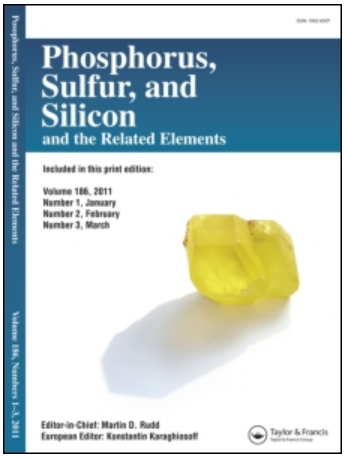

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Synthesis, Separation and Characterization of Thiacalix[4]arenes Diastereomers

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*Two different **1**, 3-Distal thiacalix[4]arenas were prepared by the reaction of thiacalix[4]arene with phenacyl and/or p-nitro phenacyl bromide in acetone or acetonitrile in the presence of dry CsOH. The prepared 1, 3-distal disubstituted thiacalixarenes afforded two pairs of diastereomers upon brominating in chloroform. The obtained diastereomers were separated by fractional crystallization in a mixture dichloromethane-acetone.*

Keywords Bromination; diastereomers; separation; thiacalixarene

INTRODUCTION

Calix[n]arenes—three-dimensional structural compounds—are for many reasons considered one of the most important synthetic construction units in molecular recognition and supramolecular chemistry.[1] Applications of calixarenes range from highly specific ligands in analytical chemistry and medical diagnostic systems to the construction of artificial enzymes and non-linear optics.[2] Thiacalixarenes,[3] a new calixarenes family, are easily prepared from the condensation reaction of *p*-alkylphenol and elemental sulfur under basic conditions. Because of the replacement of methylene groups in classical calixarenes by sulfur atoms in thiacalixarenes, the latter systems have many novel features and represent very promising building blocks and molecular scaffolds

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for the synthesis of more complicated supramolecular systems. Only a limited number of methods for the synthesis of chiral thiacalixarenes[4] are currently known.

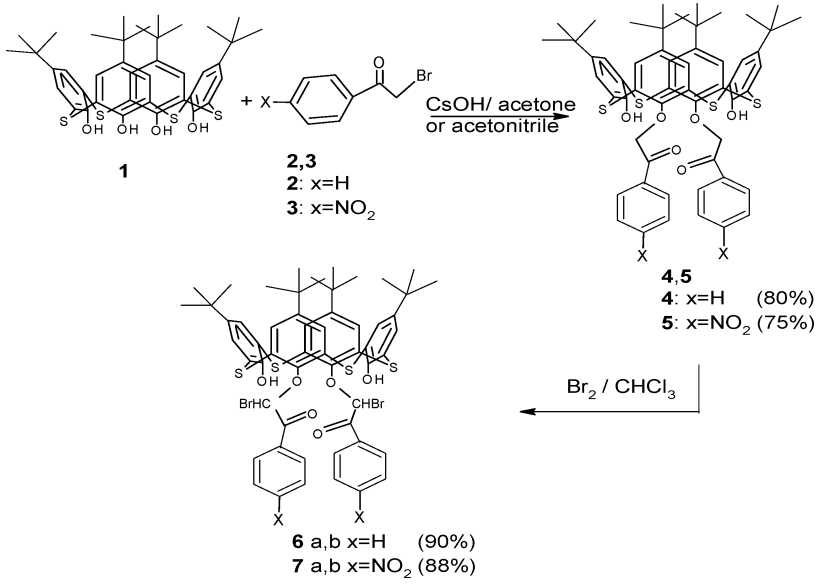
As part of our efforts to generate new chiral thiacalixarenes for enantiomeric discrimination, we here report the synthesis, characterization, and separation of four thiacalixarenes diastereomers.

RESULTS AND DISCUSSION

1,3-Distal disubstituted thiacalixarene **4** have been isolated as side products in our previous work[5] with a low yield by the reaction of thiacalixarenes **1** with phenacyl bromide **2** in acetonitrile in the presence of Cs_2CO_3 as a catalyst. The method has been modified to increase the yield of compound **4** to 80% by changing the base, as well as the molecular ratio of the reactants, where in place of Cs_2CO_3, CsOH was used with stoichiometry 1:2:2, respectively.

The same reaction was repeated using *p*-nitrophenacyl bromide **3** to prepare 1,3-distal disubstituted thiacalixarenes **5** in 75% yield (Scheme 1).

The structures of the obtained compounds were confirmed by ^{1}H-NMR, MALDI-TOF-MS spectroscopy. As reported by Iki et al., the use of Cs metal as a catalyst would lead to products of 1,3-distal substituted



SCHEME 1 Synthesis and separation of two pairs of diastereomers.

thiacalixarene.[6] The ^{1}H-NMR spectra of compounds **4** and **5** were found to be similar for the t-Bu-H, Ar-H and -OCH_2-CO- peaks, and for Ph-H where **4** shows three different peaks one for *o*-Ph-H, other for *m*-Ph-H and the third for *p*-Ph-H, on the other hand compound **5** shows two doublets. Bromination of the two active methylene groups in thiacalixarenes **4**,**5** (Br_2, 2 equiv. in chloroform) produced two pairs of chiral thiacalixarenes **6a**, **6b**, **7a**, and **7b** in 90% (for the mixture of **6a** and **6b**) and 88% (for the mixture of **7a** and **7b**) yield respectively. The separation of the two different diastereomers **6a**, **6b** and **7a**, **7b** were based on the fractional crystallization of the crude **6** and/or **7** from dichloromethane-acetone mixture. The NMR spectra of 1,3-distal **4**,**5** showed the Ar-H protons as two singlets where those protons appeared as four doublets in **6a**, **7a**, and eight doublets in **6b**, **7b**, respectively (cf. Fig. 1).

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. Mass spectrometric analysis was carried out on a MALDI-TOF-MS REFLEX III (Bruker-Daltonics, Germany).

1, 3-Distal Disubstituted Thiacalixarenes 4 and 5—General Procedure

Thiacalixarene **1** (1.00 g, 1.4 mmol) was suspended in dry acetonitrile or acetone-containing melting dried CsOH (0.41 g , 2.8 mmol) and phenacyl bromide (0.55 g, 2.8 mmol) or *p*-nitro-phenacyl bromide (0.68 g, 2.8 mmol). The reaction mixtures were refluxed for 24 h; after cooling, the reaction mixture was treated in two different ways: in case of phenacyl bromide the product **4** was separated from the solid layer; and in case of the *p*-nitro phenacyl bromide the product **5** was separated from the filtrate layer.

Compound 4

^{1}H (400 MHz, $CDCl_3$, 25°C): δ (ppm): 0.81 (s, 18H, 2 Bu^t); 1.32(s, 18H, 2 Bu^t); 6.17 (s, 4H, 2 —OCH_2CO—); 6.95 (s, 4H, Ar-H); 7.48 (t, 4H, *m*-Ph-H, J= 7.9);7.59 (t, 2H, *p*-Ph-H, J=7.9); 7.67 (s, 4H, Ar-H); 8.16 (d, 4H, *o*-Ph-H, J= 7.9); 8.35 (s, 2H, OH)., IR, (KBr, v/cm^{-1})3395, 3366 cm^{-1} (OH), 1699 cm^{-1}, (OH); M.P. 241–242°C *m/z* 957 (MH^+).

Compound 5

^{1}H (400 MHz, $CDCl_3$, 25°C):δ (ppm): 0.80 (s, 18H, 2 Bu^t); 1.35(s, 18H, 2 Bu^t); 6.20 (s, 4H, 2 -OCH_2CO-); 6.95 (s, 4H, Ar-H); 7.7 (s, 4H, Ar-H);

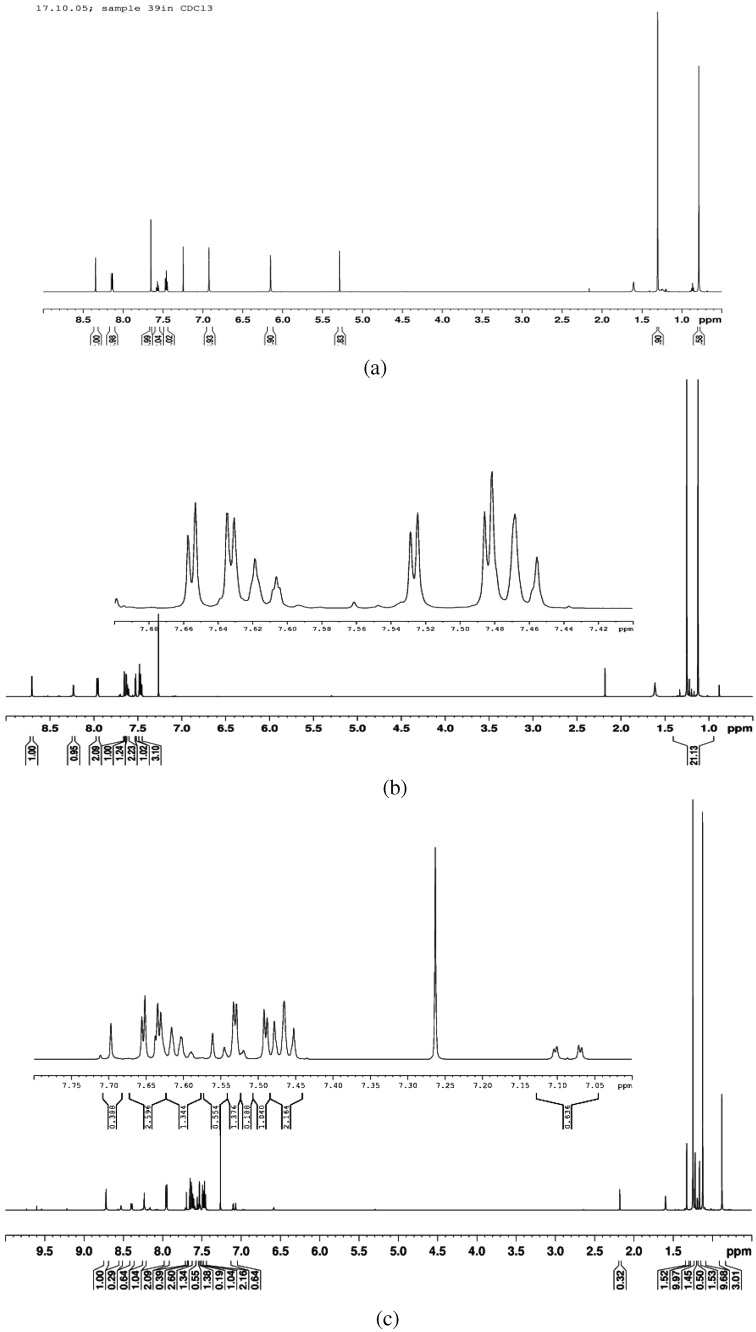


FIGURE 1 (a) ^{1}H-NMR Spectra of Compound **4**; (b) ^{1}H-NMR Spectra of Compound **6a**; (c) ^{1}H-NMR Spectra of Compound **6b**.

8.12 (s, 2H, OH). 8.35 (d, 4H, *o*-Ph-H); 8.40 (d, 4H, *m*-Ph-H, J = 9.5). M.P.170°C; *m/z* 1047 (MH^+).

Bromination of 1,3-Distal Disubstituted Thiacalixarenes 4, 5—General Procedure

A solution of bromine in 5 ml of $CHCl_3$ was added dropwise to a solution of 0.5 g of compound 4 and/or **5** in 20 ml $CHCl_3$ in 30 min. The bromine color disappeared during the addition. The reaction mixture was stirred for further 30 min. The chloroform layer was evaporated in vacuo. The crude solid was recrystallized from dichloromethane-acetone into **6a** and **6b** as first and second fractions from **4**; **7a** and **7b** diastereomers as first and second fractions from **5**.

Compound 6a

^1H (400 MHz, $CDCl_3$, 25°C): δ (ppm): 1.1 (s, 18H, Bu^t); 1.30(s,18H, Bu^t); 7.47 (t, 4H, *m*-Ph–H, J = 7.9); 7.48 (d, 2H, Ar-H, J = 4); 7.53 (d, 2H, Ar-H, J= 4) 7.62 (t, 2H, p-Ph-H, J = 7.9); 7.64(d, 2H, Ar-H, J = 4); 7.66 (d, 2H, Ar-H, J = 4); 7.95 (d, 4H, *o*-Ph-H, J = 7.9); 8.22 (s, 2H, =CHBrCO-,); 8.7 (s, 2H, OH). M.P. 200°C (decomp.).; *m/z* 1117 (MH^+).

Compound 6b

^1H (400 MHz, $CDCl_3$, 25°C): δ (ppm): 1.1 (s, 18H, Bu^t); 1.30 (s, 18H, Bu^t); 7.07 (d, 1H, Ar-H, J = 1.5); 7.1 (d, 1H, Ar-H, J = 1.5); 7.45(t, 4H, *m* = Ph-H, J = 7.9); 7.48 (d, 1H, Ar-H, J = 2); 7.51 (d, 1H, Ar-H, J = 2); 7.52 (d, 1H, Ar-H, J = 2); 7.59 (t, 2H, *p*-Ph-H, J = 7.9); 7.61(d, 1H, Ar-H, J = 2); 7.62 (d, 1H, Ar-H, J = 2);7.64 (d, 1H, Ar-H, J = 2); 7.94 (d, 4H, *o*-Ph-H, J = 7.9); 8.20 (s, 2H, =CHBrCO-); 8.71(s, 2H, OH). M.P. 190°C (decomp.); *m/z* 1117 (MH^+).

Compound 7a

^1H (400 MHz, $CDCl_3$, 25°C): δ (ppm): 1.05 (s, 18H, Bu^t); 1.25(s, 18H, Bu^t); 7.33 (s, 2H, =CHBrCO-,); 7.38 (d, 2H, Ar-H, J = 2);7.43 (d, 2H, Ar-H, J = 2) 7.61 (d, 2H, Ar-H, J = 2); 7.71 (d, 2H, Ar-H, J = 2); 8.7 (s,2H, OH); 8.37 (d, 4H, *m*-Ph-H,J = 6.9); 8.39 (d, 4H, *o*-Ph-H, J = 6.9). M.P. 190°C (decomp.).; *m/z* 1207 (MH^+).

Compound 7b

^1H (400 MHz, $CDCl_3$, 25°C): δ (ppm):. 0.70 (s, 18H, Bu^t); 1.20(s, 18H, Bu^t); 6.91 (d, 1H, Ar-H, J = 1.9); 6.93 (d, 1H, Ar-H, J = 1.9); 7.52 (d, 2H, Ar-H, J = 1.9);7.54 (d, 2H, Ar-H, J = 1.9) 7.64 (d, 2H, Ar-H,J = 1.9); 7.65 (s, 2H, =CHBrCO–); 7.66 (d, 2H, Ar-H, J = 1.9); 7.69 (d, 2H, Ar-H, J = 1.9);7.71 (d, 2H, Ar-H, J = 1.9); 7.42 (d, 4H, *m*–Ph–H, J = 6.9);

8.58 (d, 4H, *o*-Ph-H, J = 6.9). 8.66 (s, 2H, OH). M.P. 136°C ; *m/z* 1207 (MH^+).

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