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Synthesis of Oligomers of Calix[4]arene with Methylene Bridge at the Upper Rims

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Abstract: Oligomeric mixture of calix[4]arene with methylene bridge at the upper rims was synthesized by the reaction of 5,17-di-*tert*-butyl-25,27-dihydroxy-26,28-dimethoxycalix[4]arene with chloromethyl methyl ether, and the major product is cyclic trimer.

Chloromethylation is an efficient method for the functionalization of calixarenes at the upper rims. Several chloromethylation procedures of calixarenes and synthesis of different derivatives from the chloromethylated products have been reported. [1-9]

Van Loon et al have reported [3] that 5,17-di-*tert*-butyl-25,27-dihydroxy-26,28-dimethoxycalix[4]arene (**1**) could be chloromethylated by chloromethyl *n*-octyl ether in the presence of stannic chloride at - 40 °C to give the bischloromethylated product, 5,17-di-*tert*-butyl-11,23-bis(chloromethyl)-25,27-dihydroxy-26,28-dimethoxycalix[4]arene (**2**), in excellent yield. We also wish to prepare this compound **2**. However, when the reaction was carried out at room temperature with chloromethyl methyl ether and zinc chloride as the chloromethylated reagent,[2] a new product **3** was obtained in quantitative yield. Strangely, this product did not contain any chlorine, but had a methylene linkage as suggested by the ^{1}H NMR spectrum as a singlet at δ 3.74 ppm. Therefore, product **3** may be a mixture of oligomers of calix[4]arene with methylene bridge at the upper rims.

Thus, 200 mg of **3** was subjected to preparative TLC to give six components with the major fraction **3a** weighing 24 mg (ca. 12 %) and together with other five components, *i.e.* 9 mg (ca. 4.5 %) of **3b**, 8 mg (ca. 4 %) of **3c**, 6 mg (ca. 3 %) of **3d**, 7 mg (ca. 3.5 %) of **3e** and 8 mg (ca. 4 %) of **3f**, respectively. From MS and ^{1}H NMR data (Table 1), it is verified that **3a** - **c**

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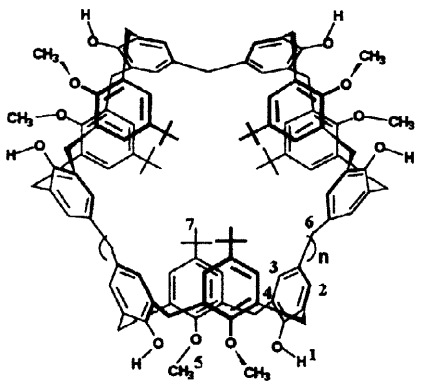
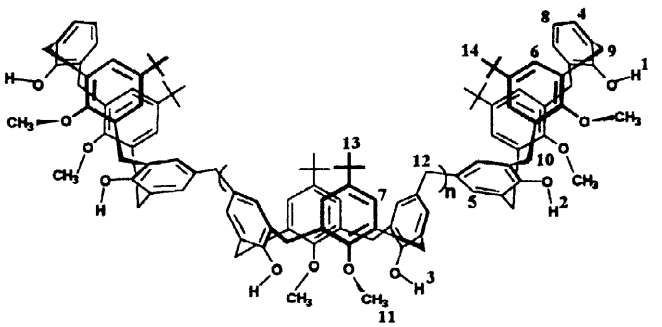
are cyclic trimer, tetramer and pentamer and 3d - 3f are open chain trimer, tetramer and pentamer, respectively. The structure of 3a was also confirmed by ^{13}C NMR spectrum [10] and the signals were assigned by ^{1}H - ^{13}C cosy spectrum. The calix[4]arene unit of these oligomer are linked by methylene bridge at the upper rims. The AB quartet (δ = 4.25 - 4.30 (d), 3.30 - 3.37(d)) pattern of methylene linkage in the ^{1}H NMR spectra indicated that the calix[4]arene unit are in the cone conformation, while the methylene linkage between the upper rims of calix[4]arene unit shows a singlet (δ = 3.75).



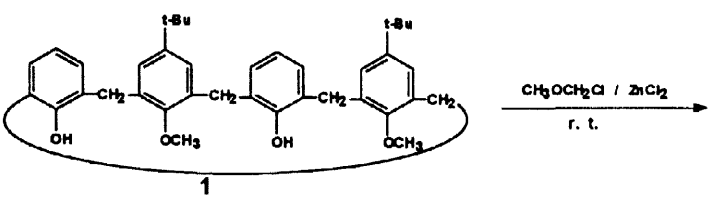


3a, n = 1 **3d**, n = 1

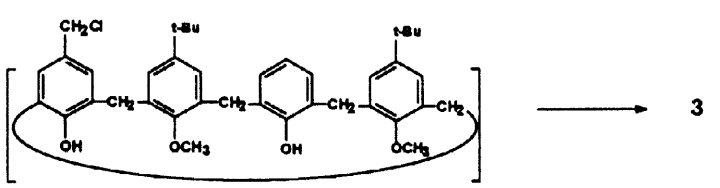
3b, n = 2 **3e**, n = 2

3c, n = 3 **3f**, n = 3

Because the chloromethylation is a step-wise reaction, the monochloromethylated intermediate **A** is formed at first. In our reaction conditions (especially at room temperature), the first formed monochloromethylated calix[4]arene **A** may attack the other aromatic ring of **1** or **A** by the Friedel-Crafts alkylation[6] to give a mixture of oligomers as follows:



1



A

Table 1. ^{1}H NMR (δ values, in $CDCl_3$ with TMS as internal standard) and MS data of **3a - f**

	3a	**3b**	**3c**	**3d**	**3e**	**3f**
H-1	7.22(s)	7.21(s)	7.21(s)	7.37(s)	7.37(s)	7.37(s)
H-2	6.89(s)	6.88(s)	6.88(s)	7.21(s)		
H-3	6.77(s)	6.78(s)	6.78(s)	7.19(s)	7.21(s)	7.21(s)
H-4	4.27(d)	4.25(d)	4.26(d)	7.06(d)	7.07(d)	7.07(d)
	3.30(d)	3.30(d)	3.30(d)			
H-5	3.93(s)	3.93(s)	3.94(s)	6.90(s)	6.90(s)	6.90(s)
H-6	3.74(s)	3.75(s)	3.75(s)	6.78(s)	6.78(s)	
H-7	1.00(s)	0.99(s)	0.99(s)	6.77(s)	6.77(s)	6.78(s)
H-8				6.68(t)	6.68(t)	6.68(t)
H-9				4.30(d)	4.30(d)	4.30(d)
				3.37(d)	3.37(d)	3.37(d)
H-10				4.26(d)	4.25(d)	4.25(d)
				3.30(d)	3.31(d)	3.30(d)
H-11				3.94(s)	3.95(s)	3.95(s)
H-12				3.76(s)	3.75(s)	3.75(s)
H-13				0.99(s)	1.00(s)	0.99(s)
H-14				0.98(s)	0.99(s)	0.98(s)
MS						
Formula	$C_{117}H_{132}O_{12}$	$C_{156}H_{176}O_{16}$	$C_{195}H_{220}O_{20}$	$C_{116}H_{132}O_{12}$	$C_{155}H_{176}O_{16}$	$C_{194}H_{220}O_{20}$
M, calcd.	1729	2305	2882	1717	2293	2870
$[M]^+$, found	1731	2307	2882	1718	2295	2872

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10. **3a**: ^{13}C NMR ($CDCl_3$): δ = 151.4, 150.8, 146.9, 132.7, 132.3, 128.6, 128.5, 125.6(aromatic *C*), 63.3(OCH_3), 40.6(upper rim CH_2), 34.0($C(CH_3)_3$), 31.3($ArCH_2Ar$), 31.2($C(CH_3)_3$).