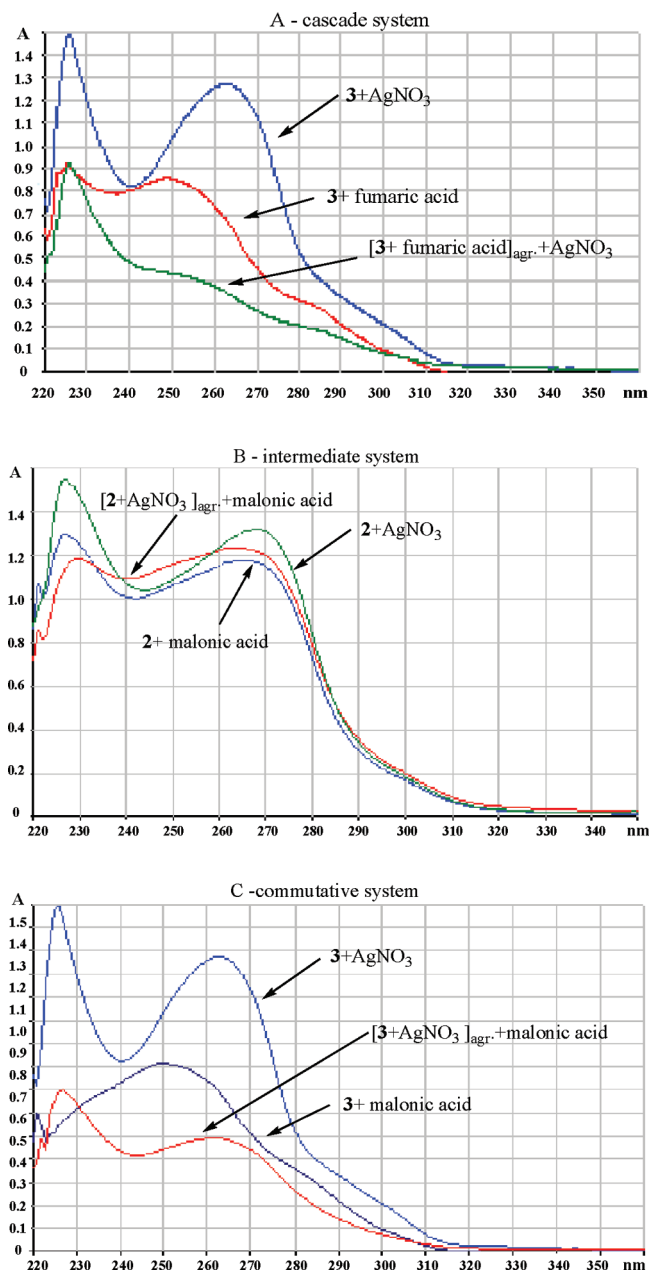
substrates, dicarboxylic acid and silver nitrate (I), were determined by UV–visible spectroscopy (Table 3).

Figure 9 shows UV spectra of two- and three-component cascade [macrocycle 3 + fumaric acid]<sub>agr.</sub>+ AgNO<sub>3</sub> (Figure 9A), intermediate [macrocycle 2 + AgNO<sub>3</sub>]<sub>agr.</sub>+ malonic acid (Figure 9B), and commutative [macrocycle 3 + AgNO<sub>3</sub>]<sub>agr.</sub>+ malonic acid (Figure 9C) systems. The intensity of the absorption bands decreases due to the formation of three-component cascade and commutative systems; that is, hypochromic effect is observed. In the case of the intermediate system, the absorption band increases at 250 nm and decreases at 230 nm.

It has been shown that comparing the efficiency of interaction of nanoscale associates (*p-tert*-butyl thiacalix[4]arenes + dicarboxylic acid) and (*p-tert*-butyl thiacalix[4]arenes + AgNO<sub>3</sub>) with a third component, in the latter case, the  $\log K_{\text{ass}}$  decreased, indicating negative allosteric effect. However, the interaction of supramolecular aggregates (compound 1 - silver nitrate (I)) as compared to *p-tert*-butyl thiacalix[4]arenes 1 with succinic acid leads to an increase in the stoichiometric coefficients i.e. increase in the number of interacting particles thus indicating a positive allosteric effect (Table 3).

## CONCLUSION

Thus, new self-assembled supramolecular associates based on functionalized *p-tert*-butyl thiacalix[4]arenes were obtained as cascade or commutative systems. It has been demonstrated that *p-tert*-butyl thiacalix[4]arenes 1–3 containing several potential coordination centers for both metal cations (bridging sulfur atoms, oxygen atoms oxymethylene fragments, amide groups and nitrogen atoms of heterocycles) and carboxylic acids (protons of amide groups and heterocyclic fragments) are coreceptors capable of simultaneously interacting with both silver nitrate (I) and dicarboxylic acids. Depending on the sequence of substrate binding by macrocycle 1–3, three-component systems have been described as a cascade or commutative. Moreover, depending on the type of three-component system (the nature of the components; cation, carboxylic acids), their formation may be accompanied by either positive or negative allosteric effects. Using macrocycles 1–3 as examples, it has been demonstrated that the conformation of *p-tert*-butyl thiacalix[4]arenes significantly affect the type of three-component system formed: cone is characterized by the formation of cascade systems; for partial cone, intermediate



**Figure 9.** UV spectra ( $10^{-5}$  mol L<sup>-1</sup>, 1 cm cell) of three-component systems: (A) cascade system [p-tert-butyl thiacalix[4]arene 3 + fumaric acid]<sub>agr.</sub>+ AgNO<sub>3</sub>, (B) intermediate system [p-tert-butyl thiacalix[4]arene 2 + AgNO<sub>3</sub>]<sub>agr.</sub>+ malonic acid, and (C) commutative system [p-tert-butyl thiacalix[4]arene 3 + AgNO<sub>3</sub>]<sub>agr.</sub>+ malonic acid in complex solvent dichloromethane/methanol.

systems; and for the 1,3-alternate stereoisomers, three types of three-component systems (cascade, intermediate, and commutative) are observed. By the method of UV spectroscopy, it has been shown that the formation of three-component systems may occur with negative or positive allosteric effects.

## EXPERIMENTAL SECTION

**Determination of the Stability Constant and Stoichiometry of the Complex by UV Titration.** UV–vis spectra were recorded by using a Perkin Elmer Lambda-35 spectrometer; the cell

thickness was 1 cm. A  $10^{-2}$  M solution of silver nitrate and carboxylic acid (oxalic, malonic, succinic, glycolic, tartaric, maleic, fumaric acids) (0.3, 0.6, 0.9, 1.3, 1.5, 1.7, 2.0 mL) in methanol was added to 2 mL of the solution of receptor 1–3 or nanoparticles based on macrocycles 1–3 and substrates in dichloromethane. The volume was brought to 4 mL with methanol, while the concentration of *p*-*tert*-butyl thiacalix[4]arene tetrasubstituted with the amidopyridine fragment ( $10^{-5}$  mol L $^{-1}$ ) remained constant. The UV spectra of the obtained solutions were then recorded. Three independent experiments were carried out for each series. Student's *t* test was used in statistical data processing.

**Dynamic Light Scattering (DLS).** The particle sizes were determined by using a Zetasizer Nano ZS instrument at 20 °C. The instrument contains a 4 mW He–Ne laser operating at a wavelength of 633 nm and incorporates noninvasive backscatter optics (NIBS). The measurements were performed at a detection angle of 173°, and the measurement position within the quartz cuvette was automatically determined by the software. Results were processed with the DTS (Dispersion Technology Software 4.20) software package.

The solutions of the investigated systems were prepared by addition of 1000 excess of silver nitrate or carboxylic acid (oxalic, malonic, succinic, glycolic, tartaric, maleic, fumaric acids) to 10 mL of  $10^{-5}$  M solution of thiacalixarene derivatives 1–3 or nanoparticles based on macrocycles 1–3 and substrates in CH<sub>2</sub>Cl<sub>2</sub> (HPLC). The mixture was mechanically shaken for 3 h and then magnetically stirred in a thermostatted water bath at 20 °C for 1 h. Three independent experiments were carried out for each combination of a ligand and metal nitrate. Student's *t* test was used in statistical data processing.

**Static Light Scattering (SLS).** For the determination of molecular weight of supramolecular associates, a series of solutions in CH<sub>2</sub>Cl<sub>2</sub> (HPLC) with various concentration of *p*-*tert*-butyl thiacalix[4]arene derivatives 1–3 and silver nitrate or carboxylic acid (oxalic, succinic, tartaric acids) were prepared at 20 °C. The solvent scattering was then measured for the various concentrations of sample. From these measurements, a Debye plot was generated. This is a plot of the variation in average intensity versus the concentration. The intercept of the extrapolation to zero concentration was calculated. Three independent experiments were carried out for each system.

**Atomic Force Microscopy (AFM).** Imaging was carried out using a Solver P47 AFM (NT-MDT, Russia) instrument equipped with a tube scanner, in tapping mode, using NSG-11 cantilevers with silicon probes (force constant: 5–22 N/m) at a scan frequency of 0.7 Hz. Images were processed with the NT-MDT software package.

The solutions of the investigated systems were prepared by addition of 1000 excess of silver nitrate or oxalic acid to 10 mL of  $10^{-5}$  M solution of thiacalixarene derivatives 1–3 or nanoparticles based on macrocycles 1–3 and substrates in CH<sub>2</sub>Cl<sub>2</sub> (HPLC). The mixture was mechanically shaken for 3 h and then magnetically stirred in a thermostatted water bath at 20 °C for 1 h.

## ■ ASSOCIATED CONTENT

Supporting Information. Tables S1–S2. Figure S1. The detailed experimental results for the determination of the association constants between the hosts and the guests and Student's *t* test. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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