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Full Paper

Synthesis and Characterization of New Thiacalix[4]arenes Bearing Semicarbazide and Thiosemicarbazide Fragments at the Lower Rim

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Starting from thiacalixarene tetraacetates, tetraacetohydrazides have been prepared and then used for the introduction of semicarbazide and thiosemicarbazide fragments into the lower rim by the reaction with phenyl isocyanate and phenyl isothiocyanate in dry toluene. The structures of the prepared compounds were investigated by FT-IR, FAB-MS, ^{1}H NMR, and X-ray crystallography, and their receptor properties were examined by liquid liquid extraction of dichromate anions.

Keywords thiacalixarene, hydrazine hydrate, phenyl isocyanate, thiosemicarbazide, extraction

Introduction

Calixarenes[1] are very important synthetic macrocyclic host molecules,which accommodate all kinds of chemical guests (*e.g.* neutral, cationic and anionic species). As a result of the above alternative interaction between calixarenes and different guests, they represent a wide range of applications. The field of supramolecular chemistry[2] is considered as one of the most important applications of calixarenes, which mainly depends on the anion-calixarene interaction. Thiacalixarene[3] has been prepared recently as a new member of calixarene family with many features due to the presence of bridging sulfur atoms. Available anion receptors[4] based on both classical calixarenes and thiacalixarenes are still rather limited. Previously, a few anion receptors were prepared by introduction of urea and thiourea moieties at the upper rim as well as at the lower rim.[5-7]

Therefore, our attention has been focused on the preparation of thiacalixarenes with analogue moieties (thiosemicarbazide and semicarbazide derivatives). This modification is expected to additionally increase anion complexation properties. Here, we report the synthesis and structure characterization of four new thiacalix[4]-arene derivatives containing semicarbazide and thiosemicarbazide moieties at the lower rim.

Results and discussion

Thiacalixarene tetrahydrazides in two different conformers **2a** into cone and **2b** into 1,3-alternate have been prepared by Stoikov *et al.*[8] by the hydrazinolysis of the corresponding thiacalixarene tetraacetates **1a** and **1b** with hydrazine hydrate by refluxing in a mixture of solvents (Et_2O and/or THF with ethanol) for 20 and 50 h, respectively. Hydrazinolysis of **1a** and **1b** was studied in this work following slightly different reaction conditions and they were separated in a shorter time of reaction for 8 and 12 h, respectively (Scheme1).

In addition to the different spectroscopic methods (IR, ^{1}H NMR, and mass spectroscopy) which were used for the determination of **2a** and **2b** structures and were adopted by Stoikov *et al.*, thiacalixarene **2a** was recrystallized from ethanol and single crystal was separated and studied by X-ray diffraction method. Its single crystals of **2a** were prepared from ethanol and its structure is shown in Figure 1. The crystallographic data in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC709181. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK [fax: 0044-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk]. X-ray diffraction data were collected on a 590 Enraf Nonius Kappa CCD difractometer by Dr. Aisha Moustafa: $C_{48}H_{64}N_8O_8S_4$, M_r=1009.344, monoclinic, a=21.5525 Å, b=21.4649 Å, c=24.8690 Å, $\alpha=\gamma$=90.00°, β=101.0229°, V=11292.7 Å^3, space group P 21/n, and Z=8. The number of reflections 5354 is recorded in the report, and the R value criterion: $I>3.00\ \sigma(I)$, R_{int}=0.036, $R_{(all)}$=0.168, $R_{(gt)}$=0.087, $wR_{(ref)}$=0.180, $wR_{(all)}$=0.198, $wR_{(gt)}$=0.180, $S_{(ref)}$=5.876, $S_{(all)}$=5.039, $S_{(gt)}$=5.888, the number of variables is 1204 parameters, θ_{max}=20.01°, h=0 to 20, k=0 to 20, l=−23 to 23.

Thiacalixarene hydrazides **2a** and **2b** were reacted with phenyl isothiocyanate or phenyl isocyanate in dry

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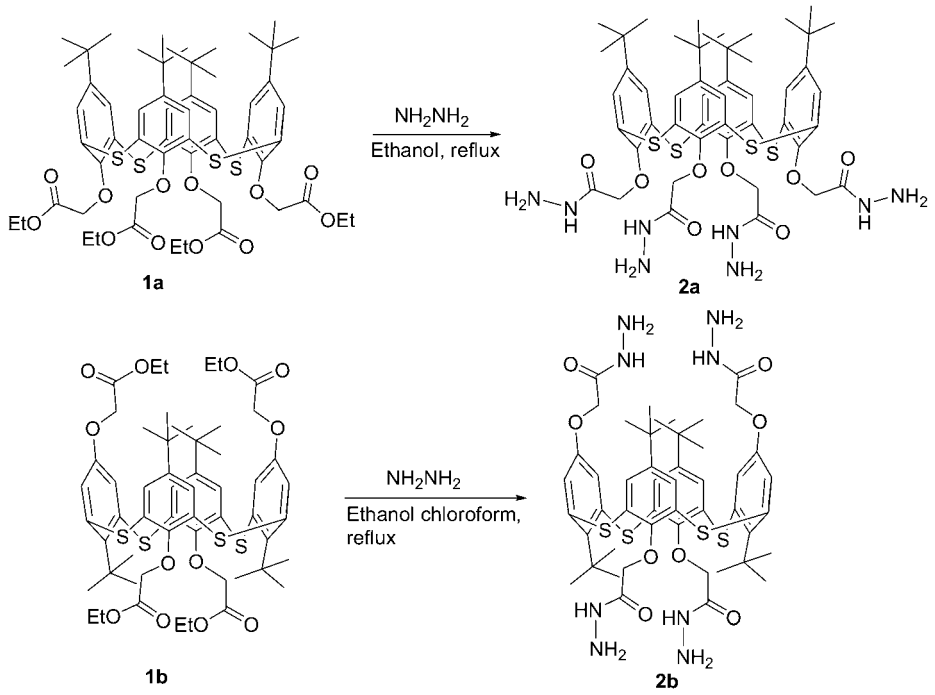
Scheme 1



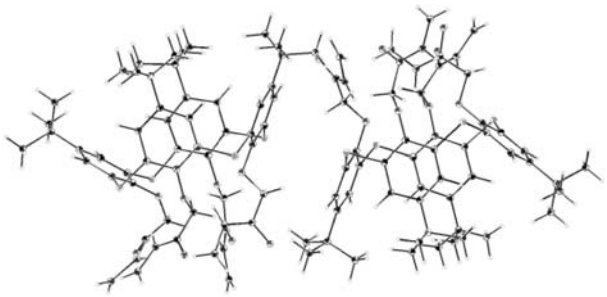
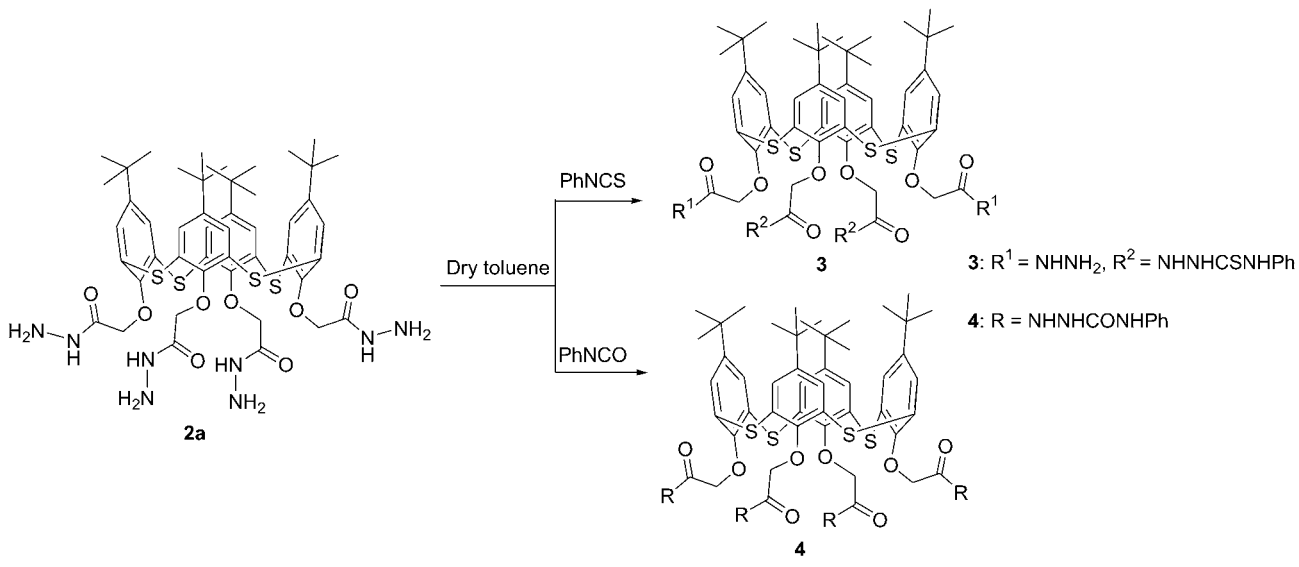


Figure 1 X-ray structure of **2a** (two molecules) in cone conformation. For the sake of clarity, H atoms are not presented.

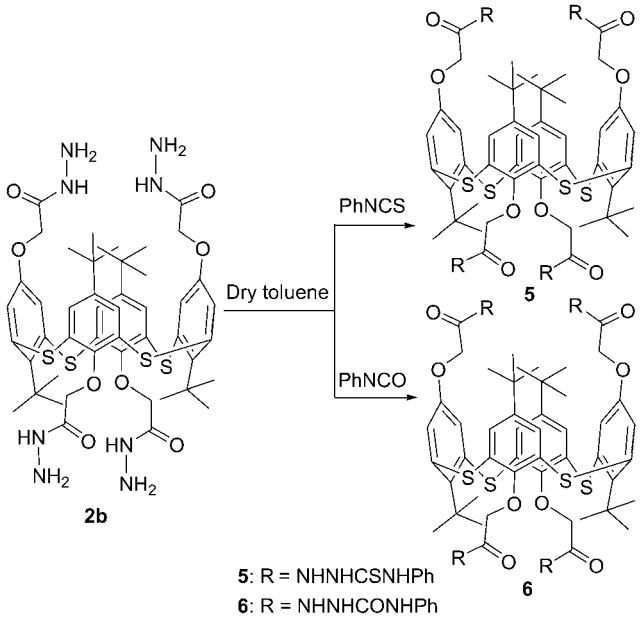
toluene to introduce thiosemicarbazide and semicarbazide fragments at the lower rim (Schemes 2 and 3). The addition of thiacalixarene hydrazide **2a** to phenyl isothiocyanate was stopped at the ratio of two molecules of isothiocyanate to form the insoluble thiacalixarene **3** containing two thiosemicarbazide fragments at the lower rim. The ^{1}H NMR spectrum of this compound exhibits two singlets of *t*-Bu groups (δ 0.88, 1.41) and two singlets of OCH_2CO groups (δ 4.79, 4.99). The phenyl protons (*m*, *p*, and *o*) peak at δ 7.22, 7.37, and 7.48. In addition, different NH peaks appear in δ 9.4—10.1.

Except for the previous reaction (**2a** with isothiocyanate), the reactions of **2a** with isocyanate and **2b** with isothiocyanate or isocyanate afforded thiacalixarenes **4**, **5**, and **6** bearing four semicarbazide or thiosemicarbazide fragments at the lower rim. FT-IR, ^{1}H NMR and

Scheme 2



Scheme 3



FAB mass spectroscopic analyses were used for determination of the structures. These compounds obtained from **2a** (cone) and **2b** (1,3-alternate) conformers have symmetrical structures. So, thiacalixarenes **4** (cone), **5** (1,3-alternate), and **6** (1,3-alternate) are symmetric structures and have simple ^{1}H NMR spectra whereas each kind of protons appear as one peak. For instance, the ^{1}H NMR spectrum of thiacalixarene **4** exhibits a singlet (δ 1.11) of *t*-Bu groups, singlet (δ 5.05) of OCH_2CO groups, multiplet (δ 6.90—6.98) of *m*-PhH groups, multiplet (δ 7.15—7.25) of *p*-PhH groups, multiplet (δ 7.38—7.46) of *o*-PhH and ArH groups, and three singlets (δ 8.1, 8.8, and 10.0) of the NH groups. Finally, the ^{1}H NMR spectra of cone and 1,3-alternate conformers showed a difference in the chemical shift of some groups because of the shielding effect by arene rings in case of 1,3-alternate conformers **5** and **6**.

Extraction studies

To estimate the receptor properties of the synthesized compounds **3**—**6** towards anions, solvent extraction of $K_2Cr_2O_7$ (as dichromate anions: $Cr_2O_7^{2-}$ / $HCr_2O_7^-$) from water into dichloromethane has been carried out in the pH range from 1.0—4.25. The results are summarized in Table 1.

The extraction data (Table 1, Figures 2 and 3) showed that the thiacalixarenes **3** and **5** containing thiosemicarbazide fragment were effective extractants for the extraction of dichromate anion while the extraction yield by thiacalixarenes **4** and **6** containing semicarbazide fragment were less effective at different pH values. For instance, the percentage of dichromate anion extracted was 78.0% for **3**, 9.0% for **4**, 78.0% for **5** and 7.0% for **6** at the pH of 1.5, respectively. The increase in extraction efficiency of thiosemicarbazide based thiacalixarenes **3** and **5** compared to semicarbazide based thiacalixarenes **4** and **6** may be explained as follows: the presence of sulfur atom in thiosemicarbazide fragment adds to the protonable amine moiety-dichromate anion interaction present in both thiosemicarbazide and semicarbazide, and another is soft-soft interaction of Cr with the sulfur donor atom (thiacalixarenes **3** and **5**) stronger than soft-hard interaction of Cr with the oxygen donor atom in thiacalixarenes **4** and **6**.

Table 1 Extraction percentage of dichromate by extractants **3**—**6** at different pH values[a]

Compound	PH		
	1.0	2.25	4.25
3	8.0	45.0	3.0
4	9.0	5.0	2.0
5	78.0	56.0	11.0
6	7.0	5.0	2.0

[a] Aqueous phase, [metal dichromate]$=1.0\times10^{-3}$ mol•L^{-1}; organic phase, dichloromethane, [ligand]$=1.0\times10^{-4}$ mol•L^{-1} at 25 ℃ for 1 h.

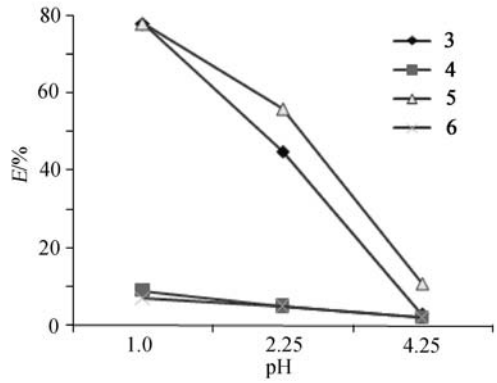


Figure 2 Plots of extraction (*E*) versus pH following the two-phase solvent extraction of dichromate anion with compounds **3**—**6**.

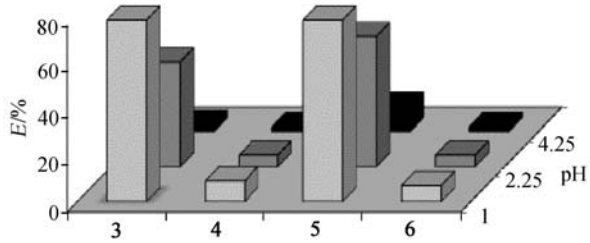


Figure 3 Extraction percentages of dichromate anion with **3**—**6** in pH 1.0—4.25.

Experimental

All NMR spectra were recorded on a Bruker DRX600 NMR spectrometer equipped with a triple-gradient TXI (H/C/N) probe operating at a magnetic field strength of 14.1 T as well as on a Varian Mercury VX-400 NMR spectrometer. Elemental analyses were obtained on a Perkin–Elmer 240c analyzer. UV-visible spectra were obtained on a spectronic 20D$^+$ spectro-

photometer. All melting point were determined on a Koffler melting points apparatus. IR spectra were obtained on a Nicolet 710 FT-IR spectrometer. Mass spectra were recorded on a JEOL-JMS 600 (FAB MS) instrument.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrakis[(hydrazinocarbonyl)methoxy]-2,8,14,20-tetrathiacalix[4]arene (cone) (**2a**)

A mixture of **1a** (1.0 g, 0.94 mmol) and hydrazine hydrate (1.0 mL, 20 mmol) was refluxed for 8 h in 50 mL of absolute ethanol. After cooling and condensation, water was added. The solid residue was separated by filtration, dried and recrystallized from ethanol. IR and ^{1}H NMR spectra were found to be identical with those described in Ref. 8.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrakis[(hydrazinocarbonyl)methoxy]-2,8,14,20-tetrathiacalix[4]arene (1,3-alternate) (**2b**)

A mixture of **1b** (1.0 g, 0.94 mmol) and hydrazine hydrate (2.0 mL, 40 mmol) was refluxed for 12 h in a mixture 50 mL of chloroform and absolute ethanol (1∶1, *V*/*V*). After cooling and condensation to almost dryness, the solid residue was washed by water, filtered, dried and recrystallized from mixture of chloroform-ethanol. IR and ^{1}H NMR spectra were found to be identical with those described in Ref. 8.

General procedure for the synthesis of 3, 4, 5, and 6

A mixture of **2a** or **2b** (0.6 g, 0.60 mmol) with phenyl isothiocyanate (0.42 mL, 6 mmol) or phenyl isocyanate (0.40 mL, 6 mmol) was refluxed for 8 h in dry toluene, concentrated and left to cool to room temperature. *n*-Hexane was added to the mixture and the solid residue was separated.

5,11,17,23-Tetra-*tert*-butyl-25,27-di[(4-phenylthiosemicarbazidyl)carbonylmethoxy]-26,28-dihyroxy-2,8,14,20-tetrathiacalix[4]arene (cone) (**3**) White crystal, yield 80%, m.p. 280 ℃; ^{1}H NMR (400 MHz, DMSO d_6) δ: 0.88 (s, 18H, *t*-Bu), 1.41 (s, 18H, *t*-Bu), 4.32—4.41(br., 4H, NH_2), 4.79 (s, 4H, OCH_2CO), 4.99 (s, 4H, OCH_2CO), 6.99 (s, 4H, ArH), 7.15—7.22 (m, 4H, *m*-PhH), 7.30—7.40 (m, 2H, *p*-PhH), 7.48 (d, J= 7.8 Hz, 4H, *o*-PhH), 7.94 (s, 4H, ArH), 9.45—10.10 (m, 8H, NH); IR (KBr) v: 1699 (CO), 3100—3350 (NH and NH_2) cm^{-1}; FAB$^+$MS *m*/*z*: 1278 (M^+). Anal. calcd for $C_{62}H_{74}N_{10}O_8S_6$: C 58.19, H 5.82, N 10.94, S 15.03; found C 58.32, H 5.67, N 10.72, S 15.22.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrakis[(4-phenylsemicarbazidyl)carbonylmethoxy]-2,8,14,20-tetrathiacalix[4]arene (cone) (**4**) White crystals, yield 85%, m.p. > 300 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.11 (s, 36H, *t*-Bu), 5.05 (s, 8H, OCH_2CO), 6.90—6.98 (m, 8H, *m*-PhH), 7.15—7.25 (m, 4H, *p*-PhH), 7.38—7.46 (m, 16H, *o*-PhH+ArH), 8.1 (s, 4H, CONH), 8.8 (s, 4H, NHCO), 10.0 (s, 4H, NHPh); IR (KBr) v: 1677 (CO), 3267 (NH) cm^{-1}; FAB$^+$MS *m*/*z*: 1484 (M^+). Anal. calcd for $C_{76}H_{84}N_{12}O_{12}S_4$: C 61.43, H 5.69, N 11.31, S 8.63; found C 61.36, H 5.61, N 11.41, S 8.43.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrakis[(4-phenylthiosemicarbazidyl)carbonylmethoxy]-2,8,14,20-tetrathiacalix[4]arene (1,3-alternate) (**5**) White crystals, yield 80%, m.p. 250 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.25 (s, 36H, *t*-Bu), 4.25 (s, 8H, OCH_2CO), 7.10—7.18 (m, 8H, *m*-PhH), 7.30—7.38 (m, 8H, *p*-PhH+CONH), 7.4 (s, 4H, NHCS), 7.43—7.51 (m, 16H, *o*-PhH+ArH), 9.8 (s, 4H, CSNHPh); IR (KBr) v: 1678 (CO), 3279 (NH) cm^{-1}; FAB$^+$MS *m*/*z*: 1548 (M^+). Anal. calcd for $C_{76}H_{84}N_{12}O_8S_8$: C 58.88, H 5.46, N 10.84, S 16.54; found C 58.97, H 5.62, N 10.71, S 16.66.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrakis[(4-phenylsemicarbazidyl)carbonylmethoxy]-2,8,14,20-tetrathiacalix[4]arene (1,3-alternate) (**6**) White crystals, yield 80%, m.p.>300 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.22 (s, 36H, *t*-Bu), 4.70 (s, 8H, OCH_2CO), 6.95—7.03 (m, 8H, *m*-PhH), 7.20—7.30 (m, 8H, *p*-PhH+NH), 7.37—7.45 (m, 16H, *o*-PhH+ArH), 7.80 (s, 4H, NH), 8.85 (s, 4H, NHPh); IR (KBr) v: 1697 (CO), 3224 (NH) cm^{-1}; FAB$^+$MS *m*/*z*: 1484 (M^+). Anal. calcd for $C_{76}H_{84}N_{12}O_{12}S_4$: C 61.43, H 5.69, N 11.31, S 8.63; found C 61.32, H 5.73, N 11.37, S 8.38.

Analytical procedure

The dichromate anion extraction experiments of thiacalix[4]arene derivatives **3**—**6** were performed following Pedersen's procedure.[9] An aqueous solution of potassium dichromate (10 mL of 1.0×10^{-4} mol•L^{-1}; 0.01 mol•L^{-1} KOH-HCl solution was used in order to obtain the desired pH at equilibrium) and thiacalix[4]arene ligand (10 mL of a 1.0×10^{-3} mol•L^{-1}) in CH_2Cl_2 was magnetically stirred in a thermostated water bath at 25 ℃ for 1 h, and finally left standing for an additional 30 min. The concentration of dichromate ion remaining in the aqueous phase was then determined spectrophotometrically. Blank experiments showed that no dichromate extraction occurred in the absence of thiacalix[4]arene. The percentage extraction (E) was calculated from the absorbance A of the aqueous phase measured at 346 nm (for pH 1.0—4.25) using the following expression:

$$E=[(A_0-A)/A_0]\times100\%$$

where A_0 and A are the initial and final concentrations of the dichromate ion before and after the extraction, respectively.

Conclusion

In conclusion, thiacalixarene tetrahydrazides were used for the introduction of semicarbazide and thiosemicarbazide fragments at the lower rim. The synthesized compounds were investigated as anion receptors towards the dichromate anion by liquid-liquid extraction. The extraction efficiency of the thiacalixarenes contain-

ing thiosemicarbazide fragments was higher than that of semicarbazide analogues, which could find remarkable applications to the design of chemical sensors.

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