

Regioselective *distal*-Dibromination of Calix[4]resorcinarene

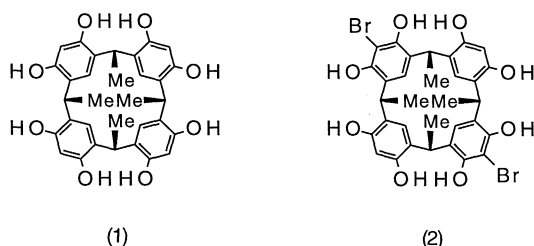
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The partial bromination of calix[4]resorcinarene with a limited amount of *N*-bromosuccinimide was examined. The ratio of the two dibromo derivatives, *distal*- and *proximal*-isomers, was 10:1, which is much different from the statistical value of 1:2. The simple procedure for the preparation of the *distal*-dibromo derivative is described.

Calix[4]resorcinarenes are promising building blocks for the construction of novel molecules in the field of supramolecular chemistry.¹⁻³ In order to design more sophisticated molecules, it was desirable to synthesize partially functionalized macrocycles.

Since the direct introduction of four functional groups at the extraannular position has been carried out by electrophilic aromatic substitutions,⁴⁻⁸ one might expect that partially functionalized calix[4]resorcinarenes would be obtained using a limited amount of reagent. Cram and coworkers reported that a calix[4]resorcinarene was brominated with three moles of *N*-bromosuccinimide (NBS) to give a statistical mixture of mono-, di-, tri-, and tetrabrominated derivatives.⁹ However, the relative distribution of the products was not investigated in detail.



We have studied the regioselectivity of the bromination of calix[4]resorcinarene (**1**) and found a simple procedure for preparing the *distal*-dibromo derivative (**2**). The partial bromination of **1** was carried out using a limited amount of NBS. Thus, a mixture of **1** (0.4 mmol) and NBS (0.8 mmol) in 20 ml of 2-butanone was stirred at 0 °C for 6 h. The crude product was treated with acetic anhydride in the presence of pyridine to give a mixture of octaacetates (**3**) - (**8**).

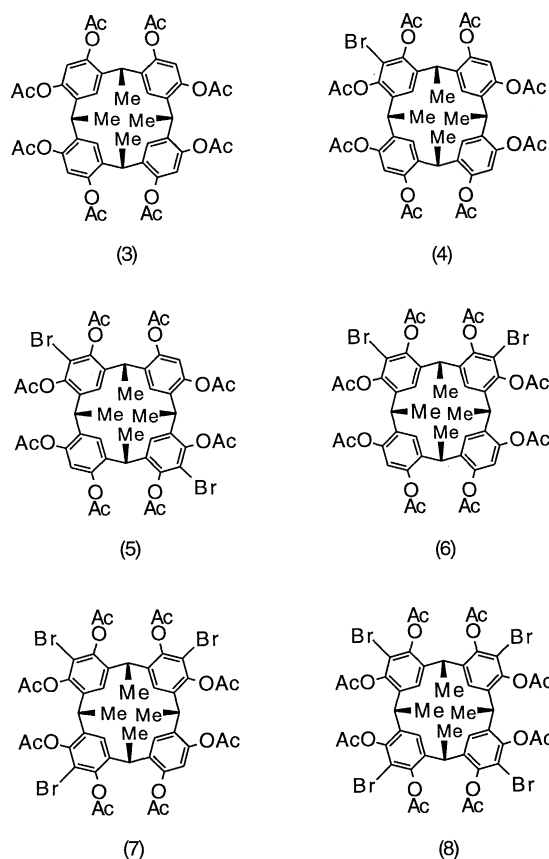
These octaacetates were isolated from the reaction mixture by preparative HPLC, and their structures were confirmed by ¹H and ¹³C NMR spectroscopies. The distribution of these octaacetates was determined by HPLC.¹⁰ The results are shown in Table 1. We also listed the calculated distribution resulting from the random bromination at the extraannular positions without any regioselectivity, *i.e.*, statistical bromination.

In the case of the statistical bromination, the relative distribution of two dibromo derivatives, **5** and **6**, is calculated to be 1:2, which is independent of the amount of NBS used. Furthermore, it is estimated that the yield of **5** is maximized to 12.5% using two molar amounts of NBS. Interestingly, when one or two equivalents of NBS was used, the relative distribution of **5** and **6** was ca. 10:1 in both case, and the yields of **5** were higher than the expected value. The low yields of **6**, **7** and **8** suggest that the second bromination at the neighboring resorcinol

Table 1. Experimental and calculated distribution of the products from the partial bromination of calix[4]resorcinarene^a

Reactant ratio		Product distribution ^b					
		3	4	5	6	7	8
NBS: 1							
1:1	Exptl	51.3	25.2	20.7	1.9	0.9	trace
	Calcd	31.6	42.2	7.0	14.1	4.7	0.4
2:1	Exptl	12.5	19.9	54.7	5.6	6.5	0.8
	Calcd	6.25	25.0	12.5	25.0	25.0	6.25

^a The reaction was done as described in the text. ^b The reaction mixture was acetylated and then analyzed by HPLC.



rings is much slower than the diametrical resorcinol ring. The decreased reactivity is attributed to the electronic effect of bromine substituent, which is transferred through an intramolecular hydrogen bond between the hydroxyl groups of the adjacent

resorcinol units. This effect leads to the predominant formation of the *distal*-dibromo compound. An analogous substituent effect was observed for the bromination of linear phenol oligomers.¹¹ It was, therefore, presumed that the *distal* selectivity was reduced in a more polar solvent. Actually, when DMF was used as a solvent, the **5/6** ratio decreased to 2.6.

The partial bromination described above was conducted under homogeneous conditions. Although the reaction mixture contained **2** as the major product, it was very difficult to separate **2** by simple operations such as repeated recrystallization. However, when the amount of the solvent was reduced, a product that predominantly consisted of **2** was precipitated during the reaction. Single recrystallization of this precipitate from methanol gave **2** in 30% yield.¹² This is, in our opinion, a reasonable value. The major advantage of this method is the ready availability of **1**, the simple procedure for the preparation of **2**, and the usefulness of **2** as a molecular platform for sophisticated supramolecules.

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References and Notes

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- 9 D. J. Cram, M. E. Tanner, and C. B. Knobler, *J. Am. Chem. Soc.*, **113**, 7717 (1991).
- 10 The octaacetates were analyzed on 4.6 mm x 150 mm Cosmosil SSL using chloroform/hexane (2:1 v/v) as the mobile phase at a flow rate of 1.0 ml/min. The retention times are as follows: **3** (7.04 min), **4** (4.81 min), **5** (3.79 min), **6** (3.15 min), **7** (2.70 min), and **8** (2.46 min).
- 11 V. Böhmer, K. Beismann, D. Stotz, W. Niemann, and W. Vogt, *Makromol. Chem.*, **184**, 1793 (1983).
- 12 IUPAC Name: 5,17-Dibromo-4,6,10,12,16,18,22,24-octa-hydroxy-2,8,14,20-tetramethylpentacyclo-[19.3.1.1^{3,7}.-19,13.1^{15,19}]octacos-1(25),3,5,7(28),9,11,13(27),15,17,-19(26),21,23-dodecaene.
Preparation. To a suspension of 2.71 g of **1** (5 mmol) in 60 ml of 2-butanone was added 1.78 g of NBS (10 mmol) with stirring at 25 °C. After a few minutes, the mixture became a yellow solution. The product started to precipitate after 30 min. The mixture was further stirred for 24 h and filtered. The wet solid was recrystallized from hot methanol to yield 1.15 g of **2** (30%), which contained two moles of methanol, m.p. 234-235 °C (dec.). ¹H NMR (DMSO-d₆, 50 °C) δ 1.577 (12H, d, CH₃, J = 7.4 Hz), 4.447 (4H, q, CH, J = 7.4 Hz), 6.241 (2H, s, ArH), 7.198 (2H, s, ArH), 7.301 (2H, s, ArH), 8.412 (4H, s, OH), 9.651 (4H, s, OH). ¹³C NMR (DMSO-d₆, 50 °C) δ 20.4, 29.0, 100.5, 101.9, 122.6, 123.6, 125.3, 126.2, 148.7, 150.9.