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

Leo C. Groenen,^a Bianca H. M. Ruël,^a Alessandro Casnati,^c Peter Timmerman,^a Willem Verboom,^a Sybolt Harkema,^b Andrea Pochini,^c Rocco Ungaro,^c and David N. Reinhoudt^{a,*}

Laboratories of ^aOrganic Chemistry and ^bChemical Physics, University of Twente, P. O. Box 217, 7500 AE Enschede, The Netherlands

^cInstitute of Organic Chemistry, University of Parma, Viale delle Scienze, 43100 Parma, Italy

Key Words: Calix[4] arenes; Tetraalkylation; Solvent Effect; Cation Effect; Intermediate Anions

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.¹ These properties are strongly influenced by the conformation of the calix[4]arene molety after substitution at the phenolic oxygen atoms.² 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.^{3,4} The syn-1,3-dialkylated calix[4]arenes seem general intermediates and can easily be synthesized selectively.⁵ 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,⁶ a second product that crystallized from methanol in 5 % yield and that was identified as the syn-1,2-bis(ethoxyethyl) ether 2a.⁷ The ¹H NMR spectrum of 2a shows one signal at δ 8.72 for two OH protons, two triplets at δ 6.77 and 6.61 for the para hydrogens of the benzene rings (each 2 H), and a triplet at δ 1.32 (6 H) for the CH₃ of the ethoxyethyl substituent. The three AX signals for the methylene protons at δ 4.67, 4.45, and 4.33 (1 : 2 : 1 H, ax) and at δ 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).8

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).¹⁰ In these reactions no or only trace amounts of syn-1,3-disubstituted compounds could be detected.¹¹

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).¹² In the reactions in DMF the dialkylated intermediates could be observed, and the results show that whereas with Na⁺ only syn-1,2-di is formed, with K⁺ 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



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

Compound	Solvent	Time (h)	Yield (%)
2a	DMF	16	35ª
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

^aReaction at 80 °C.

Reaction conditions		Conformations of tetraethyl ether after reaction with excess of Etl ^a			hyl ether s of Etl ^a	Products after reaction with 2.2 equiv of EtI ^b
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	mono, 1,2-di, and tetra (cone)
NaH	THF/DMF 10:1	62	28	10	¢	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
КН	THF	c	64	5	31	tetra
KOtBu	MeCN	5	84	2	9	mono and tetra
KOtBu	THF	c	77	с	23	no reaction

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

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

^bProducts were identified from a ¹H NMR spectrum of the crude reaction mixture.¹¹

^cNot detected in the ¹H NMR spectrum. ^dOnly 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⁺ or Na⁺ as the counter ions (in DMSO- d_6 at RT) and that the coalescence temperature for conformational interconversion of the tetraanions decreases from above 140 °C for Li⁺, to 80 °C for Na⁺ and 20 °C for K⁺ as the counter ion.¹⁵ 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 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.

Acknowledgments. The research described in this paper was supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for Scientific Research (NWO), and by the EEC Twinning Project ST2J-0215.

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

REFERENCES AND NOTES

- 1. Gutsche, C. D. *Calixarenes*. Monographs in Supramolecular Chemistry, Vol. 1; Stoddart, F. J., Ed.; The Royal Society of Chemistry: Cambridge, 1989.
- Ghidini, E.; Ugozzoli, F.; Ungaro, R.; Harkema, S.; El-Fadl, A. A.; Reinhoudt, D. N. J. Am. Chem. Soc. 1990, 112, 6979-6985. Shinkai, S.; Otsuka, T.; Fujimoto, K.; Matsuda, T. Chem. Lett. 1990, 835-838.
- 3. Iqbal, M.; Mangiafico, T.; Gutsche, C. D. Tetrahedron 1987, 21, 4917-4930.
- 4. Iwamoto, K.; Fujimoto, K.; Matsuda, T.; Shinkai, S. Tetrahedron Lett. 1990, 31, 7169-7172.
- Collins, E. M.; McKervey, M. A.; Harris, S. J. J. Chem. Soc., Perkin Trans. 1 1989, 372-373. van Loon, J.-D.; Arduini, A.; Coppi, L.; Verboom, W.; Pochini, A.; Ungaro, R.; Harkema, S.; Reinhoudt, D. N. J. Org. Chem. 1990, 55, 5639-5646.
- 6. Chang, S.-K.; Cho, I. J. Chem. Soc., Perkin Trans. 1 1986, 211-214.
- 7. 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.
- 8. 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) Å³, $D_c = 1.15$ g cm⁻³, Z = 8, T = 293 K, Mo K_{α} radiation, ω -20 scan mode, $3 < \theta < 22.5^\circ$. Refinement of 4482 observed reflections ($F_0^2 > 3\sigma(F_0^2)$) 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.⁹
- 9. Structure Determination Package; B. A. Frenz and Associates Inc., College Station, TX, and Enraf-Nonius, Delft, 1983.
- 10. 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 ¹H 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 δ 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.
- 12. We have chosen this reaction as a model reaction because the four conformations of the product can easily be distinguished in a ¹H NMR spectrum of a mixture of these.¹³ 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,^{13,14} 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.
- 13. Groenen, L. C.; van Loon, J.-D.; Verboom, W.; Harkema, S.; Casnati, A.; Ungaro, R.; Pochini, A.; Ugozzoli, F.; Reinhoudt, D. N. J. Am. Chem. Soc. 1991, in the press.
- 14. Araki, K.; Iwamoto, K.; Shinkai, S.; Matsuda, T. Chem. Lett. 1989, 1747-1750.
- Gutsche, C. D.; Iqbal, M.; Nam, K. S.; See, K.; Alam, I. Pure Appl. Chem. 1988, 60, 483-488. Gutsche, C. D.; Alam, I.; Iqbal, M.; Mangiafico, T.; Nam, K. C.; Rogers, J.; See, K. A. J. Inclusion Phenom. Mol. Recognit. Chem. 1989, 7, 73-81.

(Received in UK 26 February 1991)