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Synthesis and cationic selectivity studies of novel calix[4]arene derivatives containing heteroatom at the lower rim

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A series of calixarene derivatives 2—5 containing heteroatom at the lower rim have been synthesized. ^{1}H NMR studies and crystallographic structures demonstrated that the calix[4]arene derivatives adopted cone conformations. Their cationic binding abilities and selectivities towards heavy and transition metal ions have been evaluated by solvent extraction of aqueous metal picrates. The obtained results indicated that the introduction of nitrogen, sulfur, and/or phosphor atoms to the calix[4]arene framework could effectively enhance their binding ability and selectivity for heavy and transition metal ions, such as Pb^{2+} or Ag^+.

calix[4]arene, synthesis, cationic selectivity, solvent extraction

Calixarenes, a kind of metacyclophane molecule, are very amenable to chemical modification at the upper or/and lower rim to improve the original ions/molecule binding abilities and selectivities. Indeed, a wide variety of lipophilic/hydrophilic calix[4]arene-based receptors have been developed through the involvement of ether, ester, ketone, carboxylic acid, amide, and thioamide binding sites to the lower/upper rim of calix[4]-arenes[1−4]. Moreover, through introduction of heteroatoms to the calixarene framework, the high binding ability and selectivity ionic receptor could be obtained due to the high affinity of heteroatoms with heavy and transition metal ions[5−9]. In the present work, a series of novel modified calix[4]arene derivatives **2**—**5** containing heteroatom at the lower rim have been synthesized (Figure 1), and ^{1}H NMR and crystallographic structures studies demonstrated that the calix[4]arene derivatives adopted cone conformations with a methanol solvent molecule included into the cavity. Solvent extraction experiments indicated that these calix[4]arene derivatives showed enhanced binding ability and selectivity for Ag^+ Hg^{2+}, and Pb^{2+}.

1 Experimental

1.1 Apparatus

The melting points were measured by an XT-4 apparatus without being corrected. ^{1}H NMR spectrum was recorded at 300 MHz in $CDCl_3$, using tetramethylsilane as an internal reference. Elemental analysis was performed on a Perkin-Elmer 2400C instrument. UV-vis spectra were recorded in a conventional quartz cell (10×10×45 mm^3) at 25℃ on a Shimadzu UV-2401 PC spectrometer. Crystal data was collected on a Siemens SMART CCD instrument.

Starting materials were commercially available unless otherwise noted. In the solvent extraction experiment, CH_2Cl_2 and H_2O were saturated with each other prior to use. $KSP(S)R_2$ (R=—OCH_3, OCH_2CH_3, $OCH(CH_3)_2$)[10]

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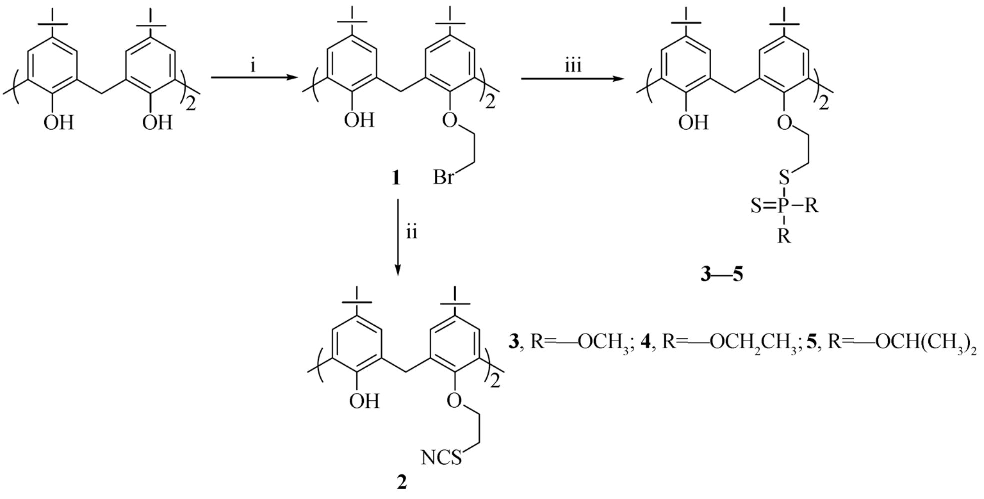


i, $BrCH_2CH_2Br$, K_2CO_3; ii, KSCN; iii, $KSP(S)R_2$

Figure 1 Synthesis route and structures of calix[4]arene derivatives containing heteroatom.

and compound **1** was synthesized according to the reported method[11].

1.2 Synthesis of modified calix[4]arenes at the lower rim

1.2.1 5,11,17,23-tetra-*tert*-butyl-26,28-[bis-2-(thiocyanatethoxy)]-25,27-dihydroxy-calix[4]arene (**2**). A sample of 5,11,17,23-tetra-*tert*-butyl-26,28-bis(bromoethoxy)-25,27-dihydroxy-calix[4]arene (**1**) 1 g (1.6 mmol) and KSCN 0.8 g (7 mmol) were added in 25 mL acetone. The mixture was refluxed for 7 h with stirring under N_2. After cooling, the solvent was evaporated under reduced pressure, and the solid was dissolved in $CHCl_3$ and washed with water (1∶1, volume ratio). The partitioned organic phase dried with $MgSO_4$ overnight. The solvent was removed and the crude product was recrystallized from $CHCl_3/CH_3OH$ (1∶1, volume ratio) to give pure product **2** in 82% yield. m.p. 201—202℃. ^1H NMR ($CDCl_3$), δ: 0.91 (s, 18H, $C(CH_3)_3$), 1.32 (s, 18H, $C(CH_3)_3$), 3.32 (d, 4H, $J = 12$ Hz, $ArCH_2Ar$), 3.35—3.48 (m, 4H, SCH_2), 4.22 (d, 4H, $J = 6$ Hz, OCH_2), 4.31 (d, 4H, $J = 12$ Hz, $ArCH_2Ar$), 6.67(s, 4H, ArH), 6.78 (s, 2H, ArOH), 7.22 (s, 4H, ArH). Anal. Calcd. (%) for $C_{52}H_{62}N_2O_8P_2S_6$: C 56.92, H 5.69, N 2.55; found (%): C 56.84, H 5.88, N 2.64.

1.2.2 5,11,17,23-tetra-*tert*-butyl-26,28-[bis-2-(α,α-dimethoxy-dithiophosphonic acid estersethoxy)]-25,27-dihydroxy-calix[4]arene (**3**). A sample of 5,11,17,23-tetra-*tert*-butyl-26,28-bis(bromoethoxy)-25,27-dihydroxy-calix[4]arene (**1**) 1 g (1.6 mmol) and $KSP(S)(OCH_3)_2$ 1.0 g (5 mmol) were added in 60 mL acetone. The mixture was refluxed for 6 h with stirring under N_2. After cooling, the solvent was evaporated under reduced pressure, and the solid was dissolved in ether and washed with water (1∶1, volume ratio). The partitioned organic phase dried with $MgSO_4$ overnight. The solvent was removed and the crude product was recrystallized from $CHCl_3/CH_3OH$ (1∶1, volume ratio) to give pure product 3 in 84% yield. m.p. 130—132℃. ^1H NMR ($CDCl_3$), δ: 0.92 (s, 18H, $C(CH_3)_3$), 1.33 (s, 18H, $C(CH_3)_3$), 3.32 (d, 4H, $J = 12$ Hz, $ArCH_2Ar$), 3.35—3.47 (m, 4H, SCH_2), 4.24 (t, 4H, $J = 6$ Hz, OCH_2), 4.31 (d, 4H, $J = 12$ Hz, $ArCH_2Ar$), 4.81-4.88 (m, 12H, OCH_3), 6.75 (s, 4H, ArH), 6.84 (s, 2H, ArOH), 7.13 (s, 4H, ArH). Anal. calcd.(%) for $C_{52}H_{74}O_8P_2S_4$: C 62.66, H 7.70; found(%): C 62.58, H 7.88.

1.2.3 5,11,17,23-tetra-*tert*-butyl-26,28-[bis-2-(α,α-diethoxy-dithiophosphonic acid estersethoxy)]-25,27-dihydroxy-calix[4]arene (**4**). The synthetic procedure is similar to synthesis of **3**. Yield: 80%. m.p. 106—108℃. ^1H NMR ($CDCl_3$), δ : 0.94 (s, 18H, $C(CH_3)_3$), 1.32 (s, 18H, $C(CH_3)_3$), 1.36 (d, 6H, $J = 1.5$ Hz, CH_3), 1.41 (d, 6H, $J = 1.5$ Hz, CH_3), 3.34 (d, 4H, $J = 12$ Hz, $ArCH_2Ar$), 3.37—3.48 (m, 4H, SCH_2), 4.23 (t, 4H, $J = 6$ Hz, OCH_2), 4.32 (d, 4H, $J = 12$ Hz, $ArCH_2Ar$), 4.82—4.87 (m, 4H, OCH), 6.76 (s, 4H, ArH), 6.82 (s, 2H, ArOH), 7.12 (s, 4H, ArH). Anal. calcd. (%) for $C_{56}H_{82}O_8P_2S_4$: C 62.66, H 7.70; found (%): C 62.64, H 7.48.

1.2.4 5,11,17,23-tetra-*tert*-butyl-26,28-[bis-2-(α,α-di-*i*-proxy-dithiophosphonic acid estersethoxy)]-25,27-dihydroxy-calix[4]arene (**5**). The synthetic procedure is similar to synthesis of **3**. Yield: 86%. m.p.: 152－154℃, ^{1}H-NMR ($CDCl_3$), δ : 0.93 (s, 18H, $C(CH_3)_3$), 1.30 (s, 18H, $C(CH_3)_3$), 1.34 (d, 12H, J = 1.5 Hz, CH_3), 1.36 (d, 12H, J = 1.5 Hz, CH_3), 3.31 (d, 4H, J = 12 Hz, $ArCH_2Ar$), 3.37－3.49 (m, 4H, SCH_2), 4.19－4.24 (t, 4H, J = 6 Hz, OCH_2), 4.30 (d, 4H, J = 12 Hz, $ArCH_2Ar$), 4.81－4.90 (m, 4H, OCH), 6.75 (s, 4H, ArH), 6.81 (s, 2H, ArOH), 7.06 (s, 4H, ArH). Anal. calcd. (%) for $C_{60}H_{90}O_8P_2S_4$: C 63.8, H 8.03; found (%): C63.64, H 8.31.

1.3 Solvent extraction experiments

The solvents, CH_2Cl_2 and H_2O, were saturated with each other prior to use in order to prevent volume changes of both phases during extraction. Equal volumes (5 mL) of a CH_2Cl_2 solution of the respective calix[4]arene (1.0×10^{-4} mol/L) and of an aqueous solution of each metal picrate (1.0×10^{-4} mol/L) were introduced into a flask, and the mixture was shaken for 5 min (the same results were obtained for 10 min shaking). The equilibrated mixture was then allowed to stand for at least 2 h at 25℃ in order to complete phase separation. The percentage cation extracted (E%) from water into dichloromethane was determined from the measured absorbance of the picrate anion remaining in the aqueous phase after extraction at 356 nm.

2 Results and discussion

2.1 Crystal structure

Crystal data and structural parameters for compounds **4** and **5** are listed in Table 1.

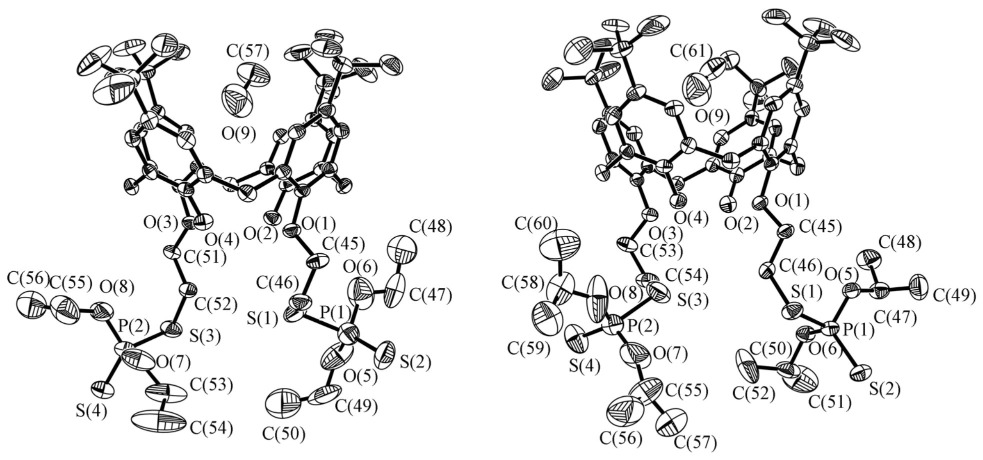
As can be seen from the Figure 2, calix[4]arene derivatives **4** and **5** adopted a similar distorted cone conformation. The degree of distortion could be evaluated from the interplanar angles between the phenyl rings and the plane of the four methylene carbon atoms. For compound **4**, the angles subtended by the unsubstituted rings were 52.1° and 55.9°, while the angles subtended by the substituted rings were 65.0° and 68.2°. For compound **5**, the interplanar angles subtended by the unsubstituted rings were 55.1° and 57.5°, and the angles subtended by the substituted rings were 65.0° and 67.6°. It seems clear that the substituted aromatic rings at the lower rim are more perpendicular to the methylene plane than the unsubstituted ones, which is ascribed to the intramolecular repulse of the substitutes. Furthermore, a methanol solvent molecule is included into the calix[4]arene cavity.

2.2 Solvent extraction

As can be seen from Table 2, the modified calix[4]arene derivatives **2**－**5** showed higher extractabilities for six

Table 1 Crystal data and structural parameters for compounds **4** and **5**

Parameter	Compound **4**	Compound **5**
Empirical formula	$C_{57}H_{86}O_9P_2S_4$	$C_{61}H_{94}O_9P_2S_4$
Formula weight	1105.44	1161.54
Temperature (K)	293(2)	293(2)
Wavelength (nm)	0.071073	0.071073
Crystal system, space group	Monoclinic, *P*2(1)/*n*	Monoclinic, *P*2(1)/*n*
a (nm)	1.3027(4)	1.3786(4)
b (nm)	1.9769(4)	2.0011(6)
c (nm)	2.4358(5)	2.4865(7)
β (°)	102.677(8)	104.350(6)
Volume (nm^3)	6.120(3)	6.646(3)
Z, Calculated density (Mg·m^{-3})	4, 1.200	4, 1.161
F(000)	2376	2504
Crystal dimensions	0.28 mm×0.24 mm×0.20 mm	0.26 mm× 0.24 mm×0.20 mm
Reflections collected/unique	21766/10741 [*R*(int) = 0.0641]	32886/11688 [*R*(int) = 0.1166]
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Final *R* indices [$I>2\sigma(I)$]	$R_1 = 0.0912$, $wR_2 = 0.2287$	$R_1 = 0.1129$, $wR_2 = 0.2514$



4 **5**

Figure 2 ORTEP representation of molecular structures of **4** and **5**.

Table 2 Solvent extractabilities of aqueous metal picrates (Co^{2+}, Cu^{2+}, Zn^{2+}, Pb^{2+}, Hg^{2+}, Ag^{+}) with calix[4]arenes derivatives **1**—**5**[a)]

Ligands	Extractabilities (%)[b)]					
	Co^{2+}	Cu^{2+}	Zn^{2+}	Pb^{2+}	Hg^{2+}	Ag^{+}
1	0.12	0.18	0.10	0.21	—[c)]	0.22
2	0.88	0.53	1.46	6.26	2.31	1.21
3	0.56	0.41	0.33	1.38	0.35	5.78
4	0.76	0.47	0.86	1.56	0.94	7.02
5	0.48	0.26	0.68	0.98	0.62	6.31

a) Temperature 25.0±0.1℃, aqueous phase (5 mL): [picrate]=1.0×10^{-4} $mol\cdot L^{-1}$, organic phase (CH_2Cl_2, 5 mL): [calix[4]arene]= 1.0×10^{-4} $mol\cdot L^{-1}$; b) defined as percent picrate extracted into the organic phase, average of twice independent runs, error < 3% of the reported value; c) — represents the extraction ability is low or no extraction ability.

metal ions than parent calix[4]arene **1**, which, based on the principle of hard and soft acids and bases (HSAB), probably attributed to the introduction of nitrogen, sulfur, and phosphor atoms to the ligands. These heteroatoms possessed relatively larger radius and showed higher affinity to "soft" metal ions. Compounds **3**—**5** exhibited higher Ag^+ extractabilities. A reasonable explanation for this result was that the calix[4]arene derivatives **3**—**5** involved four sulfur atoms at the lower rim of calix[4] arene skeleton, and the proper distance between the sulfur atoms resulted in their stronger coordinate ability with silver (I) ions. Interestingly, in comparison with compounds **3**—**5**, derivative **2** exhibited different selectivity towards all the metal picrates used in the experiment and the extractability for the metal ions by compound **2** decreased in the following order: $Pb^{2+} > Hg^{2+} > Zn^{2+} > Ag^{+} > Co^{2+} > Cu^{2+}$. The major difference between compound **2** and **3**—**5** was the introduction of different heteroatoms to the lower rim of calix[4]arene. For derivative **2**, the modified nitrogen atoms displayed higher ionic binding ability to Pb^{2+}. It was concluded, therefore, that proper modification of calix[4]arene at the lower rim with heteroatoms could not only increase their binding ability toward metal ions, but also change the selectivity to them.

2.3 Binding mode

The binding mode of calix[4]arene derivatives **2**—**5** with metal ions was deduced from a typical ^1H NMR investigation of complexation between compound **5** and silver (I) picrate in $CDCl_3$. The ^1H NMR spectra of the complex are showed in Figure 3, and the corresponding sectional amplificatory spectra are exhibited in Figures 4 and 5 in order to unambiguously analyze and assign chemical shift of proton signals before and after the complexation of **5** with silver (I). It can be seen from Figure 4, the protons signal (d) of free phenols remarkably downfield shifted from δ6.81 to 7.09 upon complexation with silver (I), implying that the oxygen

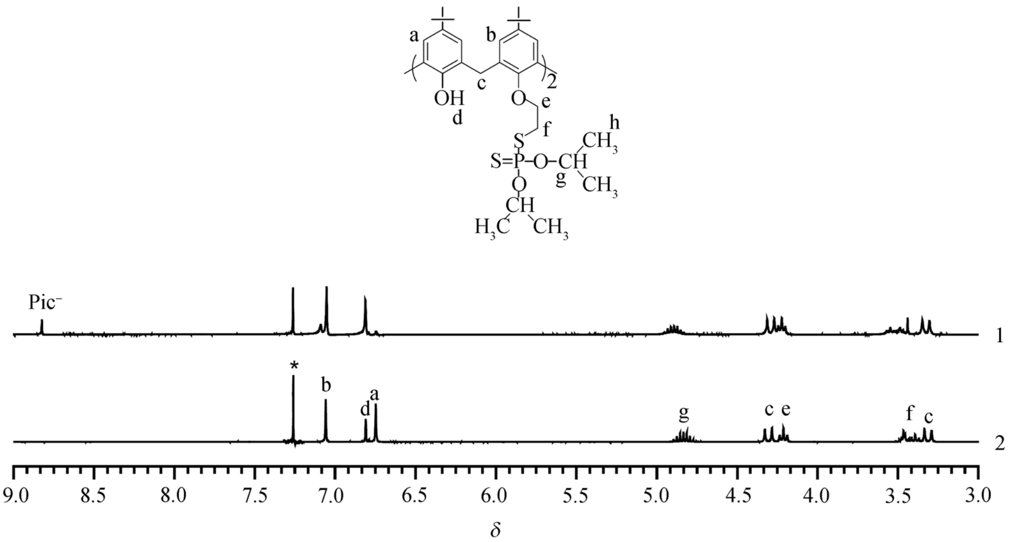


Figure 3 ^{1}H NMR spectra of calix[4]arene derivative **5** (2) and its complexation with silver (I) picrate (1) in $CDCl_3$. "*" Presents solvent peak.

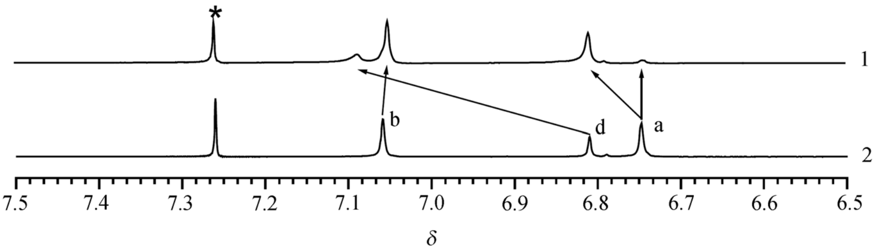


Figure 4 Sectional amplificatory ^{1}H NMR spectra of calix[4]arene derivative **5** (2) and its complexation with silver (I) picrate (1) in $CDCl_3$. * Presents solvent peak.

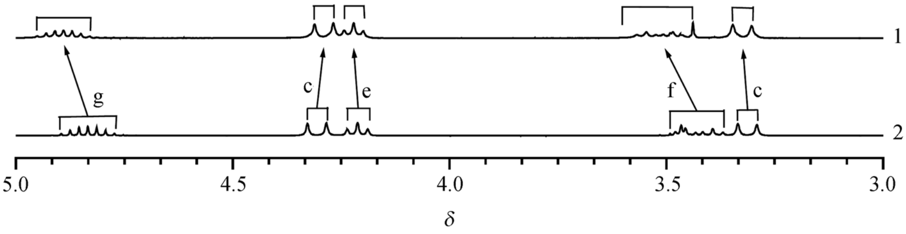


Figure 5 Sectional amplificatory ^{1}H NMR spectra of calix[4]arene derivative **5** (2) and its complexation with silver (I) picrate (1) in $CDCl_3$.

atoms of the phenols coordinated with Ag^+ and lead to the decrease of electron cloud density of oxygen atoms and shield effect towards phenol protons. Accordingly, aromatic protons signals (a) also shifted to the down-field due to the same reason. Furthermore, upon complexation of calix[4]arene receptor **5** with silver (I) ion, the relative larger protons signals f and g revealed the sulfur atoms participated in coordination with silver (I). In summary, based on the results obtained above, the proposed binding mode is showed in Figure 6, in which the metal ion is located in a 3D cavity preorganized by calix[4]arene skeleton and modified "double arms", and the dimension of the cavity could be adjusted by flexible "double arms".

3 Conclusion

A series of heteroatom modified calix[4]arenes at the lower rim have been synthesized, ^{1}H NMR studies and crystallographic structures demonstrated that the calix[4] arene derivatives adopted cone conformations. Their

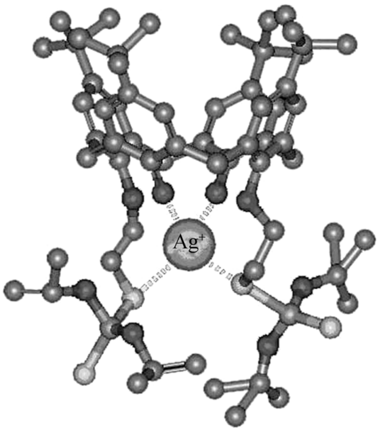


Figure 6 The binding mode of **5**-silver (I) complex deduced by ^{1}H NMR studies (the structure of calix[4]arene derivative **5** was derived from the crystal structure and refined by WebLab ViewerPro software).

cationic binding abilities and selectivities with heavy and transition metal ions have been evaluated by solvent extraction experiments of aqueous metal picrates (Co^{2+}, Cu^{2+}, Zn^{2+}, Pb^{2+}, Hg^{2+}, Ag^+). The obtained results indicated that the introduction of nitrogen atoms could enhance their binding ability and selectivity for Pb^{2+}, and modification of sulfur or phosphor atoms to the calix[4]arene lower rim could increase their affinity forAg$^+$. The investigations provided not only the theoretical background for design and synthesis of high binding ability and selectivity calixarene receptors towards heavy and transition metal ions, but also showed potential application in the purification of polluted water and environmental protection.

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