

## **syn-1,2-Dialkylated Calix[4]arenes : General Intermediates in the NaH/DMF Tetraalkylation of Calix[4]arenes**

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*Abstract:* In DMF or acetonitrile with NaH as a base at room temperature the tetraalkylation of calix[4]arenes **1a** and **1b** proceeds via the syn-1,2-disubstituted products to the tetraalkylated calix[4]arenes in the cone conformation. With KH as a base the tetraalkylated calix[4]arenes are predominantly formed in the partial cone conformation, and the reaction proceeds via both the syn-1,3-di and the syn-1,2-disubstituted products. Also the solvent influences the pathway via which tetraalkylation takes place. The syn-1,2-disubstituted calix[4]arenes **2-6** can be isolated in 15-55 % from the NaH/DMF or MeCN reactions when only 2.2 equiv of the electrophile are used.

Calix[4]arenes (**1**) are useful building blocks for host molecules with different properties.<sup>1</sup> These properties are strongly influenced by the conformation of the calix[4]arene moiety after substitution at the phenolic oxygen atoms.<sup>2</sup> The control of the conformation is therefore highly desirable. However, the conformational outcome of tetrasubstitution cannot yet be satisfactorily explained as a function of the reaction conditions. The temperature, the solvent, and the counter cation of the base that is used influence the conformation of the product.<sup>3,4</sup> The syn-1,3-dialkylated calix[4]arenes seem general intermediates and can easily be synthesized selectively.<sup>5</sup> In this communication we present some of our results that shed new light on the mechanism of the tetraalkylation of calix[4]arenes.

Reaction of calix[4]arene **1a** with 6 equiv of NaH as a base and subsequently with 5 equiv of bromoethyl ethyl ether in *N,N*-dimethylformamide (DMF) at 80 °C afforded besides the expected tetraalkylated cone conformer,<sup>6</sup> a second product that crystallized from methanol in 5 % yield and that was identified as the syn-1,2-bis(ethoxyethyl) ether **2a**.<sup>7</sup> The <sup>1</sup>H NMR spectrum of **2a** shows one signal at  $\delta$  8.72 for two OH protons, two triplets at  $\delta$  6.77 and 6.61 for the para hydrogens of the benzene rings (each 2 H), and a triplet at  $\delta$  1.32 (6 H) for the CH<sub>3</sub> of the ethoxyethyl substituent. The three AX signals for the methylene protons at  $\delta$  4.67, 4.45, and 4.33 (1 : 2 : 1 H, ax) and at  $\delta$  3.34 (4 H, eq) confirm that the calix[4]arene is in the cone conformation and is 1,2-disubstituted. The X-ray structure of a single crystal of **2a** unambiguously proved

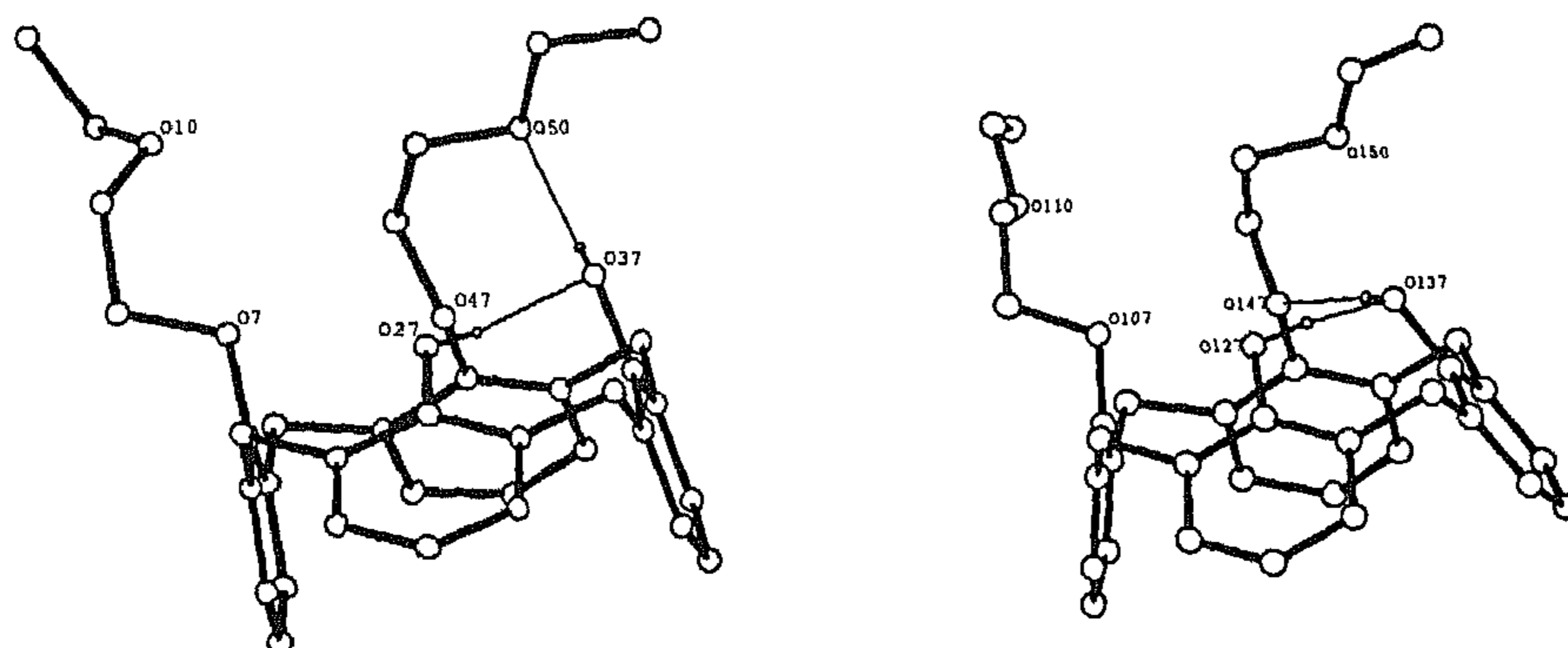


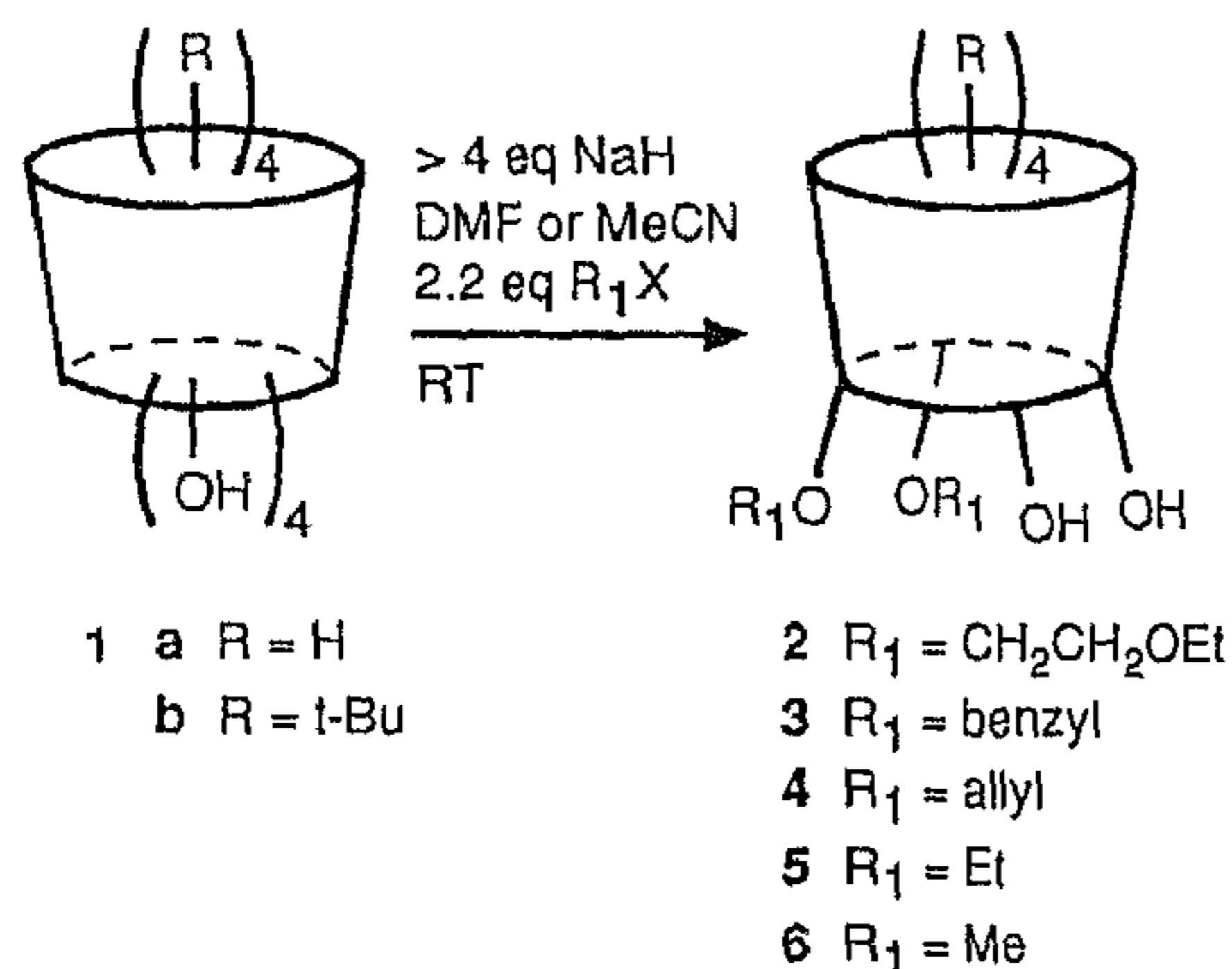
Fig. 1. The two independent molecules in the unit cell of the X-ray structure of compound 2a.

that the product is indeed the *syn*-1,2-bis(ethoxyethyl) ether of calix[4]arene (see Fig. 1).<sup>8</sup>

This unexpected result suggests that under these conditions the *syn*-1,2-dialkylated calix[4]arene is an intermediate for the selective formation of the cone conformation in the NaH/DMF reaction. Indeed, when **1a** or **1b** was treated with excess of NaH in DMF or acetonitrile (MeCN) and subsequently with only 2.2 equiv of an electrophile, the *syn*-1,2-disubstituted calix[4]arenes **2-6** were obtained in moderate yields (Scheme 1, Table 1).<sup>10</sup> In these reactions no or only trace amounts of *syn*-1,3-disubstituted compounds could be detected.<sup>11</sup>

We have investigated whether a general relationship exists between the reaction conditions, the nature of the dialkylated intermediates, and the conformation of the final product, the tetrasubstituted calix[4]arene. The reactions of *p*-*tert*-butylcalix[4]arene **1b** with either excess or only 2.2 equiv of ethyl iodide (EtI) in different base (excess) / solvent mixtures show that the final conformation does depend strongly on the conditions of the reaction (see Table 2).<sup>12</sup> In the reactions in DMF the dialkylated intermediates could be observed, and the results show that whereas with Na<sup>+</sup> only *syn*-1,2-di is formed, with K<sup>+</sup> more *syn*-1,3-di than *syn*-1,2-disubstituted calix[4]arene is formed.

How can we explain these results? After the first alkylation step, the further alkylation of a



Scheme 1

Table 1. Yields of *syn*-1,2-Dialkylated Calix[4]arenes.

Compound	Solvent	Time (h)	Yield (%)
2a	DMF	16	35 <sup>a</sup>
3a	MeCN	24	15
3b	MeCN	16	55
4b	DMF	16	37
5a	DMF	16	35
5b	MeCN	16	41
6b	DMF	16	34
6b	MeCN	16	26

<sup>a</sup>Reaction at 80 °C.



**Table 2.** Results of Ethylation of *p-tert*-Butylcalix[4]arene with Different Bases and Solvents.

Reaction conditions		Conformations of tetraethyl ether after reaction with excess of EtI <sup>a</sup>				Products after reaction with 2.2 equiv of EtI <sup>b</sup>
base	solvent	cone	paco	1,2-alt	1,3-alt	
NaH	DMF	100	c	c	c	mono, 1,2-di, and tetra (cone)
NaH	MeCN	100	c	c	c	mono, 1,2-di, and tetra (cone)
NaH	THF/DMF 10:1	62	28	10	c	mono and tetra
NaH	THF	d	d	d	d	no reaction
KH	DMF	2	64	17	17	mono, 1,2-di / 1,3-di (1:4), and tetra
KH	THF	c	64	5	31	tetra
KOtBu	MeCN	5	84	2	9	mono and tetra
KOtBu	THF	c	77	c	23	no reaction

<sup>a</sup>Reported percentages are based on the integration of the aromatic signals in a 250 MHz <sup>1</sup>H NMR spectrum of the crude reaction mixture; <sup>13</sup>paco = partial cone, 1,2-alt = 1,2-alternate, 1,3-alt = 1,3-alternate.

<sup>b</sup>Products were identified from a <sup>1</sup>H NMR spectrum of the crude reaction mixture.<sup>11</sup>

<sup>c</sup>Not detected in the <sup>1</sup>H NMR spectrum. <sup>d</sup>Only a little amount of monosubstituted product had been formed after 24 h.

calix[4]arene can theoretically proceed via four different disubstituted intermediates, *viz.* the *syn*-1,2, the *syn*-1,3, the *anti*-1,2, or the *anti*-1,3-disubstituted calix[4]arene. Which of the four is formed must depend on the structure of the monoalkylated calix[4]arene trianion. Gutsche and coworkers have reported that the tetraanion of a calix[4]arene exists in the cone conformation with Li<sup>+</sup> or Na<sup>+</sup> as the counter ions (in DMSO-*d*<sub>6</sub> at RT) and that the coalescence temperature for conformational interconversion of the tetraanions decreases from above 140 °C for Li<sup>+</sup>, to 80 °C for Na<sup>+</sup> and 20 °C for K<sup>+</sup> as the counter ion.<sup>15</sup> Apparently, a strong template effect of one or more cations keeps the four negatively charged oxygen atoms close together in the cone conformation. This template effect might also be operative in the monoalkylated trianion and would thus explain the formation of only *syn*-disubstituted calix[4]arenes. How the nature of the cation and of the solvent influences the selective formation of 1,2- or 1,3-dialkylated calix[4]arenes is not clear. We can only speculate about the conformation of the monoalkylated trianion with its associated cations and solvent molecules.

Once the disubstituted calix[4]arene dianion is formed, the number of conformations of the final product is reduced. The *syn*-1,2-di cannot lead to the 1,3-alternate conformation of a tetraalkylated calix[4]arene, and the *syn*-1,3-di not to the 1,2-alternate. Further alkylation will proceed from the dialkylated calix[4]arene dianion(s) to the trialkylated calix[4]arene monoanion(s) and the tetraalkylated product. The properties of these anions are likewise dependent on the reaction conditions and the cation present.

We have shown that the tetraalkylation of calix[4]arenes can proceed via at least two different dialkylated intermediates, depending on the reaction conditions. Detailed studies of the structure and properties of the intermediate anions in the alkylation of calix[4]arenes seem indispensable for clarification of the exact mechanism of tetraalkylation and for control of the conformation of the final tetraalkylated calix[4]arene.

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**Supplementary Material.** Tables of positional parameters, bond distances, and bond angles of the X-ray structure of compound **2a** (11 pages).

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- The first and till now only *syn*-1,2-disubstituted calix[4]arenes that were synthesized by direct substitution are the bis[(2-pyridyl)methyl] ethers of **1a** and **1b**. Bottino, F.; Giunta, L.; Pappalardo, S. *J. Org. Chem.* **1989**, *54*, 5407-5409.
- Crystal data:  $C_{36}H_{40}O_6$ , monoclinic,  $P2_1/n$ ,  $a = 15.142$  (5),  $b = 11.527$  (4),  $c = 37.793$  (8) Å,  $\beta = 97.15$  (2)°,  $V = 6545$  (6) Å<sup>3</sup>,  $D_c = 1.15$  g cm<sup>-3</sup>,  $Z = 8$ ,  $T = 293$  K, Mo  $K_{\alpha}$  radiation,  $\omega$ -2 $\theta$  scan mode,  $3 < \theta < 22.5^\circ$ . Refinement of 4482 observed reflections ( $F_o^2 > 3\sigma(F_o^2)$ ) gave an  $R$ -factor of 7.1 %. The crystal structure contains two independent molecules with different hydrogen bonding schemes. Hydrogen atoms were treated as riding on their parent atoms, except for the phenolic H-atoms, of which positions and thermal parameters were refined. The total number of parameters refined was 774. All calculations were done with SDP.<sup>9</sup>
- Structure Determination Package; B. A. Frenz and Associates Inc., College Station, TX, and Enraf-Nonius, Delft, 1983.
- The new compounds **2-5** and the cone conformer of the tetraethyl ether of **1b** showed satisfactory spectroscopic and elemental analyses.
- Before isolation of a *syn*-1,2-disubstituted product a 250 MHz <sup>1</sup>H NMR spectrum of the crude reaction mixture was recorded in order to determine its composition. Unreacted calix[4]arene and the mono-, *syn*-1,2-di-, and *syn*-1,3-dialkylated intermediates were distinguished by their characteristic OH signals at  $\delta$  10.4-10.2, 10.2-9.8 and 9.6-9.2 (1 : 2), 9.1-8.6, and 7.9-7.5, respectively. Tetrasubstituted products (cone) could in some cases be detected.
- We have chosen this reaction as a model reaction because the four conformations of the product can easily be distinguished in a <sup>1</sup>H NMR spectrum of a mixture of these.<sup>13</sup> A disadvantage is that this reaction does not allow us to study the influence of higher temperatures. Although it has been reported that the tetraethyl ether of *p*-*tert*-butylcalix[4]arene is flexible only at temperatures above 100 °C,<sup>13,14</sup> we observed that, after heating a solution of the cone in DMF with NaH at 50 °C for 24 h, the cone had partly isomerized to the partial cone conformer, the ratio of cone to partial cone being 1 : 1.
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