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Preparation of a novel C_3 symmetrical hexahomotrithiacalix[3]arene that binds Ag^+ with high selectivity

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It has been demonstrated that a novel C_3 symmetrical receptor, hexahomotrithiacalix[3]arene **1a**, which contains sulfur bridges, is able to form a complex with Ag^+.

Keywords: homocalixarenes, ionophores, metal ion selectivities, sulfides

Calixarenes and related macrocycles have received considerable attention for their supramolecular chemistry as ionophoric receptors and potential enzyme mimics in biology. Chemical modification of calixarene represents a simple though effective and versatile way of producing receptors with highly selective cation binding properties.[1]

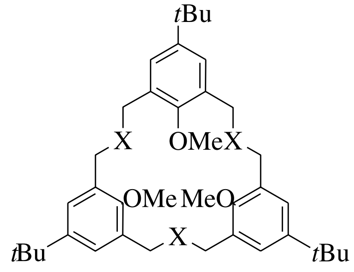
Certain metal ions are known to interact with aromatic hydrocarbons to form π-complexes. Electron transfer between the aromatic moiety and the positively charged metal ion contributes the bonding in these π-complexes.[2] However, such interactions are very weak; therefore only a low percentage (approximately 10%) of metal ions can be extracted from an aqueous solution by such aromatic hydrocarbons.[3] In contrast, as metal ions strongly bind to heteroatoms, calixarenes, which have skeletal heteroatoms such as sulfur, nitrogen, or oxygen, are able to extract metal ions from aqueous solution with greater efficiency.[4]

Although many hetero-calix[4]arene and related compounds have been reported,[5] few studies have been conducted on hetero-calix[3]arene compounds that contain sulfur bridges.

We have previously reported that calix[3]arenes containing ethanedithia-groups as pendant groups in the bridges show very high Ag^+ selectivity (Ex % =%) relative to alkali and alkaline earth metals and most of the other transition metal cations.[6] Herein, we describe the preparation and ion selectivity of hexahomotrithiacalix[3]arene **1a**, which contains sulfur bridges (Fig. 1).

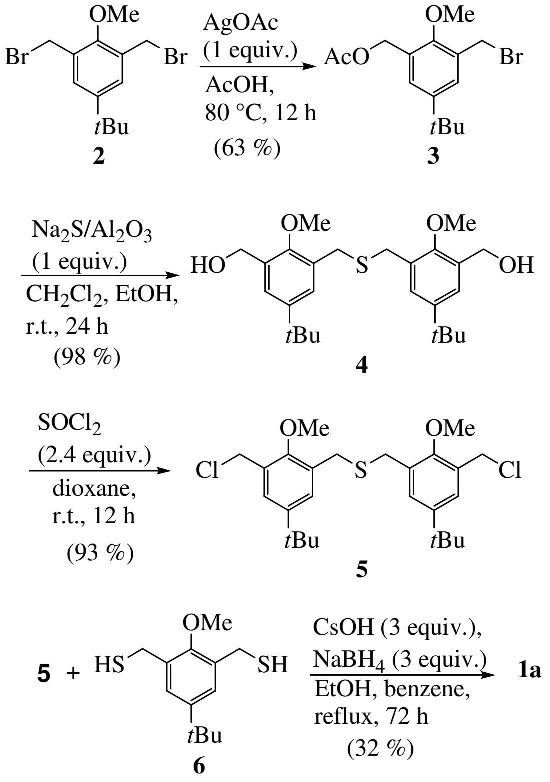
Hexahomotrithiacalix[3]arene **1a** was prepared from 2,6-bis(bromomethyl)-4-*tert*-butylanisole **2** in a four-stage process with a total yield of 18 % (Scheme 1).

Although two possible conformational isomers of **1a**, the cone and partial-cone conformations, exist, the protons of the ArCH_2SCH_2Ar methylene group and the protons of the methoxy groups appeared as singlets even at temperatures below –50 °C, and the rate of the conformational ring flipping of **1a** is faster than the NMR time scale even at this temperature.



1a; X=S,
1b; X=SO_2, **1c**; X=O

Fig. 1 Structure of homocalix[3]arenes.



Scheme 1 Multi-step synthesis of **1a**.

The ionophoric properties of compound **1a** towards alkali and alkaline earth metals and most of the transition metal cations (K^+, Na^+, Cs^+, Ag^+, Tl^{3+}, Cr^{3+}, Co^{2+}, Cd^{2+}, Al^{3+}, Pb^{2+}, Ba^{2+}, Cu^{2+}, Ni^{2+}, Zn^{2+}) were evaluated using the picrate extraction method.[9] Solvent extractions of aqueous metal picrates into an organic host solution (CH_2Cl_2, 0.25 mM) containing **1a** were performed at 25 °C (Fig. 2). The percentages of extraction (Ex%) were calculated by measuring the picrate concentration in the aqueous phase. Compound **1a** had a maximum affinity for Ag^+ (Ex % = 44.1%) in comparison with other metal ions (Ex % < 5.4%), and thus possesses high selectivity for Ag^+ (Fig. 3). In contrast, hexahomotrisulfonylcalix[3]arene **1b**,[10] which was prepared by oxidation of **1a** with *m*-CPBA in dichloromethane, and hexahomotrioxacalix[3]arene **1c**[4c] demonstrated poor Ag^+ affinity, having Ex % of 4.7 % and 2.1%, respectively. The remarkably high selectivity of **1a** for Ag^+ over all other metal ions suggests that the lone pairs of sulfur atoms converge to form a soft coordination site for Ag^+. Conversely, neither **1b** nor **1c** formed complexes with Ag^+,

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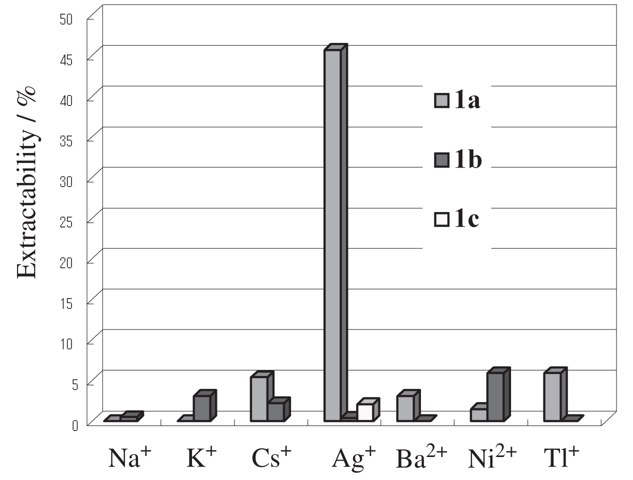


Fig. 2 Percent extraction of metal ions by calixarenes.

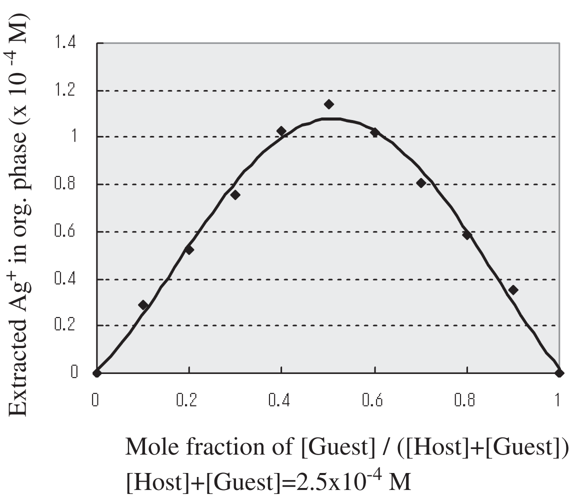


Fig. 3 Job plots of the extractions of Ag$^+$ with host **1a**.

suggesting that Ag$^+$ does not have affinity for the π-electrons of the benzene rings of **1b** and **1c**, or nine or six oxygen bridges. Taken together, these results suggest that the electron effect of the three sulfur bridges could play an important role in complex formation with Ag$^+$. However, the extraction rate was lower than the calix[3]arenes containing ethanedithia groups which we reported before.[6] A difference of extraction rate may be a consequence of the number of sulfur atoms.

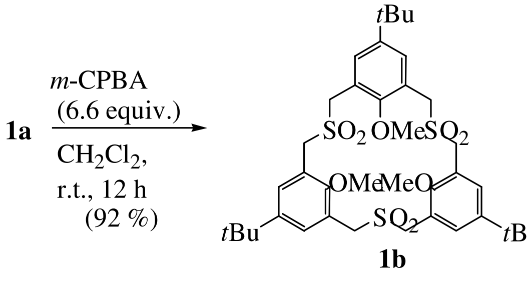
In order to determine the number of Ag$^+$ cations involved in complex formation with **1a**, we computed Job plots of Ag$^+$ extractions with host **1a** under uniform conditions throughout the tested range of concentrations (Fig. 4). The maximum molarity of a **1a**-Ag$^+$ solution was 0.5 M, demonstrating 1:1 complex formation between **1a** and Ag$^+$.

In summary, we report a process for the preparation of a novel Ag$^+$ receptor, hexahomotrithiacalix[3]arene **1a,** and have demonstrated highly selective complex formation between **1a** and Ag$^+$ at a ratio of 1:1.

Experimental

All melting points (Yanagimoto MP-S1) were uncorrected. Proton nuclear magnetic resonance (1H NMR) spectra were recorded on a Nippon Denshi JEOL FT-300 spectrometer. Chemical shifts are reported as δ values (ppm) relative to internal Me4Si. Mass spectra were obtained on a Nippon Denshi JMS-01SA-2 mass spectrometer at an ionisation energy of 70 eV; *m/z* values reported include the parent ion peak. IR spectra were obtained on a Nippon Denshi JIR-AQ2OM spectrophotometer as KBr disks. UV spectra were measured by Shimadzu 240 spectrophotometer. Elemental analyses were performed by Yanaco MT-5.

Synthesis of 2-acetoxymethyl-6-bromomethyl-4-tert-butylanisole (**3**): To a solution of 2,6-bis(bromomethyl)-4-*tert*-butylanisole **2** (10.42 g, 30 mmol) in acetic acid (150 ml) was added silver acetate (5.01 g, 30 mmol), and the mixture was stirred for 12 h at 85 °C. AgBr was filtered off from the reaction mixture. The extract was washed with water and saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (SiO_2, $CHCl_3$) to afford 2-acetoxymethyl-6-bromomethyl-4-*tert*-butylanisole **3** as colourless prisms (6.30 g, 63 % yield).



Scheme 2 Oxidation of **1a**.

^{1}H NMR ($CDCl_3$, 300M Hz) δ 1.31 (s, 9H), 2.12 (s, 3H), 3.92 (s, 3H), 4.58 (s, 2H), 5.15 (s, 2H), 7.34 (d, *J*=2.4, 1H),7.39 (d, *J*=2.4, 1H); MS *m/z* 328 (M$^+$); Anal. Calcd for $C_{15}H_{21}BrO_3$: C, 54.72; H, 6.43. Found: C, 54.85; H, 6.44; IR. (KBr): υ_{max} (cm^{-1}): 3443, 2954, 2873, 2825, 2360, 1733, 1489, 1360, 1246, 1137, 1100, 1022, 1003, 955, 927, 885, 811, 783, 635, 590, 487, 431. M.p. 53 °C.

Synthesis of bis[(5-tert-butyl-3-hydroxymethyl-2-methoxyphenyl) methyl]sulfide (**4**): To a solution of 2-acetoxymethyl-6-bromomethyl -4-*tert*-butylanisole **3** (726 mg, 2.2 mmol) in dichloromthane (86 ml) and absolute ethanol (9 ml) was added Na_2S/Al_2O_3 (814 mg, 2.71 mmol/g, 2.2 mmol) as a finely crushed powder in four equal portions at 15 min intervals, and the mixture was stirred for 24 h at room temperature under argon gas. Na_2S/Al_2O_3 powder was filtered off, and the solution was evaporated *in vacuo*. The residue was purified by recrystallisation from diethyl ether and *n*-hexane to afford bis[(5-*tert*-butyl-3-hydroxymethyl-2-methoxyphenyl)methyl]sulfide **4** as a white powder (660 mg, 98 % yield).

^{1}H NMR ($CDCl_3$, 300M Hz) δ 1.31 (s, 18H), 3.77 (s, 10H), 4.71 (s, 4H), 7.27 (d, *J*=2.1, 2H),7.33 (d, *J*=2.7, 2H); MS *m/z* 446 (M$^+$); Anal. Calcd for $C_{26}H_{38}O_4S$: C, 69.9; H, 8.6. Found: C, 68.6; H, 8.6; IR. (KBr): υ_{max} (cm^{-1}): 3409, 2961, 1482, 1362, 1307, 1255, 1204, 1111, 1009, 947, 883, 813, 790, 648. M.p. 90.5–91.5 °C.

Synthesis of bis[(5-tert-butyl-3-chloromethyl-2-methoxyphenyl) methyl]sulfide (**5**): To a solution of bis[(5-*tert*-butyl-3-hydroxymethyl-2-methoxyphenyl)methyl]sulfide **4** (2.47 g, 5.7 mmol) in dioxane (13 ml) was added $SOCl_2$ (1.61 g, 13.6 mmol) at 0 °C, and the mixture was stirred for 12 h at room temperature. Water was added to the reaction mixture and the extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by recrystallisation from diethyl ether and *n*-hexane to afford bis[(5-*tert*-butyl-3-chloromethyl-2-methoxyphenyl)methyl]sulfide **5** as a white powder (2.06 g, 93 %).

^{1}H NMR ($CDCl_3$, 300M Hz) δ 1.31 (s, 18H), 3.77 (s, 4H), 3.84 (s, 6H), 4.66 (s, 4H), 7.30 (d, *J*=2.4, 2H), 7.34 (d, *J*=2.4, 2H); MS *m/z* 482 (M$^+$); Anal. Calcd for $C_{26}H_{36}Cl_2O_2S$: C, 64.6; H, 7.5. Found: C, 64.5; H, 7.5; IR. (KBr): υ_{max} (cm^{-1}): 2950, 1688, 1602, 1480, 1364, 1268, 1173, 1106, 997, 942, 886, 813, 790, 689, 639, 555. M.p. 82 °C.

Synthesis of hexahomotrithiacalix[3]arene (**1a**): mixture of bis[(5-*tert*-butyl-3-chloromethyl-2-methoxyphenyl)methyl]sulfide **5** (2 g, 4.1 mmol) and 2,6-bis(mercaptomethyl)-4-*tert*-butylanisole **6** (1.06 g, 4.1 mmol) in benzene (100 ml) was added dropwise to a solution of CsOH (2.44 g, 12.4 mmol) and $NaBH_4$ (511 mg, 12.4 mmol) in ethanol (900 ml) for 48 h under reflux. When the addition was complete, the solution was stirred for 24 h under reflux. The reaction mixture was evaporated *in vacuo*, and the residue was washed with water and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (SiO_2, benzene) to afford hexahomotrithiacalix[3]arene **1a** as colourless prisms (870 mg, 32 % yield).

^{1}H NMR ($CDCl_3$, 300M Hz) δ 1.29 (s, 27H), 3.17 (s, 9H), 3.64 (s, 12H), 7.28 (s, 6H); MS *m/z* 666 (M$^+$); Anal. Calcd for $C_{39}H_{54}O_3S_3$: C, 70.2; H, 8.2. Found: C, 70.3; H, 8.3; IR (KBr): υ_{max} (cm^{-1}): 2953, 2823, 1602, 1490, 1307, 1253, 1204, 1130, 1103, 1011, 937, 883 812, 794, 643. M.p. 93–95 °C.

Synthesis of hexahomotrisulfonylcalix[3]arene (**1b**): To a solution of hexahomotrithiacalix[3]arene **1a** (10 mg, 0.02 mmol) in CH_2Cl_2 (0.4 ml) was added *m*-chloroperbenzoic acid (35 mg, 0.1 mmol) at 0 °C, and the mixture was stirred for 12 h at room temperature. The reaction mixture was evaporated *in vacuo*. The residue was purified by washing with methanol to afford hexahomotrisulfonylcalix[3]arene **1b** as a colourless powder (10 mg, 92 %).

^1H NMR ($CDCl_3$, 300M Hz) δ 1.32 (s, 27H), 3.41 (br, 9H), 4.11 (br, 12H), 7.69 (s, 6H); MS *m/z* 762 (M^+); Anal. Calcd for $C_{39}H_{54}O_3S_3$: C, 61.4; H, 7.1. Found: C, 61.1; H, 7.1; IR (KBr): υ_{max} (cm^{-1}): 3446, 2962, 1488, 1322, 1258, 1204, 1158, 1117, 1003, 897, 762, 492, 432. M.p. >300 °C.

Solvent extraction

Two-phase solvent extraction was carried out between water (3.7 ml, [alkali hydroxide] = 0.1 M, [metal nitrate] 7 0.1 M, and [PicOH] = 2.5×10^{-4} M) and CH_2Cl_2 (3 ml, **1a** = 2.5×10^{-4} M, **1b** = 2.5×10^{-4} M or **1c** = 2.5×10^{-4} M). The mixture was stirred for 30 min at 25 °C. The mixture was centrifuged (3000 rpm, 2 min, 25 °C). The extractability was determined by UV-vis spectroscopy from the decrease in the absorbance of the picrate ion in the aqueous phase.

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