REDUCTIVE AND OXIDATIVE REACTIONS OF CALIX[4]ARENE DERIVATIVES

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Summary:Reductive cleavage of 25,26,27,28-tetramethoxy-p-tert-butylcalix[4]arene with K results in the formation of 26,28-dimethoxy-p-t-butylcalix[4]arene. The reaction of 25,27dihydroxycalix[4]arene with NO₂BF₄ in acetonitrile results in its oxidation to calixdiquinone **6**.

Calixarenes are cyclic phenol-formaldehyde oligomers capable of including small organic molecules into their cavities.¹ During the last years considerable synthetic efforts have been invested on improving the binding capabilities of the calixarenes by modifying the ligating groups at the *intra*annular (lower rim) positions.² We have shown³ that the complete array of OH groups of *p-t*-Bu-calix[4]arene (1) and of *p-t*-Bu-calix[8]arene can be removed in a two-step process using the method developed by Kenner and Williams.⁴ In the first step, the OH groups are derivatized into diethyl phosphate esters which are cleaved in the second step by their treatment with K in liquid NH₃. More recently we⁵ and Reinhoudt and coworkers⁶ have shown that the method is applicable for the preparation of partially OH-depleted calixarenes such as **2**.



Since the OH-depleted calixarenes can be used as synthetic intermediates for the preparation of calixarenes with *intra*annular binding groups different from OH, we searched for alternative methods for their large scale preparation without the use of liquid

ammonia. An attractive alternative for the OH \rightarrow H replacement is the conversion of the OH groups into methyl ethers followed by their reductive cleavage with alkali metals.⁷ This cleavage can be carried out at room temperature using a variety of organic solvents, which may play an important role in determining the product of the reaction. For example, anisole is cleaved exclusively at the alkyl-oxygen bond when the solvent is THF while the aryl-O bond is preferentially cleaved when the reaction is carried out in hexane. The crowded 2,6-di-t-Bu-4-methylanisole undergoes exclusive aryl-O cleavage, irrespectively of the solvent.⁷ We therefore decided to prepare the tetramethoxy derivative of *p*-t-butylcalix[4]arene (3) in order to attempt the cleavage of its aryl-O bonds.

Treatment of 1 with 50% aqueous NaOH, dimethyl sulfate and phase transfer catalysis resulted in high yield (74% isolated compound after recrystallization) conversion of 1 into 3. Calixarene 3 has been previously prepared by Gutsche and coworkers by treatment of a DMF-THF solution of 1 with NaH followed by reaction of the resulting phenolate with methyl iodide.⁸ In order to attempt to cleavage of the aryl-O bonds, calixarene 3 was treated with excess K under different conditions (Table 1). In all cases the isolated product was the dimethoxy-*p*-*t*-butylcalix[4]arene 4, i.e. no aryl-O bond was cleaved. Calixarene 4 has been previously obtained by treatment of 1 either with diazomethane⁸ or with methyl tosylate (2 equiv) and K_2CO_3 (1 equiv) in refluxing acetonitrile.⁹

Substrate	Solvent	Conditions	Product
3	THF	reflux overnight	4
3	cyclohexane	reflux overnight	4
3	t-Butylamine	RT overnight	4
5	THF	RT overnight	1 + 2
5	NH ₃	-78 °C ^{5b}	2

Table 1. Reductive cleavage of p-t-Bu-calix[4]arene derivatives with K in different solvents

Since the bis(diethyl phosphate) ester 5⁵ undergoes exclusive aryl-O cleavage by treatment with K/NH₃ it was of interest to see whether the same cleavage could be accomplished by reacting 5 with K in THF at room temperature. The reaction resulted in a mixture of aryl-O and ArO-P cleavage products (a 1:1 mixture of 1 and 2) together with small amounts of an undentified product. From the above results it can be concluded that the best method at present for the preparation of the OH-depleted calixarenes is by treatment of their diethyl phosphate ester derivatives with K/liquid NH₃. The use of the

methyl ether derivatives results only in the regeneration of the OH functionality-

The OH depleted calixarenes could be used as synthetic intermediates for the preparation of *intra*annular substituted calixarenes. We therefore explored the reactions of dihydroxycalixarene **2**. X-ray diffraction showed that the phenolic rings present in **2** are positioned at nonvicinal positions of the macrocycle.⁵ Attempted nitration of **2** resulted in a intractable mixture of compounds. We therefore attempted the nitration of **2** using the mild nitrating agent NO₂BF₄ in acetonitrile. The isolated product was not the dinitro product as expected but the diquinone calixarene **6**.¹⁰



The yellow diquinone **6** was separated by medium-pressure chromatography (SiO₂, eluent: 40% CH₂Cl₂, 60% petroleum ether 60-80 °C). **6** displays at room temperature in CDCl₃ 1H and 1³C NMR spectra compatible with a flexible structure on the NMR timescale. The 1H NMR spectrum (200 MHz, CDCl₃) displays singlets for the t-Bu (δ = 1.23 ppm) and methylene (δ = 3.66 ppm) and three signals for the aromatic protons (δ = 6.64, 7.03 and 7.24 ppm). The quinonic structure of **6** is clearly displayed by the IR spectrum (vco= 1655 cm⁻¹) as well as by the ¹³C NMR spectrum which shows two carbonyl resonances at δ 189.02 and 187.05 ppm.

Several calixquinones have been previously reported in the literature. Taniguchi and coworkers reported the preparation of calix[4]quinone from 1 by three different routes.¹¹ Their synthesis involved the removal of the t-Bu group of 1, the introduction of a functional group (amino, amido or hydroxy) to the *para* position and the oxidation of the resulting product. In order to see whether the calix[4]quinone can be obtained in one step, we reacted 1 or calix[4]arene¹² (i.e. 1 with no t-Bu groups at the para positions) with NO₂BF₄ in acetonitrile, but no calix[4]quinone could be detected (NMR) in the product mixture. Ungaro, Reinhoudt and coworkers reported the preparation of two calix[4]arenes in which two phenol rings were oxidized to quinones.¹³ The key step for the preparation of the compounds was O-alkylation of two phenol rings and oxidation of the two unsubstituted phenol rings with TI(NO₃)₃.3H₂O. Our results indicate that at least

under certain conditions, NO₂BF₄ can also be used as an oxidation agent for the conversion of phenols to p-quinonoid rings.

Work is in progress to determine the crystal structure and redox properties of calixarene 6.

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10. 700 mg of 2 (1.13 mmol) were dissolved in 90 mL dry acetonitrile, and to the stirred solution at 10 °C were added 423 mg (3.18 mmol) of NO₂BF₄. After 45 minutes the reaction mixture was poured into cold water. Extraction with ether and evaporation of the organic phase resulted in 720 mg impure material. The diquinone was purified by medium pressure chromatography (silica, eluent: 90% petroleum ether, 10% EtOAc), affording 105 mg (15%) **5**, mp 201-204 °C.

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