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Functionalization at the Extraannular Positions of Calix[4]resorcinarene Using a Mannich-type Thiomethylation.

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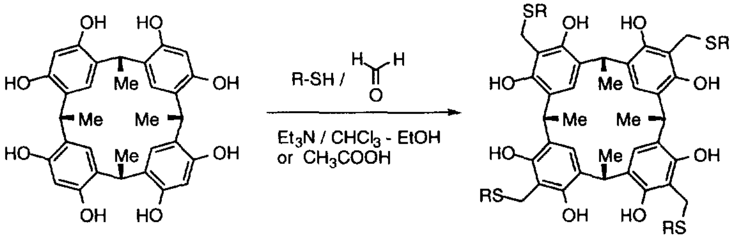
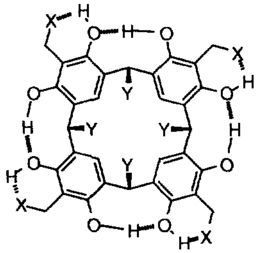
Abstract: Treatment of calix[4]resorcinarene **1** with thiols and formaldehyde in the presence of triethylamine gave thiomethylated calix[4]resorcinarenes **2** in moderate yields. The thiomethylation also took place in acetic acid. Copyright © 1996 Elsevier Science Ltd

Calix[4]resorcinarenes are widely used as host molecules or building blocks for functionalized molecules in the field of supramolecular chemistry.[1,2] Since the eight hydroxyl groups at the extraannular positions play an important role in molecular recognition,[3,4] functionalizations of the macrocycles without conversion of the phenolic hydroxyl groups are of interest. In contrast to the related calixarenes,[5,6] few methods for introducing functional groups at the aromatic rings have been reported.[7,8] Due to the presence of electron-donating hydroxyl groups, the 2-position of resorcinol is susceptible to electophilic aromatic substitution. Therefore, several tetra-substituted calix[4]resorcinarenes have been synthesized by the substitutions. Especially, a variety of aminomethylated calix[4]resorcinarenes have been prepared by Mannich reactions upon treatment with formaldehyde and appropriate amines.[9-11] These studies prompted us to investigate the Mannich-type thiomethylation of calix[4]resorcinarenes, because the thiomethylation is applicable to 2-naphthol.[12] Since phenol forms hydrogen bonding complexes with thioethers,[13] the substitution of four thiomethyl groups between the two hydroxyl groups is expected to form a circular hydrogen bonding network as shown in formula **A**, thereby stabilizing the cone conformation. Such hydrogen bonding networks were observed in calix[4]resorcinarenes having four aminomethyl[10] or acyl substituents.[14]



1 **2**



A

The reaction of calix[4]resorcinarene **1** with arenethiol and formalin proceeded in the presence of triethylamine (see Table, conditions B). In addition, we have found that the thiomethylation occurred in acetic acid (see Table, conditions A). Arenethiols gave the corresponding compounds possessing four thiomethyl substituents in moderate yields under both conditions.[15] On the other hand, when 2-methyl-2-propanethiol was used as a thiol in acetic acid, the yield was very low due to the precipitation of the di- and trisubstituted products during the reaction.

Table. Thiomethylation of Calix[4]resorcinarene (**1**) with Formaldehyde and Thiols[a] to Give **2**

	R	Conditions[b]	Time/h	Yield/%[c]	Mp / Recrystallization Solvent
a	2-Naphthyl	A	27	43	140 °C(dec.) /acetone-ethanol
		B	18	40	
b	C_6H_5	A	23	42	160-162 °C(dec.) /toluene
		B	24	71	
c	4-ClC_6H_4	A	73	51	163 °C(dec.) /methanol
d	4-MeC_6H_4	A	21	52	174-177 °C(dec.) /ethanol-water
e	*tert*-Bu	A	24	7[d]	210-212 °C(dec.) /ethanol
		B	24	42	

a) **1** (1 mmol), 37% formalin (12 mmol), thiol (5 mmol), 60°C.

b) A: acetic acid (20 ml). B: triethylamine (5 mmol) / ethanol (10 ml)-chloroform (10 ml).

c) Isolated yields by recrystallization. d) Isolated yield by TLC separation and recrystallization.

The infrared spectrum of **2e** in $CDCl_3$ showed two types of intramolecular hydrogen bonded OH vibrations at 3379 and 3238 cm^{-1}, which were tentatively assigned to the OH···O and OH···S, respectively.[16] These spectral features suggest the presence of a circular hydrogen bonding network. In contrast, the ^1H NMR spectrum in $CDCl_3$ showed only one signal for the OH protons. Furthermore, the ^{13}C NMR spectrum revealed the symmetrical structure of the resorcinol ring. Although the signals were slightly broadened at -50°C, the conformational freezing of the C_4 structure (formula A) could not be observed. These results indicate that the proton exchange is so fast that **2** exists in a cone conformation with effective C_{4v} symmetry on the NMR time scale.

The thiomethylated calix[4]resorcinarenes, except for **2c**, are soluble in nonpolar solvents such as chloroform and benzene. We are now investigating their host-guest complexation behavior in nonpolar organic media.

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15. All new compounds were characterized by elemental analysis and ^1H NMR, ^{13}C NMR and IR spectra.
16. For comparison, 4,6-di-*tert*-butyl-2-*tert*-butylthiomethylresorcinol shows ν_{OH} at 3636 (free OH) and 3312 (intramolecular hydrogen bonded OH···S) cm^{-1} in $CDCl_3$.

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