total), and the solution was stirred for 12 h at 25 °C. The reaction mixture was applied to a small column of Dowex 50X8 (H⁺), and it was eluted with distilled water (2.5 mL). The eluent was neutralized with 10% NaOH (67 μL), a solution of phenacyl bromide (43.4 mg) in acetone (2.5 mL) was added, and the reaction mixture was refluxed for 2 h. The acetone was removed by rotary evaporation, and the remaining aqueous phase was extracted with ether. The ether extract was dried and concentrated, and the residue was purified by preparative thin-layer chromatography (silica gel GF, Analtech Uniplate Taper Plates, chloroform solvent). A band with R_f 4.5–5.5 was scraped off the plate and eluted with chloroform to yield a mixture of the phenacyl esters of 3-hydroxy-3-methylpentanoic acid and maleic acid. The former compound proved to be exclusively the R isomer as judged by ¹H NMR in the presence of the chiral shift reagent (–)-Eu(hfc)₃ (see Figure 1).

Supplementary Material Available: NMR spectra of compounds 3, 5, 6, and 8 (5 pages). Ordering information is given on any current masthead page.

Calix[4]arenes Bridged at the Lower Rim

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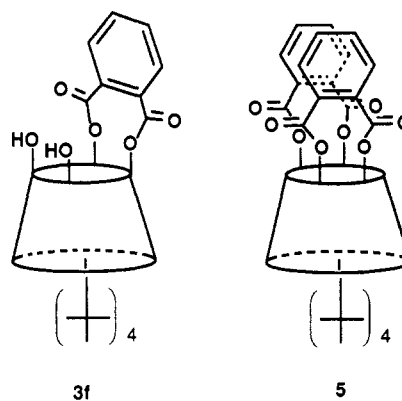D-6500 Mainz, West Germany*

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Calix[4]arenes[1] are building blocks constructed from phenols and formaldehyde like cyclodextrins are built from glucose units. An important method to discriminate between the sugar units of cyclodextrins is to use capping reagents of different size.[2] Depending on the shape of the bridge, selective A,C or A,D capping can be accomplished. In calixarene chemistry only a limited number of bridged calix[4]arenes are known. Two examples exist of calix[4]arenes with a bridge at the upper rim.[3,4] At the lower rim p-tert-butylcalix[4]arene has been bridged with a poly(oxyethylene) chain (calix crowns),[5,6] with a terphenyl unit (calix spherands),[6] and with a ferrocene unit.[7]

Our objective was to cap p-tert-butylcalix[4]arene (1) at the lower rim with bridges of different shape and rigidity to be able to discriminate between the different phenolic hydroxyl groups and to fix the calix[4]arene in a rigid cone conformation. Such a discrimination is a prerequisite for the potential use of calix[4]arenes as building blocks for larger synthetic (receptor) systems.

Results and Discussion

CPK models suggested that benzophenone-3,3'-disulfonyl dichloride (2a), which is used in cyclodextrin chemistry for selective A,C capping, should also be a suitable bridging reagent for calix[4]arenes. Indeed, we found that slow addition of a solution of 2a in THF to a solution of the dipotassium salt of p-tert-butylcalix[4]arene

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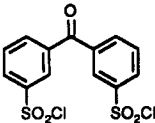§Laboratory of Chemical Physics, University of Twente.

Chart I

3f   5

(1) in THF resulted in the formation of the desired intrabridged compound 3a in 28% isolated yield (Scheme I). However, in addition to 20% of starting material, a second product was isolated in 9% yield, which was identified as the doubly interbridged bis(calix[4]arene) 4a by positive ion FAB mass spectrometry, consisting of two calix[4]arene units connected by two benzophenone-3,3'-disulfonyl bridges. The ¹H NMR spectra of both compounds are very similar, showing two singlets for the tert-butyl groups, an AB system for the methylene bridge protons, and two singlets for the aromatic protons of the calix[4]arene, which was typical for a diametrically disubstituted calix[4]arene in a rigid cone conformation.

In order to study the effect of the nature of the bridge on the formation of mono- and bis(calix[4]arenes) we used the two capping units 2b and 2c, which have a structure similar to the benzophenone-3,3'-disulfonyl dichloride bridge (2a). (For structures and yields see Table I.) With use of diphenyl sulfone 3,3'-disulfonyl dichloride (2b) as a capping reagent, the overall yield dropped but the relative amount of bis(calix[4]arene) 4b increased significantly. In the case of benzophenone-3,3'-dicarboxylic acid dichloride (2c) only the singly intrabridged calix[4]arene 3c was isolated. A rationalization of the above results may be given in terms of the shape of the bridging unit. Probably the ring-closure reaction in the case of capping reagent 2b is less efficient due to a nonoptimal fit, and therefore relatively more bis(calix[4]arene) is formed.

The 3,3'-substituted biphenyls 2d and 2e have a good fit, but they are more rigid than compounds 2a–2c; therefore, only singly intrabridged calix[4]arenes 3d and 3e were isolated. In the case of 3,3'-bis(bromomethyl)-biphenyl (2e) the reaction conditions were changed to K₂CO₃/CH₃CN because with KOtBu/THF no bridged products could be isolated.

(1) For a review see: Gutsche, C. D. *Calixarenes*; Stoddart, F. J., Ed.; Monographs in Supramolecular Chemistry; The Royal Society of Chemistry: Cambridge, 1989; Vol. 1.
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(4) To be published.
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Scheme I
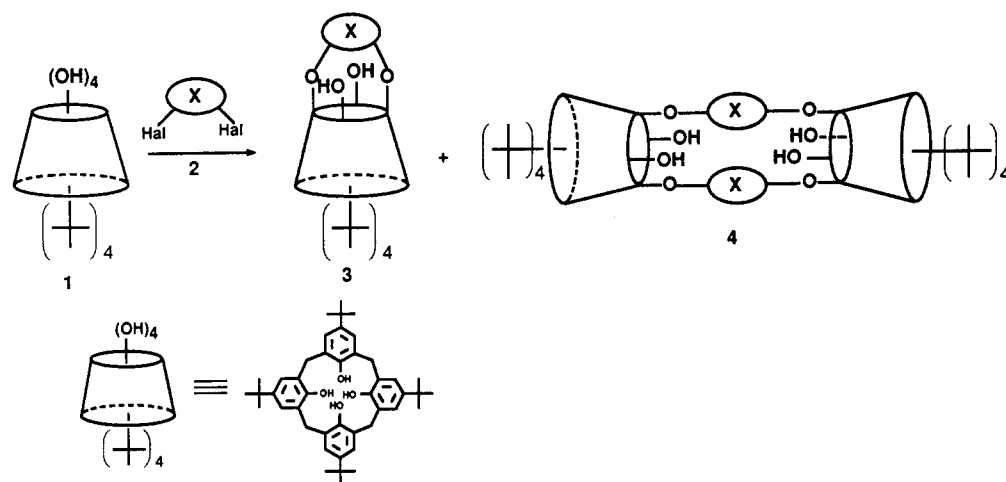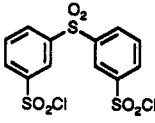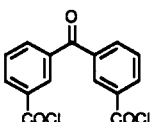
Table I. Reaction Conditions and Yields (%) of the Reaction of 1 with 2a–g

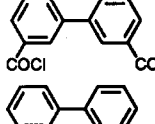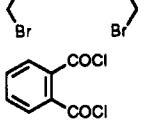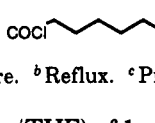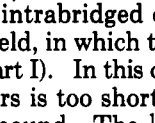|	bridging reagent 2	method	addn time, h	3	4	recovered 1
a		A[a]	24	28	9	20
b		A[a]	24	9	9	20
c		A[a]	8	26	0	7
d		A[a]	9	20	0	30
e		B[b]	6	39	0	0
f		A[b]	24	30[c]	0	26
		C[b]	24	27[d]	0	22
g		B[a]	4	86	0	0

[a] Room temperature. [b] Reflux. [c] Proximally intrabridged calix[4]arene. [d] Yield of doubly intrabridged calix[4]arene 5: 18%.

Reaction (KOtBu/THF) of 1 with *o*-phthaloyl dichloride (**2f**) gave a singly intrabridged calixarene **3f** as the only product in 30% yield, in which two adjacent phenol rings are connected (Chart I). In this case, the distance between the reactive centers is too short to form a diametrically intrabridged compound. The ^{1}H NMR spectrum of **3f** shows two singlets for the *tert*-butyl groups and three AB systems in a ratio of 1:1:2 for the methylene bridge protons. *To the best of our knowledge, this is the first example of a proximally intrabridged calix[4]arene.*[8] When 1 was reacted with 2 equiv of **2f**, with CsF as a base in refluxing

acetonitrile, the *doubly intrabridged* calix[4]arene **5** was isolated from the reaction mixture in 18% yield in addition to 27% of **3f** and 22% of recovered 1. Compound **5** exists in a rigid cone conformation according to the two AB systems for the methylene bridge protons and the singlet for the *tert*-butyl groups in the ^{1}H NMR spectrum.

Finally, the very flexible and reactive sebacoyl chloride (**2g**) afforded the singly intrabridged calix[4]arene **3g** in 86% yield. In this case the reaction can be compared with the selective diametrical dialkylation.[9] The crystal structure of this compound could be solved (Figure 1).

(8) Very recently Pappalardo described the first example of a proximally disubstituted calix[4]arene: Bottino, F.; Giunta, L.; Pappalardo, S. *J. Org. Chem.* **1989**, *54*, 5407.

(9) van Loon, J.-D.; Arduini, A.; Verboom, W.; Ungaro, R.; van Hummel, G. J.; Harkema, S.; Reinhoudt, D. N. *Tetrahedron Lett.* **1989**, *30*, 2681.

Table II. Melting Points and Characteristic Spectral Data of Compounds 3a–g, 4a,b, and 5[a]

compd	mp, °C	ArH (s)	OH (s)	ArCH₂Ar (AB q)	J, Hz	t-Bu (s)	C=O (s)	ArC—H (d)	ArCH₂Ar (t)	t-Bu (q)	FAB-MS m/e (M + 1)⁺
				¹H NMR (CDCl₃), δ					**¹³C NMR (CDCl₃), δ**		
3a	200-3	6.86	4.75	3.49	14.1	0.93	193.6	125.3	33.3	30.8	955
		7.09		4.18		1.25		126.7		31.6	
3b	>300 dec	6.86	4.23	3.51	14.3	0.93		125.5	33.3	30.5	991
		7.11		4.27		1.20		126.7		30.8	
3c	>300 dec	6.95	5.26	3.53	14.4	1.04	191.7	125.3	34.2	31.0	883
		7.11		3.87		1.06	164.4[i]	126.4		31.4	
3d	>300 dec	6.95	5.32	3.53	14.4	1.04	163.8	125.9	33.8	31.0	855
		7.01		3.92		1.08		126.3		31.4	
3e	>250 dec	6.89	5.03	3.28	13.0	0.98		125.4	31.7	31.1	827
		6.95		4.22		1.18		125.5		31.7	
3f	285 dec	6.93[b], 7.19[c]	e	3.57,[f] 3.32, 3.58[g]	13.7	1.18	165.3	125.5, 126.7	32.7, 35.5	31.3	779
		7.03, 7.27		4.28, 3.97, 3.99		1.26		125.8, 127.0	33.1	31.4	
3g	>300 dec	6.81	5.43	3.40	14.0	0.93	171.6	125.4	32.7	30.9	815
		7.13		3.90		1.35		125.8		31.7	
4a	>300	6.73	4.57	3.27	14.2	0.88	191.8	125.6	32.4	30.8	1910 (M + 2)⁺
		7.07		4.04		1.28		126.4		31.6	
4b	>240 dec	6.77	4.78	3.30	14.2	0.90		j	j	j	1982 (M + 2)⁺
		7.11		4.09		1.32					
5	>300	7.08[d]		3.39, 3.65[h]	13.9	1.26	167.3	126.3	31.5	31.3	909
		7.35		3.63, 4.20				126.4	35.9		

[a] All compounds gave satisfactory elemental analyses. [b] Doublets, J = 2.4 Hz. [c] Doublets, J = 2.5 Hz. [d] Doublets, J = 2.2 Hz. [e] The OH signal is located in a multiplet of the bridge at δ 7.8–7.75. [f] The ratio of the AB q systems from left to right is 2:1:1. [g] J = 14.0 Hz. [h] J = 13.0 Hz. [i] Carbonyl of ester function. [j] Not determined due to low solubility.
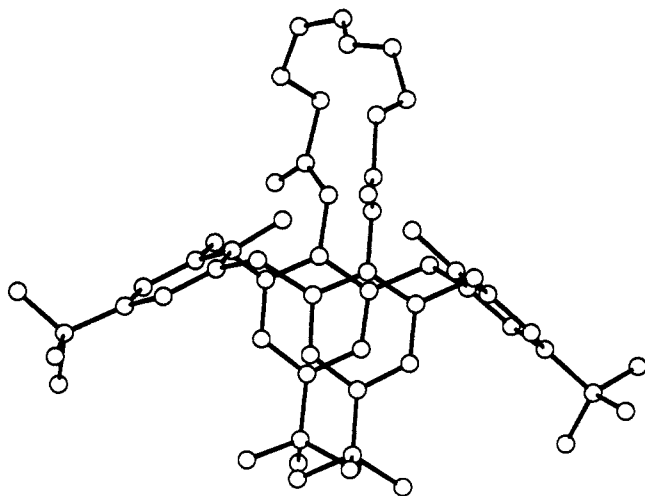

Figure 1. View of compound 3g.

The calix[4]arene has a distorted cone conformation. The phenol rings connected via the sebacoyl bridge are almost parallel with an angle of 2.1°. These rings are almost perpendicular to the mean plane through the connecting methylene groups (angles 96.1° and 94.1°). The angle between the mean planes of the remaining two phenol groups is 111.8°. The angles of these planes with the mean "methylene plane" are 147.4° and 144.4°.

We can conclude that diametrical and proximal capping of calix[4]arene 1 is possible, giving products in a rigid cone conformation. Depending on the structure of the difunctional reagent, bis(calix[4]arenes) can be synthesized also.[10] Further reactions of calix[4]arenes 3 via the two remaining hydroxyl groups are under investigation.

Experimental Section

Melting points are uncorrected. ¹H NMR and ¹³C NMR spectra were recorded in CDCl₃ with Me₄Si as internal standard. Positive

ion FAB mass spectra were recorded with use of *m*-nitrobenzyl alcohol as matrix.

All chemicals were reagent grade and were used without further purification. The difunctional reagents 2f and 2g were obtained from Aldrich. Benzophenone-3,3′-disulfonyl dichloride[11] (2a), diphenyl sulfone 3,3′-disulfonyl dichloride[12] (2b), benzophenone-3,3′-dicarboxylic acid dichloride[13] (2c), and 3,3′-bis-(bromomethyl)biphenyl[14] (2e) were prepared according to literature procedures. Biphenyl-3,3′-dicarboxylic acid dichloride (2d) was prepared from its dimethyl ester[15] by standard procedures. Tetrahydrofuran (THF) was freshly distilled over sodium/ benzophenone ketyl. Petroleum ether refers to the fraction boiling at 40–60 °C. Dropwise addition over a period of several hours was always carried out with a perfusor. All reactions were carried out under a nitrogen atmosphere. Solutions were dried over MgSO₄.

General Procedures for the Reaction of Calix[4]arene 1 with Compounds 2a–2g. Method A. To a suspension of *p*-*tert*-butylcalix[4]arene (1) (0.65 g, 1.0 mmol) in THF (125 mL; 200 mL in the case of 2f) was added KOtBu (0.23 g, 2.0 mmol). After being stirred for 30 min at room temperature, a solution of compounds 2a–d,f (1.08 mmol) in THF (50 mL; 70 mL in the case of 2d due to the low solubility) was added dropwise to the reaction mixture. The addition times and reaction temperatures are given in Table I. After addition of a concentrated NH₄Cl solution (15 mL, not in the case of 2f), most of the THF was removed under reduced pressure. CH₂Cl₂ (150 mL) was added to the residue whereupon the organic layer was washed with brine (2 × 75 mL). After removal of the solvent under reduced pressure, the residue was separated by flash chromatography[16] [silica gel, CH₂Cl₂:petroleum ether = 4:1 (3a,b, 4a,b), CH₂Cl₂:petroleum ether = 2:1 (3c), CH₂Cl₂:petroleum ether = 1:2 (3d), CHCl₃:Et₂O = 99:1 (3f)] to afford pure compounds that could not be recrystallized

(10) For a rational design of bis(calix[4]arenes) see: Kraft, D.; van Loon, J.-D.; Owens, M.; Verboom, W.; Vogt, W.; McKervey, M. A.; Böhmer, V.; Reinhoudt, D. N. Submitted for publication.

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(14) Thulin, B.; Wennerström, O. *Acta Chim. Scand. B* **1983**, *37*, 297.
(15) Takagi, K.; Hayama, N.; Inokawa, S. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3691.
(16) The eluents were chosen so that the intrabridged compounds had an R_f value of 0.3–0.5. In cases in which doubly interbridged bis(calix-[4]arenes) were formed, R_f values of 0.1–0.2 were observed for these compounds.

from the usual organic solvents. In the cases of the compounds **3c** and **3d** an additional purification was performed by fractional precipitation from CH_2Cl_2/Et_2O and $CH_2Cl_2/MeOH$, respectively. The yields, melting points, and spectral data are summarized in Tables I and II.

Method B. To a suspension of *p-tert*-butylcalix[4]arene toluene complex (1) (1.0 g, 1.36 mmol) in CH_3CN (300 mL) was added K_2CO_3 (0.38 g, 2.74 mmol). In the case of **2e**, a small amount of KI was added also. After being stirred for 30 min at reflux temperature (**2e**) or at room temperature (**2g**), a solution of the bridging reagent **2e,g** in CH_3CN (100 mL) was added dropwise to the reaction mixture. The addition times and reaction temperatures are given in Table I. In the case of **2e** the reaction mixture was refluxed for additional 16 h. After removal of the CH_3CN under reduced pressure, CH_2Cl_2 (150 mL) was added to the residue whereupon the organic layer was washed with brine (2 × 75 mL). After removal of the solvent under reduced pressure, the residue was purified by flash chromatography[16] [silica gel, CH_2Cl_2 (**3e**), $CHCl_3$:petroleum ether = 3:1 (**3g**)] to give pure compounds, which in the case of **3e** could not be recrystallized from the usual organic solvents. The yields, melting points, and spectral data are summarized in Tables I and II.

Method C. To a suspension of *p-tert*-butylcalix[4]arene (1) (0.65 g, 1.0 mmol) in CH_3CN (250 mL) was added CsF (0.61 g, 4.0 mmol). After the mixture was stirred for 30 min, a solution of compound **2f** (1.08 mmol) in THF (50 mL) was added dropwise to the refluxing reaction mixture in 24 h. After removal of the solvent under reduced pressure, CH_2Cl_2 (150 mL) was added to the residue whereupon the organic layer was washed with brine (2 × 75 mL). After removal of the solvent under reduced pressure, the residue was separated by flash chromatography[16] [silica gel, CH_2Cl_2:Et_2O = 50:1]. The yields, melting points, and spectral data are summarized in Tables I and II.

X-ray Crystallography of Compound 3g. The crystal structure of compound **3g** was determined by X-ray diffraction. Crystal data: $C_{54}H_{70}O_6$, orthorhombic, space group $P2_12_12_1$; $a = 10.026$ (2) Å, $b = 18.350$ (3) Å, $c = 26.679$ (5) Å, $V = 4908$ (1) Å^3, $Z = 4$, $d_{calc} = 1.103$ g cm^{-3}, $\mu = 0.65$ cm^{-1}. Reflections were measured in the $\omega/2\theta$ scan mode, using graphite-monochromated Mo Kα radiation [scan width (ω) 1.00 + 0.34 tan θ]. The structure was solved by direct methods and refined with full-matrix least-squares methods. A total of 2523 reflections with $F_o{}^2 > 3\sigma(F_o{}^2)$ was used in the refinement. The number of parameters refined was 361 [scale factor, positional and thermal parameters]. The final R factors were $R = 8.0\%$ and $R_w = 9.1\%$. All calculations were done with SDP.[17]

In the crystal structure some disorder was found in the aliphatic chain, as evidenced by the high values of the thermal parameters in this part of the molecule. In order to keep the number of parameters small, thermal parameters were refined isotropically for C and O atoms, with the exception of the C atoms of the aliphatic bridge and the terminal C atoms of the *tert*-butyl groups, which were refined anisotropically. H atoms were added in their calculated positions and treated as riding atoms in the refinement. No hydrogens were added to the aliphatic chain carbon atoms, because of the disorder found. The phenolic H atoms could not be located from a difference Fourier synthesis and have not been included in the refinements.

Registry No. 1, 60705-62-6; **2a**, 17619-15-7; **2b**, 7357-41-7; **2c**, 6472-69-1; **2d**, 6423-26-3; **2e**, 24656-53-9; **2f**, 88-95-9; **2g**, 111-19-3; **3a**, 128217-27-6; **3b**, 128217-28-7; **3c**, 128217-29-8; **3d**, 128242-26-2; **3e**, 128217-30-1; **3f**, 128217-31-2; **3g**, 128217-32-3; **4a**, 128217-33-4; **4b**, 128217-34-5; **5**, 128217-35-6.

Supplementary Material Available: Figure showing **3a** with atom labels and tables of positional and thermal parameters, bond distances, and angles (9 pages). Ordering information is given on any current masthead page.

C-Nitration of 2,6-Di- and 2,4,6-Tri-*tert*-butylpyridine with Nitronium Tetrafluoroborate[1]

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Electrophilic substitution of pyridine occurs preferentially on the heteroatom (N-substitution). Nitration of pyridine with mixed nitric–sulfuric acid gives a low yield of the 3-nitro product, indicative that the nitration is that of the pyridinium ion formed by protonation in the acid medium.[2] The most convenient method of preparing 4-nitropyridine is that through nitration of pyridine *N*-oxide, followed by deoxygenation (for example with phosphorous trichloride).[3] Nitronium salts when reacted with pyridine gave *N*-nitropyridinium salts (N-nitration).[4] Nitration of 2,6-dimethylpyridine and 2,4,6-trimethylpyridine also occurred on nitrogen. The resulting pyridinium salts are effective transfer nitration reagents.[5,6] Whereas 2,6-di-*tert*-butylpyridine[7] has found extensive use as proton trap in synthetic chemistry,[8] electrophilic chemistry of hindered pyridines has not been explored.

We have now found that when reacting sterically crowded 2,6-di- and 2,4,6-tri-*tert*-butylpyridine with nitronium tetrafluoroborate nitration occurred exclusively in the ring. Thus, when 2,6-di-*tert*-butylpyridine was reacted with $NO_2{}^+BF_4{}^-$ in dry CH_2Cl_2 or CH_2Cl_2/sulfolane, apart from unreacted starting material, 28% 2,6-di-*tert*-butyl-4-nitropyridine and 6% 2,6-di-*tert*-butyl-3,4-dinitropyridine were formed.

Similarly, 2,4,6-tri-*tert*-butylpyridine when reacted with $NO_2{}^+BF_4{}^-$ in CH_2Cl_2 gave 36% 2,4,6-tri-*tert*-butyl-3-nitropyridine as the only product after workup.

Removal of the *tert*-butyl groups by acid-catalyzed transalkylation was also attempted in an attempt to obtain nitropyridines. *tert*-Butylnitropyridines were refluxed over superacidic Nafion-H or with CF_3SO_3H in excess benzene.

(1) Aromatic Substitution. 59. For part 58, see: Olah, G. A.; Farooq, O.; F. Farnia, S. M.; Wu, A. *J. Org. Chem.* **1990**, *55*, 1516.

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(17) Structure Determination Package, B. A. Frenz and Associates Inc., College Station, TX, and Enraf-Nonius, Delft, The Netherlands, 1983.