Modeling K+ and Ag+ Complexation by Thiacalix[4]arene Amides Using DFT: The Role of Intramolecular Hydrogen Bonding

Liliya I. Shamova,*,† Grigory A. Shamov,‡ Igor S. Antipin,† and Alexandr I. Konovalov†,‡

A. M. Butlerov Chemical Institute, Kazan State University, Kremlevskaya Street, 18, 420008 Kazan, Russian Federation, and Kazan Scientific Centre of the Russian Academy of Sciences, Lobachevskogo Street, 2, 420111 Kazan, Russian Federation

Complexation of methyl-glycine-amide functionalized thiacalix[4]arene with K+ and Ag+ has been studied using density functional theory (DFT) in the gas phase. To account for the conformational possibilities of the ligand, the free ligand and its potassium complexes were subjected to global minima searches on the molecular mechanics (MM) level of theory with the OPLS (optimized potentials for liquid simulations) force field. For the free ligand, the order of the energies and geometries of the ligand conformers is in agreement between MM and DFT; however, the position of K+ in the ligand's cavity was predicted differently by these methods. Hydrogen bonding of amide hydrogens in the ligands' podand arms was found to take place predominantly with the ether oxygens of the same arm rather than the other arms' carbonyls. According to DFT calculations, the silver cation preferred to coordinate with one sulfur bridge and three carbonyl groups, whereas potassium cation favored interaction with the four carbonyl oxygens of the podand amide arms. Neither cation preferred the N-mode of coordination. For all obtained conformers, intramolecular hydrogen bonds disfavor complexation, increasing the preorganizational energy to be paid.

Introduction

Thiacalixarenes are a modification of classic calixarenes in which methylene bridges between aromatic rings are substituted by sulfur atoms.[1] The most appealing property of these compounds, whose synthesis and modification protocols have been developed extensively during the past decade, is their enhanced ability to metal complexes formation due to the presence of sulfur atoms. Even unsubstituted thiacalix[4]arene, unlike its classic calix[4]arene counterpart, demonstrates significant binding ability toward a large number of transition metal ions.[2] As their classical analogues, the thiacalix[4]arenes exist in four conformations: cone, partial cone (paco), 1,2-alternate, and 1,3-alternate, which are shown in Scheme 1. For unfunctionalized calixarenes, these conformers interconvert into each other; however, their mutual interconversion is suppressed when the substituents on the lower rim are larger than ethyl.[1] Conformational behavior and resulting spatial structure of substituted and unsubstituted thiacalixarenes strongly affect their complex formation ability.[2]

Calixarenes containing pendant carbonyl groups have been well-established as being selective for alkali metal ions with calix[4]arene esters, ketones, and amides showing a strong preference for sodium.[3] However, the introduction of a sulfur atom in the calix[4]arene macrocycle switched the selectivity of this host from alkali toward transition metal ions, for example, silver ion, which was shown for tetra(diethyl)amide-*p-tert*-butylthiacalix[4]arene in the cone conformation.[4]

In the past years the ever-increasing power of computers allowed extended theoretical calculations of the structure and conformational equilibrium of such rather big molecules as calixarenes and their derivatives.[5] Recently, detailed reviews were published concerning ab initio calculations of calixarenes[6] and spectroscopic and theoretical studies of calixarene and thiacalixarene molecules.[7]

The conformational behavior of the parent thiacalix[4]arene and *p-tert*-butyl-thiacalix[4]arene was investigated by X-ray crystal studies,[1–3] NMR,[1] and computational methods.[8,9] Both molecules adopt the cone conformation of a C_4 symmetry in the solid state and in solution[1] which allows for the formation of a circle of four hydrogen bonds on the lower rim. However, a C_2 symmetrical (so-called pinched cone) conformation was found in the condensed phase for thiacalix[4]arene by another research group,[8] and it was supposed that the observed by X-ray C_4 symmetrical structure is the superposition of different C_2 symmetrical structures.

The average distance between two neighboring oxygen atoms in the *p-tert*-butylthiacalix[4]arene molecule is 2.80 Å (2.70 Å for classic *p-tert*-butylcalix[4]arene[9]). This suggests weaker hydrogen bonding and enhanced conformational flexibility of the thiacalix[4]arene molecule, which was proved by both NMR in solution[1] and calculations.[8,9] The cone conformer is identified as the most stable by all calculations followed by paco, 1,3-alternate, and 1,2-alternate.

The cone conformer usually gets the pinched cone geometry if hydroxyl groups on the lower rim get substituted to other fragments, such as alkyl ether groups. Such a substitution can also lead to changes in the relative stability of the conformers. Lhotak et al.[10] showed that distally (i.e., across the ring) dialkylated methyl ether of thiacalix[4]arene adopts the 1,2-alternate conformation in the solid state and the cone conformation in solution.

A recent study of the conformational behavior of partially alkylated thiacalix[4]arenes bearing methyl, ethyl, or propyl groups at the lower rim was published.[11] NMR experiments, as well as B3LYP (6-311G** basis set) calculations, revealed that in all cases of partial substitution the cone conformation becomes

* Corresponding author. E-mail: lshamova@yahoo.com.
† Kazan State University.
‡ Kazan Scientific Centre of the Russian Academy of Sciences.

SCHEME 1: Conformations of the Lower Rim Substituted Calix[4]arenes

cone   partial cone   1,2-alternate   1,3-alternate
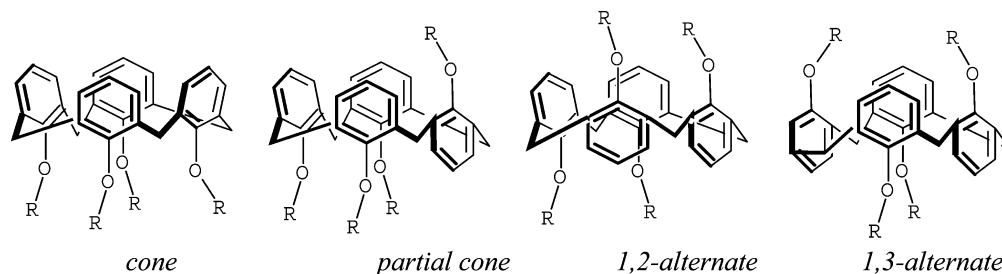
distorted going from the flattened to the pinched cone geometry; the authors emphasize the importance of hydrogen bonds as a factor stabilizing different conformations both in the solid state and in solution.

The ^{1}H NMR study of thiacalix[4]arene tetramethyl ether showed that in solution it exists in a thermodynamic equilibrium of at least three different conformations,[12] whereas the ^{1}H NMR spectrum of thiacalix[4]arene tetraethyl ether reveals the presence of all four possible conformers in $Cl_2CDCDCl_2$ solution at room temperature. The conformer distribution at 303 K was cone/partial cone/1,2-alternate/1,3-alternate 17:55:2:26; for tetrapropyl ether at elevated temperature it was 31:58:4:7.[1] In the solid state the thiacalix[4]arene tetraethyl ether adopts the 1,3-alternate conformations, just like *p-tert*-butylthiacalix[4]arene tetraethyl and tetrapropyl ethers.[13]

The pinched cone−pinched cone transition equilibrium of tetraethoxythiacalix[4]arene was the object of both theoretical and NMR studies.[14] The calculations made on HF/STO-3G, HF/6-31G**, and B3LYP/6-31G** levels showed that the stable pinched cone conformer of thiacalix[4]arenes has a C_s symmetry. The pinched cone C_s/pinched cone/C_s transition energy barrier in the gas phase is 7.13 kcal/mol (B3LYP/6-31G**), whereas NMR studies of this transition in chloroform gave the value 11.9 kcal/mol. Lately, the same authors showed that the general Amber force field is not able to predict the correct values of the energy barriers.[15] A better approximation to the experimental results was found using single-point RI-MP2 calculations (aug-cc-pVDZ basis set) on the density functional theory (DFT)-optimized geometries. As a possible explanation for the failure of HF and DFT calculations, the authors suggested lack of treatment of the dispersion interaction between aromatic rings of the calixarenes.

An early study dedicated to modeling of the thiacalix[4]-bis(crown-*n*) (with *n* = 5 and 6) complexes with alkali metal ions in the gas phase and in an explicit aqueous phase was made by Lamare et al.[16] using classical molecular dynamics (MD) simulations with the Amber force field, with the missing parameters for the thiacalixarene sulfur adjusted using X-ray data. In both thiacalix[4]bis(crown-*n*)s complexes, cations do not interact effectively with the crown part either moving from one crown to the other through the aromatic cavity or being included into the latter.

The binding energy between an isolated Zn^{2+} ion and adjacently deprotonated species of the *p-tert*-butylthiacalix-[4]arene cone conformer was calculated by Ruangpornvisuti to be approximately −672.47 kcal/mol (B3LYP/6-31G*).[17] Recently, 1:1 complexes of the tetraaminothiacalix[4]arene different conformers with Zn^{2+} [18] and second deprotonated species of thiacalix[4]arene with Zn^{2+} and Cu^{2+} were studied by Suwattanamala et al. using B3LYP/6-31G(d) and PBE1PBE/6-31G(d) methods.[19] The importance of the bridging sulfur atoms in the coordination of the metal ions is shown by analysis

SCHEME 2: Structure of the Studied Thiacalixarene Ligand
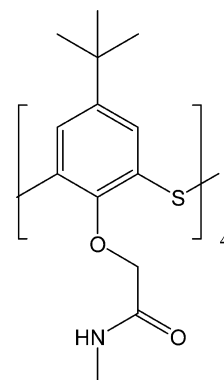
of molecular electrostatic potential surfaces. For both metal ions, the most stable structure of the thiacalix[4]arene−metal ion complex is the second deprotonated species possessing opposite pattern and the metal coordinated to two phenolate oxygens and two phenol oxygens. Also, no structure containing the sulfur atom coordination mode of binding was found for Zn^{2+} complexes of dibromo-dipropoxythiacalix[4]arene and dipropoxy-thiacalix[4]arene, computed using hybrid DFT with a small basis set.[20]

In this paper we will model relative stabilities of configurational and conformational isomers of the *p-tert*-butylthiacalix-[4]arene tetra(*N*-methyl)amide (shown on Scheme 2) and the structure of its complexes with potassium and silver ions based on the results of DFT calculations. K and Ag were selected to be objects of this study because they give two polar types of cations—hard and soft Lewis acids—and have the same charge, and because of their biological and environmental importance. The closed d-shell in case of Ag^+ guarantees that mostly relatively weak covalent interactions are established with the ligands,[21] and in case of K^+, they have mainly ionic character. Bouhroum et al.[4] studied the interaction of *p-tert*-butyl-thiacalix[4]arene *N,N*-diethylamide in the cone conformation with Ag^+ cation by ^{1}H NMR spectroscopy and found that the larger shifts observed for the $OCH_2C(O)N$ and the ArH protons of the thiacalix[4]arene can be attributed to a cation more deeply enclosed with interactions with the sulfur atoms and the aromatic rings of the macrocycle. Stoikov et al.[22] measured the percents of extraction of Ag and K picrates by the *p-tert*-butylthiacalix[4]arene *N*-octylamide and observed the extraction ability decreasing in a row 1,3-alternate > cone > partial cone and Ag^+ extracting generally twice better than K^+. However, in the latter experimental study,[22] the mode of binding of Ag^+ and K^+ to thiacalix[4]arenes tetraamides, as well as the intramolecular hydrogen-bonding pattern inside their macrocyclic cavity, was not determined, as neither X-ray structures nor structural study results are available either for these ligands or for their metal complexes.

DFT Modeling of Thiacalix[4]arene Complexation

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TABLE 1: Some Parameters of Hydrogen Bonds in Isomers of the Ligand and Their Relative Energies (E_{rel}) Derived from the MM (OPLS) and DFT/PBE Calculations

conformer	no. of H-bonds	av length of H-bond, Å	H-bond type	E_{rel} (OPLS), kcal/mol	E_{rel} (PBE), kcal/mol
cone (-4438.73635 au)	6	2.16	3(NH$\cdots$O=C$-$), 3(NH$\cdots$O$_{eth}$)		0.00
cone[a]	4	2.26	NH$\cdots$O$_{eth}$	0.00	0.14
paco[a]	5	2.26	NH$\cdots$O=C$-$, 4(NH$\cdots$O$_{eth}$)	15.64	1.44
paco	3	2.01	2(NH$\cdots$O=C$-$), NH$\cdots$O$_{eth}$		4.77
paco	3	2.14	NH$\cdots$O=C$-$, 2(NH$\cdots$O$_{eth}$)		4.80
1,2-alternate[a]	5	2.21	NH$\cdots$O=C$-$, 4(NH$\cdots$O$_{eth}$)	25.82	2.13
1,3-alternate[a]	4	2.28	NH$\cdots$O$_{eth}$	16.48	2.35
1,3-alternate (syn$-$syn)	2	2.24	NH$\cdots$O$_{eth}$		7.02
1,3-alternate (anti$-$anti)	3	2.27	NH$\cdots$O$_{eth}$		5.16
1,3-alternate (syn$-$anti)	1	2.15	NH$\cdots$O$_{eth}$		12.73

[a] Fom MM (OPLS) calculations.

The modeling of the binding modes of the selected cations we attempt here (both the hard potassium and soft silver ones) with the amido-thiacalix[4]arene is of interest because it could give us a better understanding of the processes of ion extraction and its selectivity, cation recognition, and future rational construction of the host molecules which can be eventually used as receptors and nanoassembly blocks.[22]

However, there is a difficulty with the modeling of the complexation of such a ligand which is both conformationally flexible and offering several kinds of donor atoms (O, N, S, aromatic C). In principle, this would require a dynamic treatment. However, at the DFT level it is still unfeasible, whereas molecular mechanics (MM) cannot properly describe the bonding of soft metals like silver. In this work we will try to use a hybrid strategy of doing global minima searches where possible with MM and then using the obtained structures as DFT starting points. Inclusion of several structures of the host–guest complex made in our study might be useful in the description of a host–guest system from a statistical viewpoint,[23,24] taking into account that, unlike in crystal, there are many motional degrees of freedom in a solution and during the extraction. Hence in this work, we will consider for each configurational isomer of the *p-tert*-butylthiacalix[4]arene amide (cone, paco, and 1,3-alternate) several conformers with different mutual orientations of the substituent groups and will find possible regimes of metal ion coordination in the thiacalix-arene–cation complexes.

Computational Details

Apart from four (cone, paco, 1,2-alternate, and 1,3-alternate) conformational possibilities introduced by the macrocyclic platform, substituted calix[4]arenes have a large variety of conformations they can adopt due to the rotation of the single bonds in their pendant arms. This spawns a large number of isomeric structures of the ligand to consider. Moreover, for the ligand shown in Figure 2 that has several kinds of donor atoms (ether and carbonyl oxygens, bridged sulfur, amide nitrogens), a cation in principle can adopt many coordination modes.

Modern density functional codes like Priroda[25−29] allow for calculations involving geometry optimization of systems like the complexes under study in this work. Thanks to the relativistic DFT implementation, the code also allows for treatment of the entire periodic table in a consistent manner. However, global minima searches or dynamic calculations on this level of theory are still prohibitively expensive. For that reason, many published works[5] use NDO semiempirical methods (AM1, PM3). These methods are known to suffer from a rather bad description of hydrogen bonding, as well as from the incorrect description of

the amide HN−CO rotational barriers, which would likely lead to the incorrect description of our ligand isomers.[30]

Thus, in the present work, we adopted a hybrid strategy: global optimizations of the free ligand and its potassium complexes have been done using the empirical MM method; then, based on its findings, the DFT geometry optimization calculations were performed for several structures found. In addition to that, some starting structures for the optimization on the DFT level on theory were constructed by hand, where guess structures were obtained as directed by the following principles: (1) a maximum number of hydrogen bonds formed between substituents' arms inside the molecule; (2) minimum repulsion between bulky *tert*-butyl groups and amide fragments. The presence of hydrogen bonds was identified using the classical geometric criteria: the proton to lone pair donor distance less than 2.5 Å and the angle defined by the amide nitrogen−hydrogen−ester or ether oxygen atoms is obtuse, that is, lies between ±90° and 180°.[31,32]

Molecular mechanics calculations were performed with the Tinker software package.[33] The all-atom OPLS (optimized potentials for liquid simulations) force field[34] was used for the ligand and the potassium cation. For the bridged sulfur atoms, parameters were taken from ref 16; some parameters for PhO−CH$_2$ were adopted from OPLS_UA and Amber force fields.[35] We provide parameters used for MM calculations in the Supporting Information. Global minimization for each conformer of the free ligand has been performed with the dihedral angle scan procedure with the low mode scan procedure similar to ref 36 as realized in Tinker.

In the OPLS force field, bonding of an alkali metal cation to a ligand is represented by nonbonded (van der Waals and electrostatic) interactions only. Thus, global optimization for our potassium−calixarene complexes using torsion angle scans is not possible, as the metal atom is not connected to the ligand; that is, it does not appear as a part of any torsion angle. Because of that, a different procedure was applied for global minimum searches for the complexes as follows.

For the ligands' isomeric structures obtained from the torsion scan procedure, the potassium cation has been placed at an arbitrary position near the ligand, and the resulting structure was subjected to Monte Carlo (MC) basin hopping global minima search.[37] As a starting geometry for the silver complexes, the potassium ones were taken with K$^+$ substituted with Ag$^+$ cation. (These structures are referred to as "silver complexes from MC" hereafter; we note that no actual MC searches were made for silver complexes due to the difficulty of modeling its coordination with empirical force fields.) For the hand-constructed ligands, their 1:1 complexes with K$^+$ and Ag$^+$ ions

were obtained by simple placing of the metal ion to the possible binding center of the receptor.

All structures of the ligands and the complexes were then optimized at the generalized gradient approximation (GGA) DFT level using the Priroda code version 6.[25,26] PBE density functional[38] was used. A literature evidence suggests (see, for example, ref 39) that the use of the popular effective core potential approach to replace core electrons of heavier elements might lead to systematic errors in calculated energies and electronic structure. For this reason, we chose to use an all-electron basis set,[40] denoted below as L11. It is well-known that, for the elements below second row, the relativistic effects become important, so to treat both metals in a consistent manner, a relativistic scalar four-component method,[41] as implemented in the Priroda code, was applied. The Gaussian orbital basis set L11 in the general contracted form was used along with a corresponding optimized Coulomb fitting set and a small-component set obtained by the kinetic balance scheme. The contraction schemes for the orbital basis are (10s, 7p, 3d)/[4s,3p,1d] for C, O, and N, (15s, 11p, 6d)/[5s,4p,2d] for S, (19s, 15p, 10d)/[6s,5p,2d] for K, (23s, 23p, 16d, 5f)/[7s,6p,4d, 1f] for Ag, and (6s, 2p)/[2s,1p] for H atoms, correspondingly. Because the basis set is of reasonably good size and quality, we did not perform BSSE (basis set superposition error) corrections in this study.

All ligands and complexes were optimized without any symmetry or geometry constraints; analytical Hessians were calculated to be sure that these structures are minima and have no negative Hessian eigenvalues.

Results and Discussion

Energy and Geometry of Free Ligands in the Gas Phase. Intramolecular interactions play a significant role in both natural[42] and synthetic receptors.[5] When the calix[4]arene substituents possess secondary amide groups, there is a possibility of intramolecular hydrogen-bond formations.[43,44] An NH group of an amide in principle can form a hydrogen bond either with the carbonyl group of the adjacent podand arm or with the phenolic oxygen of its own arm forming a five-membered ring. In the case of *p-tert*-butylcalix[4]arene tetraethyl amide in the cone conformation, X-ray data showed that the pendant amide groups are all involved in the intramolecular hydrogen bonding with three of the carbonyl groups and one phenolic oxygen.[45] Only the latter type of hydrogen bond was recently found in the X-ray structure of the 1,3-alternate thiacalix[4]-bisazacrown where secondary amide groups are immobilized in crown moieties.[46] However, configuration of the hydrogen-bonding network might differ in the gas phase/nonpolar solution.

The number of the podand's NH···OC hydrogen bonds is thought to be a major factor influencing relative stabilities of the thiacalixarene conformers. We used two methods of searching for the most energetically favorable conformers: first, when geometry of the ligands was generated by hand with an eye of having the largest number of hydrogen bonds between the podand arms; and second, when the initial geometries for the optimization were obtained by the global minima searches (MM) procedure as described above. The energies for isomers found by both methods of searching are presented in the Table 1. The energy of the conformers calculated on the DFT level has a clear dependence on number, type, and length of the hydrogen bonds inside and between the podand arms.

Let us first discuss geometry and energy of the hand-constructed conformers. After optimization, we obtained two paco conformers with a different pattern of the intramolecular
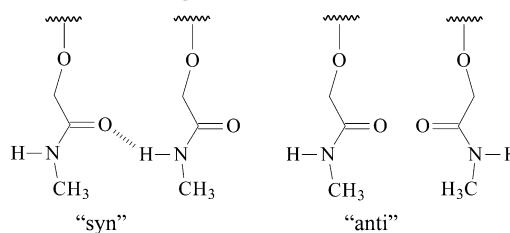
hydrogen bonds differing only in 0.03 kcal/mol. In the more favorable conformer, there are two very short NH···OC hydrogen bonds (1.92 and 1.97 Å), and there is a close contact between the phenolic oxygen and one of the methylene protons, 2.15 Å. Both paco conformers are much less energetically favorable than the cone conformer with six hydrogen bonds: three NH···O=C− bonds between the podand arms and three NH···O_{eth} bonds inside the podand fragments. The high stability of the conformation with an intramolecular hydrogen bond is in line with results of Okunola et al.[47] who found for calix[4]arene tetrabutylamide in the solid state the pinched cone conformation with a C_{2v} symmetry and two intramolecular hydrogen bonds between two amide NH groups and the neighboring carbonyl oxygens.

We assumed that presence of the hydrogen bond on the one side of the macrocycle in case of the 1,3-alternate conformation might influence complex formation on the other side. That is why we obtained three 1,3-alternate conformers, namely, syn−syn, anti−anti, and syn−anti, qualified on the base of a mutual orientation of carbonyl and NH amide groups of the calixarene substituents on the both sides of a macrocycle, as sketched in Scheme 3.

For the 1,3-alternate configurational isomer, the "anti−anti" conformer is significantly more energetically favorable than the "syn−syn" conformer; in the latter, the −CH_2−C(O)−NH−CH_3 groups are oriented to form hydrogen bonds but, being pinched between bulky *tert*-butyl substituents, are unable to do so: the NH···OC distances in the 1,3-alternate (syn−syn) are 2.66−2.75 Å. In fact, carbonyls are closer to the methyl protons of opposite amide groups (2.42 and 2.35 Å, respectively). No hydrogen bonds stabilize this isomer; that is why the 1,3-alternate (anti−anti) conformer, in which −CH_2−C(O)−NH−CH_3 fragments are far from each other and from *tert*-butyl groups, is more stable, because of less steric hindrance. Noteworthy, cone and 1,3-alternate (syn−syn) conformers additionally have bifurcated hydrogen bonds between NH and C=O and O−CH_2 groups.

If we advert to the ligand conformers obtained by the MM global search procedure, we notice that both MM/OPLS and subsequent DFT PBE/L11 calculations predict as most energetically favorable the cone conformer and almost the same stability sequence cone > paco > 1,3-alternate > 1,2-alternate. The energy differences between the conformers, however, are much larger as predicted by the MM global optimization.

As in the case of the hand-constructed one, the cone conformer has a C_{2v} pinched cone geometry, but unlike the former, it is symmetrical, which is true for all of the MM/OPLS global search obtained isomers. Only paco and 1,2-alternate conformers have hydrogen bonds between the podand arms (NH···OC distances 2.07 and 2.00 Å, respectively). Conversely, in all conformers, each of four amide fragments forms the intramolecular hydrogen bond between the NH proton and
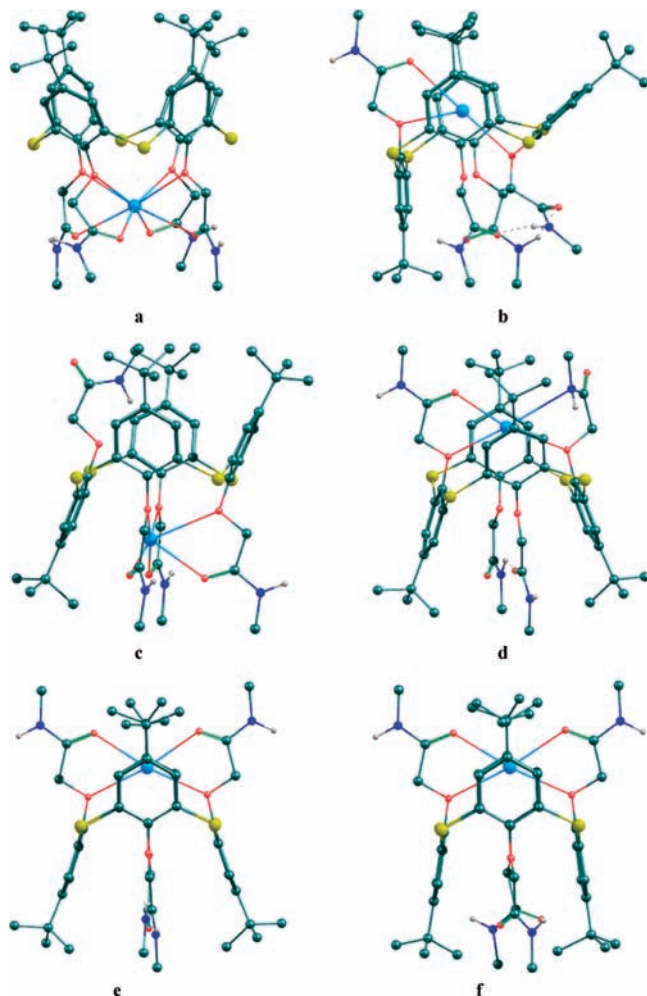
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Figure 1. Optimized DFT PBE/L11 structures of conformers of hand-constructed K^+ complexes: (a) cone·K^+; (b) paco·K^+ (one arm); (c) paco·K^+ (three arms); (d) 1,3-alternate·K^+ (syn−syn); (e) 1,3-alternate·K^+ (syn−anti); (f) 1,3-alternate·K^+ (anti−anti).

phenolic oxygen of the same podand arm which is in line with an experiment.[46] All of the conformers obtained by MM search, except the cone conformer, are energetically more favorable than the hand-constructed ones. Thus, hydrogen bonds between the amide podand arms of the *p-tert*-butylthiacalix[4]arene tetra(*N*-methyl)amide conformers do not form, at least in vacuo, due to sterical bulkiness of the spatially proximate *tert*-butyl groups.

K^+ Complexes. The six K^+ complexes with the hand-constructed ligands (Figure 1) were obtained simply placing cations near donor atoms of the ligands and optimizing the resulting structure at the DFT level. The geometry and the calculated cation−donor atom bond orders demonstrate that the coordination number of K^+ in the complexes ranges from eight in the cone conformer to six in the paco and four in the 1,3-alternate conformers. In the cone and paco conformers, actually the M^+−O ether (O_{eth}) bond orders are quite small but comparable with the M^+−O carbonyl (O_{carb}) bond orders: for example, average values for the cone conformer are 0.09 and 0.15, respectively (see the Supporting Information), indicating a very ionic bonding.

For the paco conformer, two possibilities of the metal ion coordination were considered: "three arms" and "one arm" structures (Figure 1). In the "one arm" paco isomer, the potassium cation even being entrapped between two phenyl rings does not have significant bonding to them, which can be seen
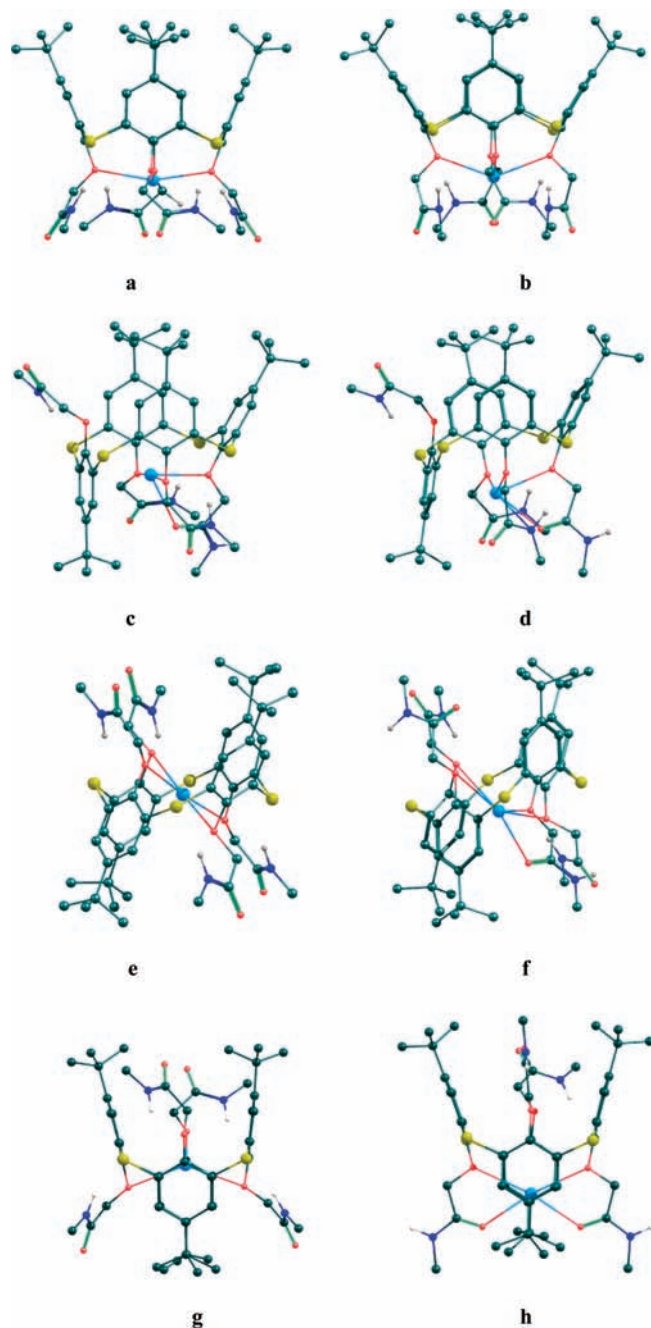

Figure 2. Structures of conformers of MC searches obtained complexes: (a) cone·K^+ (optimized with MM OPLS); (b) cone·K^+ (MM OPLS, then DFT PBE/L11); (c) paco·K^+ (MM OPLS); (d) paco·K^+ (MM OPLS, then DFT PBE/L11); (e) 1,2-alternate·K^+ (MM OPLS); (f) 1,2-alternate·K^+ (MM OPLS, then DFT PBE/L11); (g) 1,3-alternate·K^+ (MM OPLS); (h) 1,3-alternate·K^+ (MM OPLS, then DFT PBE/L11).

from the interatomic distances and the M^+−C aromatic (C_{Ar}) bond orders.

The hydrogen bonds in the binding sites of the ligands, after complex formation with the metal ions, in most cases cease, as was observed experimentally for some amide derivatives of calix[4]arene.[43,48]

The energetic properties of all the complexes computed at the DFT PBE/L11 level are summarized in Table 2. Complexation energies, $\Delta E_{complex}$, are defined as the total energy of complex (E_{ML}) minus the sum of total energies of the most energetically favorable ligand of the corresponding configuration (E_L) and the metal ion (E_M). We can consider energy of binding

TABLE 2: Calculated Energies of Complexes of K$^+$ and the *p-tert*-Butylthiacalix[4]arene Tetra(*N*-methyl)amide (Ligand) Isomers and Their Preorganization, Complexation, and Binding Energies Using DFT/PBE L11-Optimized Geometries

complex	atoms involved in coordination	E, au	E_{rel}, kcal/mol	$\Delta E_{complex}$, kcal/mol	$\Delta E_{preorg.}$, kcal/mol	$\Delta E_{binding}$, kcal/mol	no. of H-bonds	av length of H-bond, Å	H-bond type
				Monte Carlo Search					
cone·K$^+$	O=C−, −O−	−5040.7398	19.33	−50.80	17.42	−68.22	4	2.44	NH···O$_{eth}$
paco·K$^+$	O=C−, −O−	−5040.7480	14.20	−57.37	17.49	−74.85	3	2.38	NH···O$_{eth}$
1,2-alternate·K$^+$	O=C−, −O−	−5040.7436	17.11	−55.14	14.61	−69.75	2	2.34	NH···O$_{eth}$
1,3-alternate·K$^+$	O=C−, −O−	−5040.7696	0.67	−62.64	13.40	−85.19	2	2.34	NH···O$_{eth}$
				Hand Constructed					
cone·K$^+$	O=C−, −O−	−5040.7677	1.84	−68.28	45.51	−113.49			
paco·K$^+$ (three arms)	O=C−, −O−	−5040.7702	0.28	−71.28	34.67	−105.96	2	2.01	NH···O=C−
paco·K$^+$ (one arm)	O=C−, −O−	−5040.7517	11.86	−59.71	12.34	−72.05	1	2.18	NH···O$_{eth}$
1,3-alternate·K$^+$ (syn−syn)	O=C−, −NH−, −O−	−5040.7550	9.83	−62.64	13.67	−76.31	2	2.33	NH···O=C−, NH···O$_{eth}$
1,3-alternate·K$^+$ (anti−anti)	O=C−, −O−	−5040.7690	1.05	−71.42	20.45	−91.88			
1,3-alternate·K$^+$ (syn−anti)	O=C−, −O−	−5040.7706	0.00	−72.47	17.17	−89.64	2	2.40	NH···O=C−, NH···O$_{eth}$

$\Delta E_{binding}$ as a difference of the complexation energy ($\Delta E_{complex}$) and the energy of preorganization ($\Delta E_{preorg.}$) that the ligand expends to achieve the binding geometry.

$$\Delta E_{complex} = E_{ML} - E_L - E_M \qquad (1)$$

$$\Delta E_{binding} = \Delta E_{complex} - \Delta E_{preorg} \qquad (2)$$

For isomeric potassium complexes, the following stability order was found: 1,3-alternate "syn−anti" > paco "three arms" > 1,3-alternate "anti−anti" > cone ≫ 1,3-alternate "syn−syn" > paco "one arm". In some cases, the structures of the complexes were found to possess hydrogen bonds: two in the paco "one arm" conformer (bond lengths 1.94 and 2.07 Å), in the 1,3-alternate "syn−syn" (2.35 Å), and in the "syn−anti" conformers (2.49 Å). However, this additional stabilization does not seem to play a major role in the overall stability order. Coordination of the metal ion with the amide N atom in the 1,3-alternate·K$^+$ "syn−syn" as well as with only one podand arm in paco·K$^+$ "one arm" was found to be absolutely unfavorable.

The most energetically stable K$^+$·1,3-alternate "syn−anti" and K$^+$·paco "three arms" complexes, that differ only by 0.3 kcal/mol, have the metal ion coordinated inside the pseudocavity formed by thiacalixarene substituents and effectively shielded from the outside space by bulky *tert*-butyl groups. The cone conformer, despite having the biggest energy of interaction with the cation ($\Delta E_{binding} = -113.49$, eight donor atom−M$^+$ bonds), displays overall less complexation efficacy due to the huge preorganization losses. In the K$^+$·1,3-alternate "syn−anti" structure the key role in the formation of such a pseudocavity is played by the NH···C(O) hydrogen bond on the opposite side of a macrocyclic plane. In the absence of this hydrogen bond in the less favorable 1,3-alternate "anti−anti" conformer, the distance between the two carbonyl oxygens that coordinate K$^+$ changes from 4.44 to 4.58 Å, which abates the shielding of the metal ion by the ligand. This indicates the importance of the mutual influence of the two binding sides of the flexible 1,3-alternate conformer.

Other regimes of coordination were found by MC searches. Figure 2 shows the structures of thiacalixarene·K$^+$ obtained after MC searches and MM (OPLS) optimization (first column) and after subsequent minimization on DFT level (second column). The MM-optimized structures show the tendency of MM to place the potassium ion closer to the four ether oxygen atoms of thiacalixarene, as compared to DFT, which tends to shift it farther down to the ester oxygens. In the paco, 1,2-, and 1,3-alternate conformers K$^+$ became coordinated to carbonyl groups after considerable readjustment of the ligand structure.

In the conformers obtained through MC searches procedure, the low values of preorganization, complexation, and binding energies indicate the wrong geometry of the potassium complexes of thiacalix[4]arene. All these complex structures except 1,3-alternate·K$^+$ are much less stable than hand-constructed isomers. This fact highlights weakness of MM in the prediction of alkali metal complexes. At the same time, the prediction of the free ligand structure as discussed above is fairly good. Probably, standard OPLS charges we use for methylamido-thiacalix[4]arene have to be readjusted to yield better geometries.

Ag$^+$ Complexes. For a transition metal ion, there are plenty of coordination possibilities in thiacalixarene: donor phenolic and carbonyl oxygen atoms, nitrogen atoms, and sulfur atoms of the macrocycle. The last coordination type was considered earlier[19] and found to be preferable in the interaction of unsubstituted thiacalix[4]arene with Zn^{2+}.

Figure 3 shows the energy-minimized structures of the thiacalixarene·Ag$^+$ complexes. The geometry and the cation−donor atom bond orders, as computed by DFT, show that the coordination number of silver ion in the majority of the complexes is four; however, two- and three-coordination geometries are also found. All these geometries can be rationalized in terms of distortions of the ideal tetrahedron with the cation in the center.[21] The calculated bond orders (see Supporting Information, Table 1) show a significant degree of covalency of the silver−ligand bonds.

The coordination with the carbonyl oxygens in all cases was more preferable than the coordination with the phenolic oxygens: M$^+$−O distances for the first ones are always shorter. The structures with coordination to S (for the cone conformer) and N atoms (for one of the 1,3-alternate conformers) were found. The structures of paco and the other two 1,3-alternate conformers involve the Ag$^+$ complexation to one aromatic ring carbon.

The most stable of the isomeric complexes is the one with the cone conformer, the case of the metal coordinated to the S atom of the macrocyclic ring. The next best conformer of the complex—paco·Ag$^+$ (S)—also has S-type coordination. The experimental evidence of the Ag$^+$ ion complexation with macrocyclic S atoms has been gained recently by ^{1}H NMR measurements for tetraallyloxy-thiacalix[4]arene in paco conformation.[49] The symmetrical orientation of the metal ion inside the cone conformer with the coordination to only carbonyl oxygen atoms is considerably less preferable.

Ag$^+$ binding to the aromatic carbon atoms in paco and one of the 1,3-alternate isomers (anti−anti), as well as with amide N atoms in the latter, does not allow for the formation of very stable complexes. The complexes with the other 1,3-alternate isomers, namely, "anti−anti" and "syn−anti", are more pre-
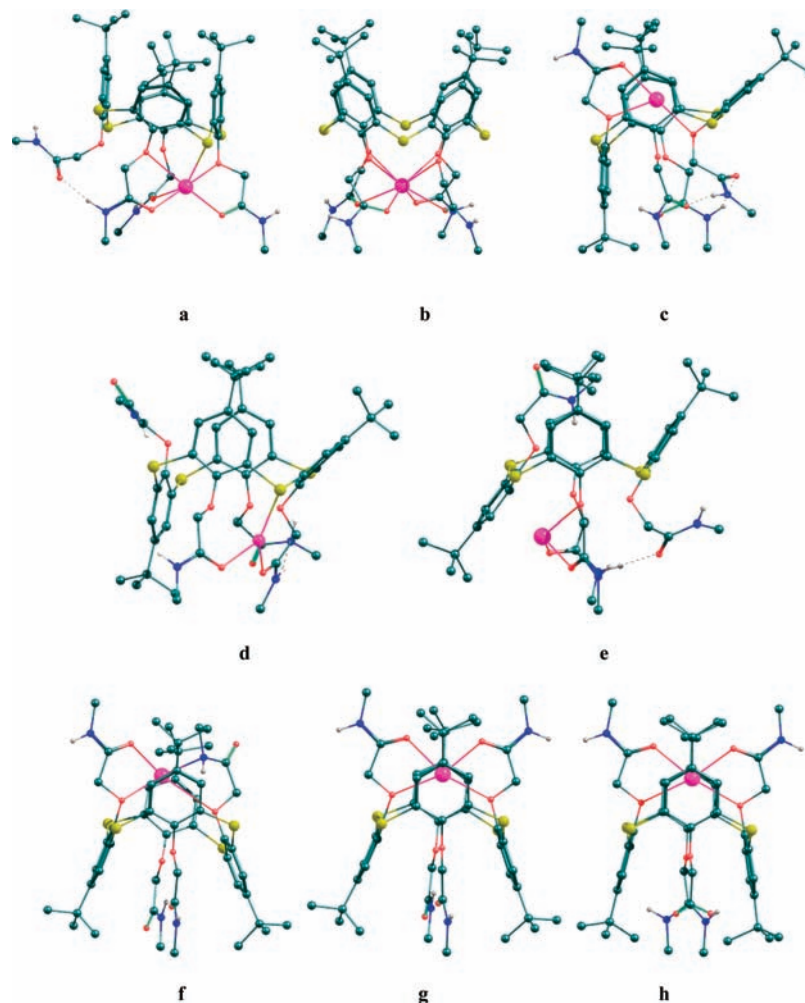
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Figure 3. Optimized DFT PBE/L11 structures of conformers of hand-constructed complexes with Ag$^+$: (a) cone·Ag$^+$ (S); (b) cone·Ag$^+$ (O); (c) paco·Ag$^+$ (one arm); (d) paco·Ag$^+$ (S); (e) paco·Ag$^+$ (O); (f) 1,3-alternate·Ag$^+$ (syn−syn); (g) 1,3-alternate·Ag$^+$ (syn−anti); (h) 1,3-alternate·Ag$^+$ (anti−anti).

ferred. The formation of a hydrogen bond between NH and C(O) groups leads to a much lower energy of the latter conformations.

In the case of Ag$^+$ complexes, our results again, as was found for K$^+$·1,3-alternate "syn−anti" complex, indicate that the binding of the metal ion influences on the geometry of the other, free of the metal ion, side of the macrocycle.

Let us consider two isomers, "anti−anti" and "syn−anti" of the 1,3-alternate, which by construction differ only with the orientation of −CH$_2$−C(O)−NH−CH$_3$ groups in the "free" of the metal ion half of the thiacalixarene. In the first isomer there is a large distance between them, as in the free ligand "anti−anti" 1,3-alternate, whereas in the last one, amide groups are close to each other (3.23 Å) and preorganized to form a hydrogen bond, as in the free "syn−syn" 1,3-alternate ligand. When Ag$^+$ binds to four O donor atoms on the opposite side of the macrocycle, the NH···OC distance decreases significantly to 2.53 Å. Thus, the metal ion coordination on one side of a macrocyclic plane might trigger the hydrogen-bond formation on the other side.

The energies of complex formation span a large range of values (Table 3). The largest gain upon complex formation (−107.21 kcal/mol) is observed for the cone·Ag$^+$ (S) conformation. This is likely due to a strong interaction between the soft sulfur atom and the metal, because when only O atoms are involved in the interaction with the Ag$^+$ cation (cone·Ag$^+$ (symmetrical) conformer, the $\Delta E_{complex}$ drops to −100.44 kcal/

mol. Moreover, there is less preorganization penalty for the ligand in the cone conformation to get in this type of complex than in the symmetrical one which involves only O−M$^+$ interactions. One can also relate this gain to one more hydrogen bond which has to be broken to convert an S-type complex to an all-O one. For the paco conformer, the energies of complexation of the S-coordinating (next best conformer) and the totally O-coordinating ligands (both have the same number of the intramolecular hydrogen bonds in their structures) differ as 4.58 kcal/mol. A slightly higher $\Delta E_{complex}$ was found for the complex "syn−anti" 1,3-alternate (−106.08 kcal/mol).

Approximately the same level of the complex formation energy (ca. 100−103 kcal/mol) was found for cone, paco, and the other two 1,3-alternate conformers; meanwhile the binding with only one podand amide arm in the paco conformer is predictably poor. Extremely high values of the deformation energy for both isomers of cone Ag$^+$ complexes can be rationalized having in mind that the free cone ligand is able to form the most number of the intramolecular hydrogen bonds (six) and that four amide arms on the lower rim create steric bulkiness obviously obstructing the cation binding with this conformer.

All structures obtained from the MC searches (see the Computational Details section above) are much less stable than the hand-constructed isomers of Ag$^+$−thiacalixarene complexes (Figure 4). For the former ones, binding of the Ag$^+$ with the

TABLE 3: Calculated Energies of Complexes of Ag$^+$ and the *p-tert*-Butylthiacalix[4]arene Tetra(*N*-methyl)amide (Ligand) Isomers and Their Preorganization, Complexation, and Binding Energies Using DFT/PBE L11-Optimized Geometries

complex	atoms involved in coordination	E, au	E_{rel}, kcal/mol	$\Delta E_{complex}$, kcal/mol	$\Delta E_{preorg.}$, kcal/mol	$\Delta E_{binding}$, kcal/mol	no. of H-bonds	av length of H-bond, Å	H-bond type
				Monte Carlo Search					
cone·Ag$^+$	−O−, N	−9755.1086	11.52	−95.69	17.63	−113.32	3	2.40	NH···O$_{eth}$
paco·Ag$^+$	O=C, −O−, C$_{Ar}$	−9755.1040	14.40	−94.25	18.39	−112.64	2	2.34	NH···O$_{eth}$
1,2-alternate·Ag$^+$	−O−, C$_{Ar}$	−9755.0838	27.02	−82.31	8.68	−90.99	0		
1,3-alternate·Ag$^+$	−O−	−9755.0771	31.23	−78.33	3.82	−82.14	2	2.32	NH···O$_{eth}$
				Hand Constructed					
cone·Ag$^+$(S)	−S−, O=C−	−9755.1269	0.00	−107.21	42.13	−149.35	1	1.84	NH···O=C−
cone·Ag$^+$ (symmetrical)	O=C−, −O−	−9755.1161	6.78	−100.44	48.85	−149.29	0		
paco·Ag$^+$ (S)	−S−, O=C−	−9755.1260	0.56	−108.09	24.78	−132.87	2	2.20	NH···N−C−,NH···O$_{eth}$
paco·Ag$^+$ (three arms)	O=C, −O−, C$_{Ar}$	−9755.1187	5.13	−103.52	22.12	−125.65	2	1.94	NH···O$_{eth}$
paco·Ag$^+$ (one arm)	O=C, −O−	−9755.1036	14.60	−94.05	16.67	−110.72	2	2.00	NH···O=C−
1,3-alternate·Ag$^+$ (syn−syn)	O=C, −NH−, C$_{Ar}$	−9755.1140	8.09	−101.47	16.20	−117.67	2	2.35	NH···O$_{eth}$
1,3-alternate·Ag$^+$ (anti−anti)	O=C, −O−	−9755.1172	6.07	−103.49	23.70	−127.19	0		
1,3-alternate·Ag$^+$ (syn−anti)	O=C, −O−	−9755.1214	3.48	−106.08	19.47	−125.55	2	2.41	NH···O=C−, NH···O$_{eth}$

aromatic C atom of the thiacalixarene macrocycle and with the N atom of the amide groups was observed. The complexes that possessed a high symmetry demonstrated ineffective complexation of the metal ions. No conformers stabilized with the intramolecular hydrogen bonds of a peptide type were found.

All the results support the higher complexation ability of the *p-tert*-butylthiacalix[4]arene tetramethylamide conformers toward Ag$^+$ than K$^+$, which agrees well with experimental studies of picrate extraction of some monocharged metal ions by the model compound *p-tert*-butylthiacalix[4]arene tetraoctylamide.[22] Our models predict that only in the complexes of cone and paco conformers there is a possibility of an advantageous interaction of the metal ion with the S atom of the ligand. We found that the complexes of the 1,3-alternate conformer with both Ag$^+$ and K$^+$ have a similar structure which cannot explain the difference in the extraction ability toward these ions. One of the possible explanations in this case may be the formation of outer-sphere complexes.

Conclusions

GGA DFT was used to study the relative stability of the conformers of the free ligand thiacalix[4]arene tetramethylamide
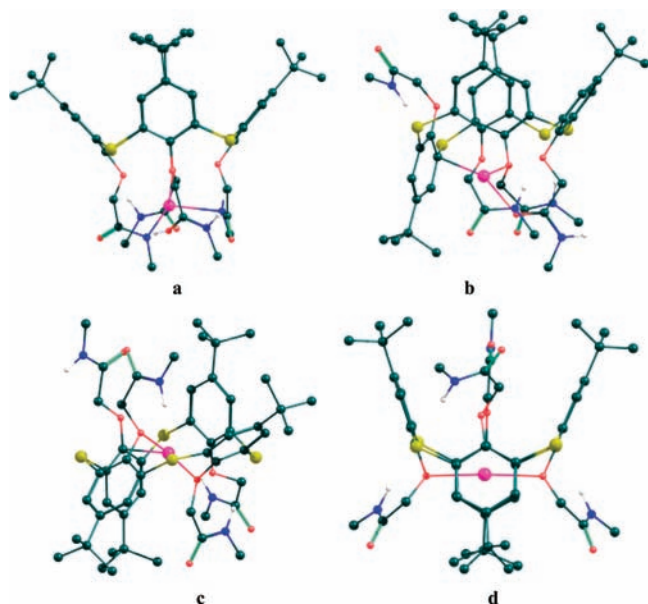
and its complexes with K$^+$ and Ag$^+$ ions in the gas phase. Several coordination modes were considered for these complexes, with two strategies for obtaining the initial geometries for DFT optimization—hand construction and global minima searches with empirical force fields.

The isomers initially obtained by the MM global search procedure were most energetically favorable in the case of the free ligands (stability sequence cone > paco > 1,3-alternate > 1,2-alternate); however, the geometries obtained by deliberate construction were more stable for all the complexes. The Monte Carlo searches procedure with the OPLS force field failed to find the best isomers of the potassium thiacalix[4]arene complex.

The energy of the free ligands calculated on the DFT level has quantitative dependence on number, type, and length of the hydrogen bonds inside and between the podand arms. Only coordination with oxygen atoms was found for the K$^+$ complexes of thiacalixarene; no sulfur coordination was found, and N-coordination was found unfavorable. For the silver cation complexes with coordination to S atom (for the cone conformer), N (for one of the 1,3-alternate conformers), C$_{Ar}$, and O atoms were found; the S-coordination mode is clearly preferred. The stability order cone > 1,3-alternate > paco was found for the Ag$^+$ complexes and 1,3-alternate > cone > paco for the K$^+$ complexes. All the results have shown a higher complexation ability of the *p-tert*-butylthiacalix[4]arene tetramethylamide conformers to Ag$^+$ than to K$^+$ which agrees with experimental data.[22]

Binding of both K$^+$ and Ag$^+$ with the 1,3-alternate "syn−anti" ligand induced the hydrogen-bond formation on the other, free of the metal ion, side of the macrocycle. For all obtained conformers, the intramolecular hydrogen bonds disfavor complexation, increasing the preorganizational energy to be paid.

Supporting Information Available: Tables containing a complete listing of all molecular mechanics parameters changed with respect to OPLS for the thiacalixarene ligand, tables containing the calculated DFT charges on metal atoms, selected bond lengths, and population bond orders in the K$^+$ and Ag$^+$ complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

Figure 4. Structures of conformers of Ag$^+$ complexes (Monte Carlo searches, then DFT PBE/L11 optimization): (a) cone·Ag$^+$; (b) paco·Ag$^+$; (c) 1,2-alternate·Ag$^+$; (d) 1,3-alternate·Ag$^+$.

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