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Synthesis and binding studies of novel bisthiacalix[4]arenes with diimime linkages

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Abstract—A series of novel bisthiacalix[4]arenes with diimine linkages of different aromatic or heteroaromatic dialdehydes have been synthesized. The structure of one of the bisthiacalixarene has been analyzed by X-ray crystallography. These molecules quantitatively extract silver ion from aqueous into organic phase under neutral conditions.

Calixarenes are one of the most important molecular scaffolds in the host–guest supramolecular chemistry.[1] A variety of sophisticated molecular hosts bearing calixarene skeleton(s) have been prepared, which is partly due to the regio- and stereoselective functionalization methods developed for this class of compounds during the last decade.[1,2] Recently, two of us reported a series of new biscalixarenes that consisted of two *p*-*tert*-butylcalix[4]arene units linked through their lower rims with bridging moieties containing diimine units of different aromatic or heteroaromatic dialdehydes.[3] The complexation behavior of these biscalixarenes was studied toward different metal ions (Na^+, K^+, Ca^{2+}, Pb^{2+}, and Ag^+) and it was found that these biscalixarenes bind silver ion preferentially but with poor selectivity over other metal ions. Recently, the strong anti-bacterial activity of silver ion has been the subject of much interest for the preparation of bio-active materials such as deodorizing cloths, agricultural sterilizing agent, and so on. Therefore, in continuation of our research for improving the recognition ability for soft metal ions, especially for silver ion, we intended to replace the conventional calix[4]arene unit of the biscalixarenes with a thiacalix[4]arene,[4] which has been shown to be an attractive host for soft metal ions.[5] Unfortunately, the employment of thiacalixarenes as building blocks or molecular scaffolds in the supramolecular chemistry is still restricted by the lack of sufficient understanding of the reactivity of thiacalixarenes toward general functionalization reactions and the regio- and stereoselectivity realized therein, which are substantially different from those of conventional methylene-bridged counterparts.[6,7] Recently, we have achieved the stereoselective synthesis of all four stereoisomers of bis(*O*-2-aminoethyl)-*p*-*tert*-butylthiacalix[4]arene **1**, that is, vicinal *O*,*O*′- and distal *O*,*O*″-bis(2-aminoethyl) derivatives with *syn* and *anti* arrangements of the two substituents with respect to the mean plane defined by the macrocycle.[7] It is obvious that these entities would provide intriguing components for the construction of varying molecular architectures. Herein, we wish to report the synthesis of thiacalix[4]arene analogs (**3**) of the biscalixarenes by using diamine *syn*-*O*,*O*″-**1** as a molecular scaffold and the performance of these bisthiacalixarenes as host molecules for silver ion. To the best of our knowledge, this is the first report on biscalixarenes bearing thiacalixarene units linked through their lower rims with bridging moieties containing imino groups.

Condensation of diamine *syn*-*O*,*O*″-**1** with 1.0 mol equiv of dialdehydes **2a**–**d** in refluxing ethanol gave bisthiacalixarenes **3a**–**d** in high yields (Scheme 1).[8] The products were virtually insoluble in the solvent to separate out as

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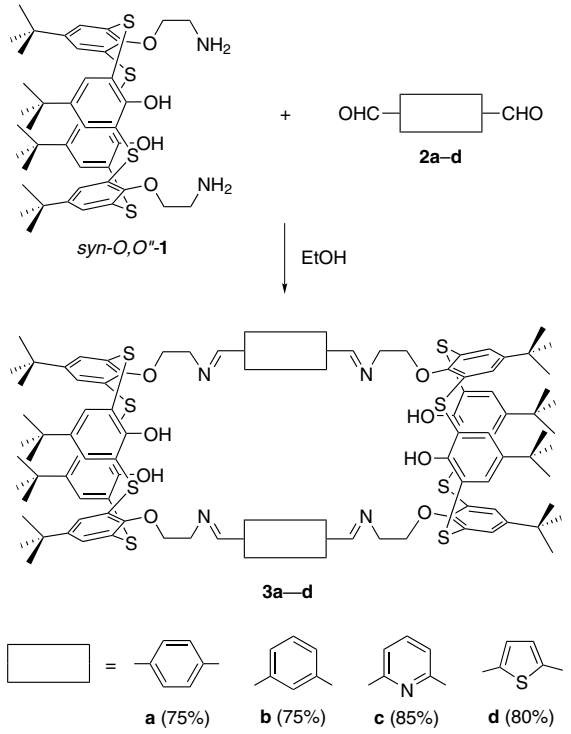
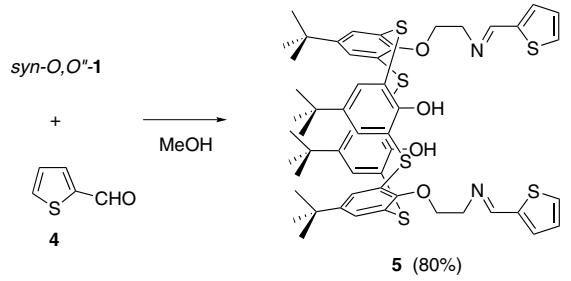


Scheme 1.

pure solids, which gave satisfactory elemental analysis after one crystallization. An open-chain compound **5** was also prepared by condensation of diamine *syn-O,O″*-**1** with 2.0 mol equiv of aldehyde **4** (Scheme 2).[9] The structures of bisthiacalixarenes **3a**–**d** were confirmed from their spectroscopic and analytical data.[8] The IR spectra of **3a**–**d** showed a C=N stretching band at 1633–1651 cm^{-1} and no absorption bands corresponding to free formyl and amino groups, which indicates that the cyclization has taken place. This was confirmed by the FAB mass spectra that showed a parent ion peak corresponding to the 2:2 cyclization products. The ^1H NMR spectra showed two singlets (36H each) for the *tert*-butyl protons, one triplet (8H) for the NCH_2 protons, another triplet (8H) for the OCH_2 protons, two singlets (8H each) for the aromatic protons and one singlet (4H) for the imino protons, the magnetic equivalences suggesting a D_{2h}-symmetric structure. Therefore, the thiacalixarene units are expected to adopt a cone conformation by virtue of a pseudo-cyclic hydrogen bond among two hydroxy protons and two ethereal oxygen atoms at the lower rims, although the possibility of



Scheme 2.

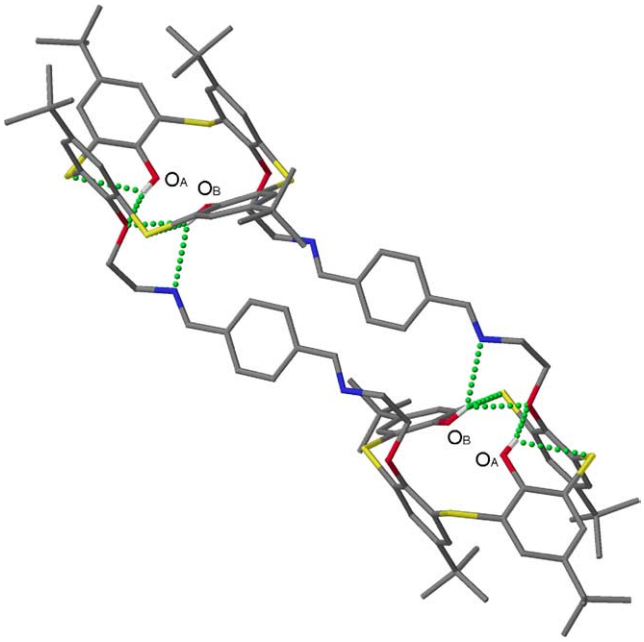


Figure 1. X-ray structure of bisthiacalixarene **3a**. Hydrogen atoms except for the hydroxy groups are omitted for clarity. Dotted lines indicate hydrogen bonds.

1,3-alternate conformation cannot completely be ruled out.

The X-ray crystallographic analysis of bisthiacalixarene **3a**, however, revealed that the compound adopts a less symmetric structure in the crystal (Fig. 1).[10] The bisthiacalixarene was of nanometer size, the length being 3.033 nm. The compound had a C_i-symmetric structure, in which two calixarene units, as well as two linkers, were related to each other by an inversion center. The two facing benzene rings of a thiacalixarene unit bearing the linking moiety were slightly tilted toward the same direction and almost parallel to each other, while the two phenolic rings were tilted so as to place the hydroxy groups inside the calixarene ring in such ways that one of the hydroxy protons (O_AH) formed two hydrogen bonds with an ethereal oxygen and a bridging sulfur atom, and another hydroxy proton (O_BH) formed three hydrogen bonds with the same ethereal oxygen, a bridging sulfur and an imino nitrogen atom, the bond lengths of $O_AH\cdots OCH_2$, $O_AH\cdots S$, $O_BH\cdots OCH_2$, $O_BH\cdots S$, and $O_BH\cdots N$ being 2.057, 2.651, 2.170, 2.594, and 2.583 Å, respectively. The two benzene units of the linking moiety were on different planes and parallel to each other.

To evaluate the binding ability of bisthiacalixarenes **3a**–**d** toward different metal ions, two-phase solvent extraction of metal picrates (Na^+, K^+, Cs^+, and Ag^+) was carried out. A chloroform solution of a bisthaicalixarene (0.1 mM) was equilibrated with an aqueous solution of a metal picrate (0.1 mM) under neutral conditions. The ion extractability (*E*) was calculated from the picrate concentration in the organic phase, which was determined by UV spectroscopy. The results are summarized in Figure 2. All the bisthiacalixarenes quantitatively and

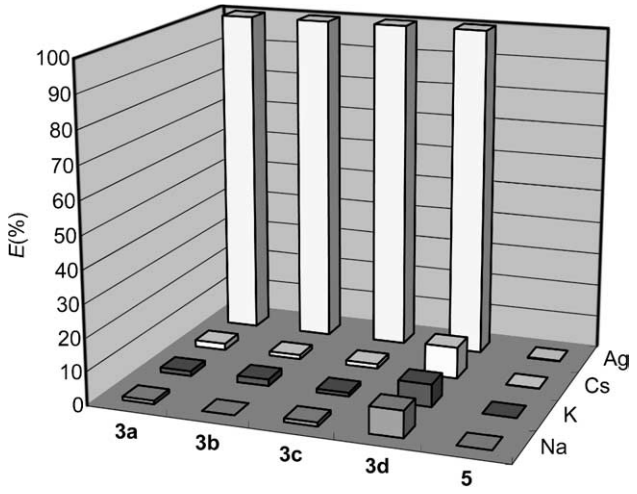


Figure 2. Extractability of metal picrates with host molecules **3** and **5**. Source phases: aqueous phase, 2.0 mL, [metal picrate] = 0.1 mM; organic phase, chloroform, 2.0 mL, [host] = 0.1 mM. The data are the average values of three independent runs.

selectively extracted silver ion from the aqueous phase into the organic phase. In the case of the corresponding conventional biscalixarenes, the extraction of silver ion was neither quantitative nor selective, where the *E* value varied depending on the aromatic unit of the linking moiety from ~50% (in the cases of *m*- and *p*-phenylene) to ~70% (in the cases of pyridine-2,6-dily and thiophene-2,5-dily).[3] We also carried out the same experiment for open-chain compound **5** and found that the compound did not extract any of these metal ions (Fig. 2). It should be noted that *p*-*tert*-butylthiacalix[4]arene per se extracts soft metal ions but the extractability depends on pH.[11] For example, silver ion is quantitatively extracted under slightly acidic conditions (pH 5.9) but the *E* value was only 7% under the neutral conditions.[12] From these observations, we may conclude that the presence of the thiacalixarene unit is not sufficient for the efficient extraction of silver ion under biologically important neutral conditions and that a proper preorganization of soft binding sites in the host molecule is necessary.

In order to gain insight into the extraction mechanism, ^{1}H NMR titration experiments were carried out. Addition of small aliquots of silver picrate to a solution of bisthiacalixarene **3a** in $CDCl_3$–CD_3OD (9:1) broadened the spectrum of **3a**, indicating that the complexation with silver picrate was occurring. During the titration, distinct change in the chemical shift was observed only for the signal of the imino protons. Figure 3 shows the change in the chemical shift of the imino protons ($\Delta\delta$) plotted against the amount of silver picrate added. The $\Delta\delta$ value increased in proportion to the amount of the picrate added and became constant after the addition of 1.0 mol equiv of the picrate, indicating that the stoichiometry of the complex is 1:1 in the solution. We tried similar titration experiments, as well as the Job's plots, for compounds **3b**–**d** but determination of the stoichiometry of these complexes failed because of severe peak broadening and in one case (**3d**), a slow metal exchange between the complexed and uncomplexed species, which made the spectrum complicated.

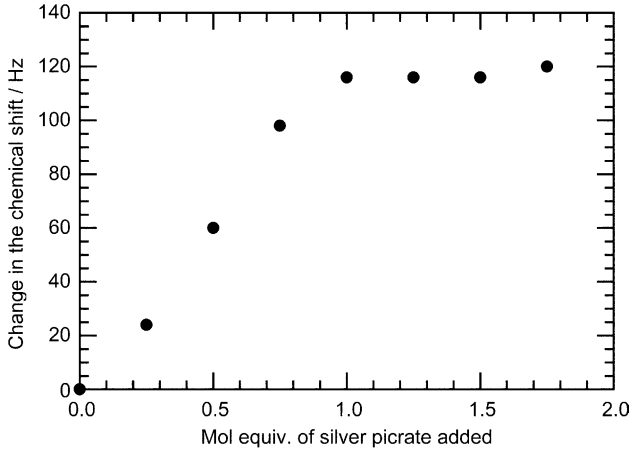


Figure 3. ^{1}H NMR titration experiment of compound **3a** with silver picrate. The chemical-shift change was measured for the signal of the imino protons.

In the case of the conventional biscalixarenes, the aromatic ring of the linking moiety affected the ion extractability (vide supra).[3] In addition, ^{1}H NMR signals of the linking moiety strongly shifted on complexation with silver ion, while the chemical shifts of the calixarene skeleton, as well as those of the *tert*-butyl groups, were not affected much. From these observations, we suggested that the host molecule binds the silver picrate by an imino nitrogen, ethereal oxygen and donor in the heteroaromatic ring.[3] On the other hand, bisthiacalixarenes **3** quantitatively extracted silver ion regardless of the linking moiety and only the ^{1}H NMR signal of the imino protons shifted considerably on complexation with silver ion (vide supra). From these observations, combined with the fact that the replacement of the conventional calixarene unit with the thiacalixarene significantly improved the ion extractability, we may conclude that the bisthiacalixarenes bind the silver picrate by an imino nitrogen and a bridging sulfur atom, presumably with the assistance of an adjacent ethereal or hydroxy oxygen.

In conclusion, we have synthesized novel bisthiacalix[4]arenes by condensation of *O*,*O*″-bis(2-aminoethyl)-*p*-*tert*-butylthiacalix[4]arene with different aromatic dialdehydes. These bisthiacalixarenes quantitatively and selectively extracted silver ion from aqueous into organic phase. This extraction behaviors were much better than those reported for the analogues having conventional calix[4]arene units. We also prepared calixpodand **5**, which did not extract any of the metal ions under the same conditions. Thus, we have demonstrated an efficient approach to preorganize binding sites suitable for silver ion by using a thiacalixarene as a molecular scaffold.

Acknowledgements

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8. General procedure for the synthesis of bisthiacalixarenes **3a**–**d**: To a solution of *O*,*O*″-bis(2-aminoethyl)-*p*-*tert*-butylthiacalix[4]arene **1** (0.806 g, 1.00 mmol) in ethanol (25 mL) was added a solution of dialdehyde **2a**–**d** (1.00 mmol) in ethanol (10 mL). The mixture was refluxed for 2 h with stirring to separate a solid, which was filtered, washed, and crystallized from dichloromethane–methanol. Compound **3a**: mp 315–317 °C (Found: C, 68.72; H, 6.79; N, 2.89. Calcd for $C_{104}H_{120}N_4O_8S_8$: C, 68.99; H, 6.98; N, 3.09); IR (KBr) 1645 cm^{-1} (C=N); ^1H NMR (400 MHz, $CDCl_3$): δ 0.77 [36H, s, $C(CH_3)_3 \times 4$], 1.34 [36H, s, $C(CH_3)_3 \times 4$], 4.12 (8H, t, $J = 6.4$ Hz, $NCH_2 \times 4$), 4.84 (8H, t, $J = 6.4$ Hz, $OCH_2 \times 4$), 6.92 (8H, s, ArH), 7.68 (8H, s, ArH), 7.72 (8H, s, ArH), 8.17 (4H, s, ArOH), 8.21 (4H, s, HC=N × 4); FAB-MS *m*/*z* 1810 [$(M+2)^+$]. Compound **3b**: mp 308–312 °C (Found: C, 68.78; H, 6.75; N, 2.86. Calcd for $C_{104}H_{120}N_4O_8S_8$: C, 68.99; H, 6.98; N, 3.09); IR (KBr) 1647 cm^{-1} (C=N); ^1H NMR (400 MHz, $CDCl_3$): δ 0.77 [36H, s, $C(CH_3)_3 \times 4$], 1.30 [36H, s, $C(CH_3)_3 \times 4$], 4.09 (8H, t, $J = 6.4$ Hz, $NCH_2 \times 4$), 4.84 (8H, t, $J = 6.4$ Hz, $OCH_2 \times 4$), 6.91 (8H, s, ArH), 7.62 (8H, s, ArH), 7.27 (2H, t, $J = 7.6$ Hz, ArH), 7.77 (4H, d, $J = 7.6$ Hz, ArH), 8.02 (2H, s, ArH), 8.29 (4H, s, ArOH), 8.30 (4H, s, HC=N × 4); FAB-MS *m*/*z* 1810 [$(M+2)^+$]. Compound **3c**: mp 310 °C (Found: C, 67.48; H, 6.39; N, 4.48. Calcd for $C_{102}H_{118}N_6O_8S_8$: C, 67.59; H, 6.56; N, 4.64); IR (KBr) 1651 cm^{-1} (C=N); ^1H NMR (400 MHz, $CDCl_3$): δ 0.77 [36H, s, $C(CH_3)_3 \times 4$], 1.33 [36H, s, $C(CH_3)_3 \times 4$], 4.18 (8H, t, $J = 5.2$ Hz, $NCH_2 \times 4$), 4.82 (8H, t, $J = 5.2$ Hz, $OCH_2 \times 4$), 6.92 (8H, s, ArH), 7.57 (2H, t, $J = 8.0$ Hz, PyH), 7.65 (8H, s, ArH), 7.97 (4H, d, $J = 8.0$ Hz, PyH), 8.17 (4H, s, ArOH), 8.47 (4H, s, HC=N × 4). Compound **3d**: mp 300–305 °C (Found: C, 65.77; H, 6.26; N, 2.87. Calcd for $C_{100}H_{116}N_4O_8S_{10}$: C, 65.90; H, 6.41; N, 3.07); IR (KBr) 1633 cm^{-1} (C=N); ^1H NMR (400 MHz, $CDCl_3$): δ 0.74 [36H, s, $C(CH_3)_3 \times 4$], 1.30 [36H, s, $C(CH_3)_3 \times 4$], 4.12 (8H, t, $J = 5.2$ Hz, $NCH_2 \times 4$), 4.92 (8H, t, $J = 5.2$ Hz, OCH_2), 6.86 (8H, s, ArH), 7.48 (4H, s, ArH), 7.56 (8H, s, ArH), 7.83 (4H, s, ArOH), 8.41 (4H, s, CH=N × 4); FAB-MS *m*/*z* 1823 [$(M+3)^+$].
9. Synthesis of calixpodand **5**: To a solution of *O*,*O*″-bis(2-aminoethyl)-*p*-*tert*-butylthiacalix[4]arene **1** (48.0 mg, 59.5 μmol) in methanol (10 mL) was added thiophene-2-carbaldehyde **4** (13.4 mg, 119 μmol). The mixture was refluxed for 24 h. The solvent was evaporated to leave a crude product, which was crystallized from chloroform–ethanol to give compound **5** (47.3 mg, 80%), mp 295–297 °C; IR (KBr) 1633 cm^{-1} (C=N); ^1H NMR (400 MHz, $CDCl_3$): δ 0.77 [18H, s, $C(CH_3)_3 \times 2$], 1.32 [18H, s, $C(CH_3)_3 \times 2$], 4.15 (4H, t, $J = 6.0$ Hz, $NCH_2 \times 2$), 4.82 (4H, t, $J = 6.0$ Hz, $OCH_2 \times 2$), 6.91 (4H, s, ArH), 6.99–7.01 (2H, dd, $J = 6.2$ and 4.4 Hz, thiophene), 7.28 (2H, d, $J = 6.2$ Hz, thiophene), 7.39 (2H, d, $J = 4.4$ Hz, thiophene), 7.60 (4H, s, ArH), 7.93(2H, s, ArOH × 2), 8.60 (2H, s, HC = N × 2); FAB-MS *m*/*z* 995 [$(M+1)^+$].
10. Crystal data: triclinic, space group *P*-1, $a = 13.9307(15)$ Å, $b = 14.5505(15)$ Å, $c = 16.2044(17)$ Å, $\alpha = 94.292(3)°$, $\beta = 106.918(3)°$, $\gamma = 106.254(3)°$, $V = 2972.9(5)$ $Å^3$, $Z = 2$. The details of the crystal data have been deposited with Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 253682.
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