A Novel Route to Calix[4]arenes. 2. Solution- and Solid-State Structural Analyses and Molecular Modeling Studies

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A versatile route to a series of *C*-alkylcalix[4]resorcinarenes has been developed, using 2,4-dimethoxycinnamates as starting materials under carefully controlled reaction conditions employing BF_3 as a Lewis acid catalyst. Depending on the reaction conditions and the nature of the ester side chain in the cinnamates, the calixarenes can adopt 1,2-alternate, 1,3-alternate, or flattened-cone conformational states. An extensive study, relating to the influence of the Lewis acid, temperature, and reaction time, has provided information on the relative ratios of the different conformations and their interconversion. Structural assignments are based on detailed spectroscopic analyses including X-ray analyses. The latter provide evidence of their molecular structure and shape in the solid state. A detailed molecular modeling study has been completed and is described. From the data obtained, good agreement with NMR data, X-ray analyses and experimental results is observed.

Introduction

Calixarenes[1] represent an interesting family of structures which exhibit characteristic cavity-shaped architecture. Extensive studies have illustrated their application in the synthesis of lypophilic,[2] water-soluble[3] cation receptors and carriers.

Our own program has focused on the development of a synthetic approach which would provide the opportunity to introduce various functions at the "outside periphery" of the calixarene skeleton in the hope that such functions would subsequently afford appropriate binding sites for various substrates. The present study illustrates the utilization of readily available cinnamate esters as starting materials for calixarene synthesis.

In a study involving the nonoxidative dimerization of 3,4- dioxygenated cinnamates to aryltetralin lignans,[4] we had utilized etheral BF_3 as the Lewis acid catalyst to achieve the desired end products. Consideration of the mechanistic pathway,[4] which is involved in this latter dimerization process, revealed the possibility that under appropriate control of reaction parameters the intermediates produced may also proceed via a tetramerization process and, in turn, to a calixarene skeleton. Indeed, when (*E*)-2,4-dimethoxycinnamic acid methyl ester (**1**) was reacted with $BF_3 \cdot Et_2O$ at room temperature, the desired calixarene system was obtained in 75% overall yield (Scheme 1).[5]

Results and Discussion

The two products in the above reaction were obtained consistently in a 2:3 ratio and assigned the calixarene structures **2a** and **2b** in the 1,2-alternate and flattened-cone conformations, respectively. These assignments were supported by the distribution patterns of resonances in the NMR spectra. In ^1H- and ^{13}C-NMR spectra of compound **2a**, the signals belonging to the aliphatic moiety exhibited a distribution in areas of integration which were essentially 1:2:1, whereas the resonances of the aromatic moiety showed a distribution of 1:1. These findings are consistent with the existence of a symmetry plane passing through the C(2) and C(14) methine groups and perpendicular to the macrocyclic ring.[6] A detailed NMR analysis of compound **2a**, involving INEPTL and DIF NOE experiments, is summarized in Tables 1 and 2. As a result, a correct assignment for all the protons and carbons of **2a** was achieved. In particular, it should be noted that the assignment of the 12- and 16-OMe signals, in conjunction with the DIF NOE measurements, allowed us to establish the correct stereochemistry at C(14). In conclusion, the product **2a** was assigned a 1,2-alternate conformation and

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(1) Gutsche, C. D. *Calixarenes*; Stoddard, J. F., Ed.; Monographs in Supramolecular Chemistry; Royal Society of Chemistry: Cambridge, 1989.

(2) Ungaro, R.; Pochini, A. Calixarenes-Based Cation Receptors and Carriers. In *Calixarenes, a Versatile Class of Macrocyclic Compounds*; Vicens, J.; Böhmer, V., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1991; pp 127-147.

(3) Shinkai, S. Functionalized Calixarenes: a New Application as Catalysts, Ligands and Host Molecules. In *Calixarenes, a Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhme, V., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1991; pp 163-178.

(4) Botta, B.; Iacomacci, P.; Vinciguerra, V.; Delle Monache, G.; Gacs-Baitz, E.; Botta, M.; Misiti, D. *Chem. Pharm. Bull.* **1990**, *38*, 3238.

(5) Botta, B.; Iacomacci, P.; Di Giovanni, C.; Delle Monache, G.; Gacs-Baitz, E.; Botta, M.; Tafi, A.; Corelli, F.; Misiti, D. *J. Org. Chem.* **1992**, *57*, 3259.

(6) Abis, L.; Dalcanale, E.; Du vosel, A.; Spera, S. *J. Org. Chem.* **1988**, *53*, 5475.

0022-3263/94/1959-1532$04.50/0

Scheme 1

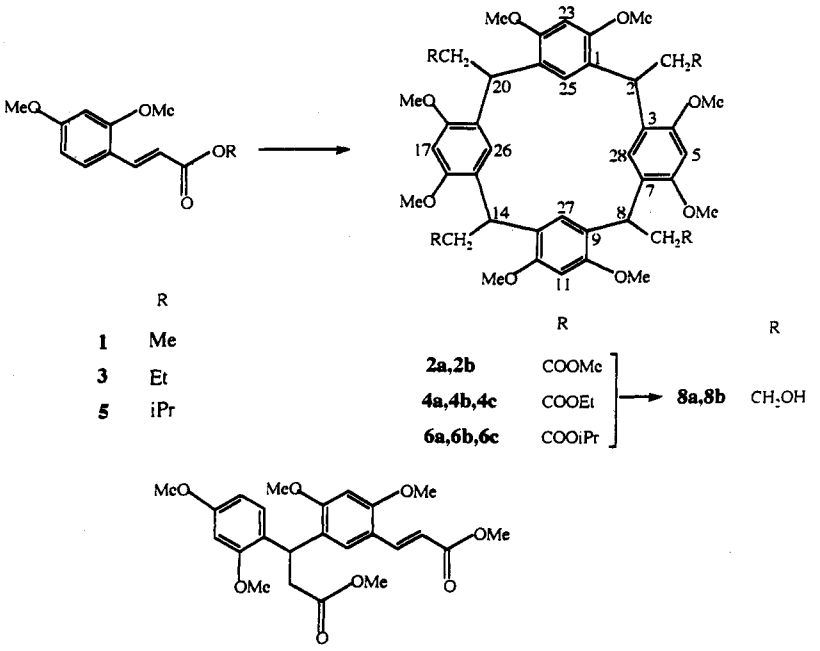

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Table 1. INEPTL Experiments on C-Alkylcalix[4]resorcinarenes

compd	selectively irradiated proton (position)	^3J related carbon signals (position)
2a	7.24 (25,28)	156.30(6,22),156.15(4,24), 33.31(8,20)
	5.45 (2)	156.15(4,24),126.16(25,28), 123.85(1,3)
	3.79 (COOMe)	155.96 (10,18),55.79(OMe), 51.27(COOMe)
	3.69 (COOMe)	156.30(6,22),56.29(OMe), 51.27(COOMe)
	2.96 (8-,20-CH_2)	173.43(CO),122.89(9,19), 33.31(8,20)
	2.35 (14-CH_2)	123.53 (13,15)
6a	7.29 (25,28)	156.27(6,22),156.18(4,24)
	5.45 (2)	156.18(4,24),126.55(25,28), 124.36(1,3)
	5.09 (14)	155.94(12,16),127.45(26,27), 123.95(13,15)
	5.06 (8,20)	124.60, 123.44 (7,21; 9,19)
	3.76 (OMe)	155.94 (12,16)
	3.65 (OMe)	156.18 (6,22)
8a	7.63 (25,28)	156.28(6,22),156.03(4,24)
	6.57 (26,27)	155.81(10,18),155.49(12,16), 31.32(8,20),27.03(14)
	5.27 (2)	156.03(4,24),126.81(25,28), 125.03(1,3)
	4.88 (14)	155.53(12,16),127.53(26,27), 125.27(13,15)
	3.80 (OMe)	155.53 (12,16)
	3.60 (OMe)	156.28 (6,22)
	2.98 (CH_2OH)	27.03 (14)

a *cis-trans-cis*—relative to C(2)—arrangement of the pseudoaxial substituents.

The presence, in ^1H- and ^{13}C-NMR spectra, of only one signal for both external (H_e as H-5) and internal (H_i as H-28) aromatic protons and the related carbons, as well as a similar pattern for the methoxy group and the aliphatic moiety, respectively, required a C_{4v} symmetry for compound **2b**. DIF NOE measurements revealed the proximity of the methine and the aromatic methoxy groups, as well as that of the CH_2 and H_i protons.

Table 2. NOE Enhancements in C-Alkylcalix[4]resorcinarenes

compd	solvent	irradiated proton (position)	observed protons (position; %[a])
2a	$CDCl_3$	7.24 (25,28)	6.41 (26, 27), 2.86 (2-CH_2)
		5.45 (2)	2.86 (2-CH_2)
		3.69 (COOMe)	6.41 (26, 27)
		2.96 (8-, 20-CH_2)	5.06 (8, 20), 2.85 (geminal)
		2.35 (14-CH_2)	6.41 (26, 27), 5.09 (14)
6a	$CDCl_3$	7.29 (25,28)	6.41 (26, 27; 3.5), 2.86 (2-CH_2, 6)
		5.45 (2)	2.86 (2-CH_2; 5)
		2.28 (14-CH_2)	6.41 (26, 27; 6.7), 5.09 (8, 20; 5.5)
	C_6D_6	6.94 (26,27)	7.93 (25, 28; 2.5), 5.70 (8, 20; 5), 5.67 (14; 5), (14-CH_2; 2.5)
		3.27 (8-, 20-CH_2)	5.70 (8, 20; 7.4), 6.94 (26, 27; 1.2), 7.93 (25, 28; 0.6)
	CD_3COCD_3	6.57 (26, 27)	7.49 (25, 28; 1.7), 5.20 (8-, 20; 1.6), 5.17 (14; 1.6), 2.17 (14-CH_2; 2.5)
8a[b]	$CDCl_3$	6.57 (26,27)	7.63 (25, 28), 4.88 (14), 4.76 (8,20), 1.24 (14-CH_2)
		4.88 (14)	1.24 (14-CH_2), 2.80 (12-, 16-OMe), 2.98 (CH_2OH), 6.57 (26, 27)
		1.24 (14-CH_2)	6.57 (26, 27), 4.88 (14), 2.98 (CH_2OH)

[a] Only for compound *6a*. [b] The $LiAlH_4$ reduction product of *4c* and *6c* showed the same DIF NOE effects as did *8a*, thus confirming an identical stereochemistry at C-14.

The product **2b** was thus assigned a flattened cone conformation with an *all-cis* arrangement of the pseudoaxial substituents.

The generality of the above reaction was evaluated in terms of two other cinnamate esters, that is, the ethyl (**3**) and isopropyl (**5**) esters, respectively. In the case of **3**, a 68% yield was obtained while the isopropyl ester afforded 80% of the calixarene skeleton. Moreover, the nature of

Table 3. ^{13}C- and ^{1}H-NMR Spectra of *C*-Alkylcalix[4]resorcinarenes in the 1,2-Alternate Conformation

	2a	4a	6a	8a
carbon				
1, 3	123.85	124.12	124.36	125.03
2	29.38	29.28	29.46	27.45
4, 24	56.15	156.13	156.18	156.03
5, 23	95.81	95.80	95.83	96.27
6, 22	156.30	156.26	156.27	156.28
7, 21	124.33	124.51	124.60	126.70
8, 20	33.31 (×2)	33.17 (×2)	33.25 (×2)	31.32 (×2)
9, 19	122.89	123.13	123.44	124.85
10, 18	155.96	155.86	155.96	155.81
11, 17	96.54	96.59	96.60	96.67
12, 16	155.86	155.85	155.94	155.53
13, 15	123.53	123.73	123.95	125.31
14	30.41	30.06	30.20	27.03
25, 28	126.16	126.25	126.55	126.81
26, 27	127.34	127.32	127.51	127.53
2-CH_2	40.65	41.09	41.67	40.00
8-, 20-CH_2	38.92 (×2)	39.12 (×2)	39.48 (×2)	37.84 (×2)
14-CH_2	39.74	40.09	40.41	39.58
4-, 24-OMe	56.29	56.26	56.24	56.63
6-, 22-OMe	55.79	55.74	55.76	56.60
10-, 18-OMe	55.74	55.70	55.70	56.26
12-, 16-OMe	56.05	55.98	55.94	55.81
proton				
2	5.45 (1H,t,8)	5.47	5.45	5.27
8, 20	5.06 (2H, dd, 6, 10)	5.05	5.06	4.75 (2H, t, 7.5)
14	5.09 (1H,t,8)	5.09	5.09	4.88
5, 23	6.38 (2H,s)	6.38	6.37	6.40
11, 17	6.40 (2H,s)	6.40	6.40	6.41
25, 28	7.24 (2H,br s)	7.29	7.29	7.63
26, 27	6.41 (2H,br s)	6.42	6.41	6.57
4-, 24-OMe	3.85	3.85	3.84	3.90
6-, 22-OMe	3.66	3.66	3.65	3.59
10-, 18-OMe	3.83	3.83	3.83	3.87
12-, 16-OMe	3.78	3.77	3.76	3.80

[a] The signals due to the chains are not reported. The carbon and proton signals were correlated through a HETCOR experiment. Multiplicities are reported only once if they do not change.

the ester function revealed a considerable influence on the relative ratios and types of conformations obtained. As noted earlier, the methyl ester provided only the flattened-cone and 1,2-alternate stereoisomers, while from both the isopropyl and the ethyl esters in addition to the 1,2-alternate (**4a**, **6a**) and the flattened-cone (**4b**, **6b**) a third type of stereoisomers (**4c**, **6c**) was obtained. Spectral ^{1}H- and ^{13}C-NMR data of products **4a**, **6a** (Table 3) and **4b**, **6b** (Table 4) were essentially coincident with those of **2a** and **2b**, respectively, thus confirming the assignment of the conformations. Conversely, compounds **4c** and **6c** displayed, in the ^{1}H- and ^{13}C-NMR spectra (Table 5), two signals for the methoxyl substituents and the aromatic protons and carbons, but only one signal for the remaining aliphatic groups. This distribution pattern requires the existence of two symmetry planes. DIF NOE experiments revealed the proximity of the methine and the methylene groups with the aromatic protons at ca. 6.2 and 6.8 ppm, respectively. Therefore, **4c** and **6c** were assigned the 1,3-alternate conformation with the pseudoequatorial side chains in an *all-cis* position.

In order to provide additional information as to the mechanism of the reaction, several experiments (summarized in Tables 6–8) were run with the ester **3** as a substrate, in which a variation in the temperature and the substrate–Lewis acid ratio was performed. At −20 °C (Table 6) with a 1:1 ratio of substrate–Lewis acid (experiment 1A) only $E \rightarrow Z$ isomerization of **3** was obtained, whereas with a ratio of 1:1.5 (experiment 2A) tetrameric products were

Table 4. ^{13}C- and ^{1}H-NMR Spectra[a] of *C*-Alkylcalix[4]resorcinarenes in the Flattened Cone Conformation

	2b	4b	6b	7b
carbon				
1,3,7,9 13,15,19,21	123.76	123.99	124.22	125.72
2,8,14,20	33.04	33.01	32.84	30.93
4,6,10,12 16,18,22,24	156.00	156.03	156.04	155.71
5,11,17,23	96.19	96.28	96.43	96.75
25,26,27,28	125.67	125.88	126.02	125.45
OMe	55.83	55.89	56.00	56.02
proton				
2,8,14,20	4.94 (4H, t, 7)	4.95 (4H, t, 7)	4.95 (4H, t, 7)	4.56 (4H, t, 8)
5,11,17,23	6.32 (2H, s)	6.30 (2H, s)	6.29 (2H, s)	6.33 (2H, s)
25,26,27,28	6.46 (2H, br s)	6.52 (2H, br s)	6.56 (2H, br s)	6.69 (2H, br s)
OMe	3.65 (24H, s)	3.63 (24H, s)	3.63 (24H, s)	3.62 (24H, s)

[a] The signals due to the chains are not reported.

Table 5. ^{1}H- and ^{13}C-NMR Spectra[a] of *C*-Alkylcalix[4]resorcinarenes in the 1,3 Alternate Conformation

	4c		6c	
	δ_C	δ_H	δ_C	δ_H
1, 19, 13, 21	124.91		124.73	
2, 8, 14, 20	32.78	5.01 (4H, dd, 9, 6.5)	32.88	5.02 (4H, dd, 9, 6.5)
3, 7, 15, 19	122.50		122.78	
4, 6, 16, 18	156.45		156.40	
5, 17	97.01	6.46 (2H, s)	97.05	6.45 (2H, s)
10, 12, 22, 24	155.68		155.87	
11, 23	95.39	6.39	95.49	6.40
25, 27	126.60		126.91	
26, 28	125.73	6.82 (2H, br s)	126.15	6.80 (2H, br s)
	56.10	3.88	56.10	3.86 (12H, s)
OMe	55.84	3.65 (12H, s) 2.69 (4H, dd, 15, 7)	55.85	3.65 (12H, s) 2.71 (4H, dd, 15, 7)

[a] The signals due to the chains are not reported.

Table 6. Reaction of Ester *3* with $BF_3{\cdot}Et_2O$ at −20 °C

expt[a]	molar ratio $3/BF_3{\cdot}Et_2O$	time (h)	% of 4a	% of 4b	% of 4c
1A	1:1.0	100			
2A	1:1.5	100	39	26	35
3A	1:3.0	100	28	35	37
4A	1:4.5	100	9	62	29
5A	1:6.0	100	8	69	23
6A	1:7.5	50	21	36	43
7A	1:9.0	50	12	52	36

[a] In experiment 1A only (*E*) → (*Z*) isomerization occurred. In experiments 2A and 3A also polymers were formed, while experiments 4A–7A gave exclusively the tetramers.

Table 7. Reaction of Ester *3* with $BF_3{\cdot}Et_2O$ at Room Temperature

expt	molar ratio $3/BF_3{\cdot}Et_2O$	time (h)	% of 4a	% of 4b	% of 4c
1B	1:0.75	50			
2B	1:1.0	50	43	21	36
3B	1:1.5	50	28	33	39
4B	1:3.0	50	15	46	39
5B	1:7.5	20	22	46	32
6B	1:9.0	20	16	50	34

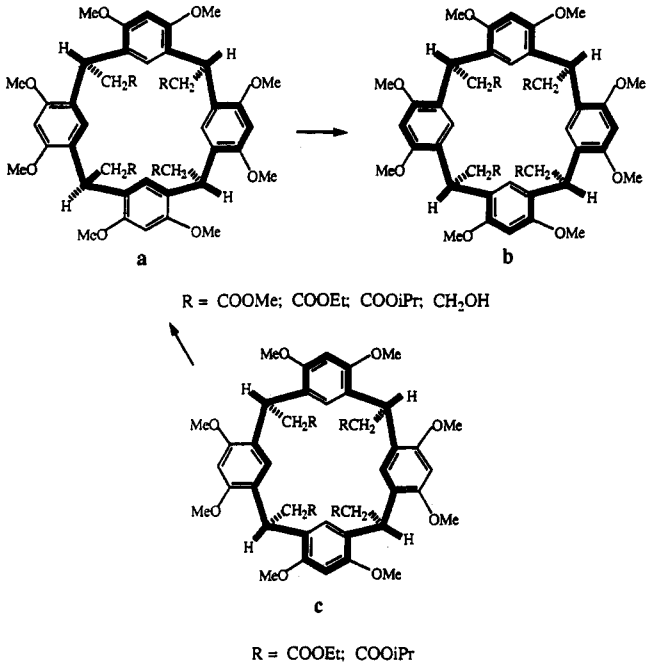
formed. It is noteworthy that by increasing the amount of $BF_3{\cdot}Et_2O$, the yield of **4b** (flattened-cone conformation) improved at the expense of **4a** (1,2-alternate conformation), while the concentration of **4c** initially did not change

Table 8. Reaction of Ester *3* with BF_3·Et_2O at Reflux

expt[a]	molar ratio *3*/BF_3·Et_2O	time (min)	% of **4a**	% of **4b**	% of **4c**
1C	1:0.75	60	23	35	42
2C	1:1.0	60	22	39	39
3C	1:1.5	60			
4C	1:1.3	60			
5C	1:1.5	8	20	43	37
6C	1:1.3	15	25	41	34

[a] In experiments 1C and 2C tetramers were obtained in an overall poor yield (see Experimental Section).

Scheme 2



(experiment 3A). In subsequent studies (experiments 4A–7A), the concentration of **4c** varied slightly while significant changes were noted in the relative ratios of **4a** to **4b**. The predominance of **4b** in the reaction mixture is more pronounced when a large excess of etheral BF_3 is used with a longer reaction time (experiments 4A, 5A).

At room temperature (Table 7), and with 1:0.75 and 1:1 ratios (experiments 1B and 2B), **3** afforded, albeit in low yield, the dimeric product **7** (see Experimental Section), while with ratios greater than 1:1.5 the reaction proceeded again to afford tetrameric products. In general, shorter reaction times were required although the ratios of **4a** to **4b** never reached the values shown in the experiments 4A and 5A. Finally, at the reflux temperature (Table 8) the same trend is observed. That is, **4b** is the major product, even with very short reaction times, for example, 8 min in experiment 5C.

Periodic analysis of the reaction mixtures by TLC revealed that the 1,2-alternate conformers **2a**, **4a**, and **6a** are first to form (kinetic products) and **2b**, **4b**, and **6b** develop with time (thermodynamic products).

It is to be noted that, in the conversion of the **a** to **b** series (Scheme 2), a configurational change at C(14) occurs *as well as* the conformational change from the 1,2-alternate to the flattened cone. Clearly such a configurational alteration presumably involves a "protodealkylation" process,[7] that is, a scission of the C(13)–C(14) or C(14)–C(15) bond, followed by ring closure to **b**. CPK molecular models reveal that indeed the side chain at C(14) in series **a** would have to suffer a severe interaction with the methoxyl substituents of the aromatic rings if a conformational flip from 1,2-alternate to flattened-cone were to occur in the conversion. The driving force to stimulate such a ring cleavage and subsequent ring closure is to place the C(14) side chain as shown in series **b** in the more favorable orientation and thereby minimize steric interactions with the adjacent substituents.

(7) Högberg, A. G. S. *J. Am. Chem. Soc.* 1980, *102*, 6046 and references cited therein.

Table 9. Reaction of Tetramers with BF_3·Et_2O

expt[a]	substrate	molar ratio subst/BF_3·Et_2O	temp	time (h)	% of **a**	% of **b**	% of **c**
1D	*4a*	1:1.5	room	15	40	60	
2D	*4a*	1:3.0	reflux	3	66	34	
3D	*6a*	1:3.0	reflux	6		100	
4D	*4b*	1:3.0	room	8		100	
5D	*4b*	1:3.0	reflux	12			
6D	*6c*	1:1.0	reflux	3			100
7D	*6c*	1:2.0	room	18	15	70	15
8D	*6c*	1:2.0	reflux	6	14	33	53
9D	*6c*	1:2.0	reflux	12	11	60	29
10D	*4c*	1:3.0	reflux	6		53	47
11D	*6c*	1:4.0	reflux	0.4			

The above-reported results are substantiated by a series of reactions of the pure tetramers with BF_3·Et_2O at increasing temperatures and substrate/BF_3·Et_2O ratios (Table 9). The 1,2-alternate isomers **4a** and **6a** gave increasing quantities of **4b** and **6b**, respectively. For example, after 6 h at a 1:3 **6a**/BF_3·Et_2O ratio (experiment 3D) conversion into the **b** isomer is complete. However, when **4b** was treated with etheral BF_3 in the same ratio at room temperature (experiment 4D), only starting material was recovered. Under reflux conditions (experiment 5D), **4b** decomposed and no evidence of either **4a** or **4c** was detected. These experiments clearly establish that isomers **b** are in the thermodynamically more stable conformation.

Studies with the series **c** (Table 9, experiments 6D–11D) revealed interesting results. The conversion of **6c** into **6b** simply involves a conformational change, and it was expected that heating the former would afford the necessary energy to achieve this conversion. However, when **6c** was heated in refluxing xylene (130 °C), no conversion was detected and **6c** remained stable. Examination of molecular models reveals that to accomplish this transformation the aliphatic chain is required to pass between the methoxy groups of the neighboring resorcinol units, thus leading to an unfavorable high-energy crowded transition state.

Conversely, as experiments 6D–11D (Table 9) indicate, **6c** can readily be converted into the **a** and **b** series, with the latter predominating, *if* etheral BF_3 is involved. For example, with a substrate/BF_3·Et_2O ratio of 1:2 (experiment 7D) a 70% yield of **6b** along with 15% of **6a** is noted in the reaction mixture, even at room temperature. These experiments suggest that conversion of the series **c** into **b**, for example, must involve series **a** as an intermediate.

These findings indicate that at least two subsequent scissions (the first one leading to the 1,2-alternate conformation series **a**, the second one leading to the flattened cone conformation) via two "protodealkylation" processes are required.

An interesting result was also obtained from the reduction of the ester groups of the side chains to primary alcohols. Treatment with $LiAlH_4$ of **2a**, **4a**, and **6a** (1,2-

Table 10. Crystal Data for *C*-Alkylcalix[4]resorcinarenes

	6a	6b
molecular form.	$C_{56}H_{72}O_{16}$	$C_{56}H_{72}O_{16}$
form. wt, D	1001.2	1001.2
cryst syst	triclinic	triclinic
space grp	*P*-1	*P*-1
a, Å	12.4834(8)	11.5913(7)
b, Å	14.0216(7)	12.6140(8)
c, Å	18.1229(8)	16.5153(6)
α, deg	100.590(3)	97.4592(4)
β, deg	107.3968(3)	101.738(4)
γ, deg	71.1749(4)	71.0932(3)
V, Å^3	2851.8	2808.9
d (expl), g/cm^3	1.16	1.18
d (calcd), g/cm^3	1.166	1.184
radiatn, Å	CuK_α (λ = 1.5418)	CuK_α (λ = 1.5418)
measured reflns	10789	10614
reflns used $I > 3.0\sigma(I)$	8017	6212
R factor	0.073	0.050

alternate conformation) as well as of **2b**, **4b**, and **6b** (flattened-cone conformation) gave the corresponding tetraalcohols **8a** and **8b**, respectively. By contrast, the reaction of **4c** and **6c** (1,3-alternate conformation) with $LiAlH_4$ afforded a mixture of **8a** and **8b**, the former being predominant. No evidence of the corresponding alcohol in series **c** could be obtained.

The reduction of the ester group in the above series to the "less bulky" hydroxymethylene group is also associated with interesting conformational and configurational changes. Clearly, kinetically controlled ring scission, as noted above, followed by reclosure would afford the conversion of **4c** or **6c** into **4a** or **6a**, respectively, as the major products in the mixture. The subsequent conversion of series **a** into the more stable series **b** is not an important reaction in the reducing medium.

The results obtained in the above reduction experiments cast important information relating to our earlier findings in the synthesis of calix[4]resorcinarenes bearing different ester side chains. In earlier studies, it was noted that the "bulky" nature of the ester side chain plays a significant role in terms of which series of stereoisomers is obtained. Notably, when the methyl ester side chain was involved, only *two* stereoisomers of the series **a** and **b** could be isolated. On the other hand, when an ethyl or an isopropyl ester side chain is present, series **c**, in addition to **a** and **b**, can be obtained. It appears that when a larger "bulky" side chain is present, conformation **c** is locked into place and conversion into series **a** or **b** is only achieved via a BF_3·Et_2O-catalyzed process. In similar fashion, series **c** is not formed at all if the ester groups are reduced to the corresponding sterically less bulky hydroxymethylene analogs.

Since the dimer **7** was presumed to be the direct precursor of **2a** (and of the 1,2-alternate conformation in general), it was treated with BF_3·Et_2O under the conditions of experiment 2A of Table 6. Monitoring of the reaction, by TLC, initially revealed the formation of **2a**; after 2 h, **7** was completely consumed and the reaction mixture consisted of **2a** and **2b**.

X-ray Diffraction Analyses

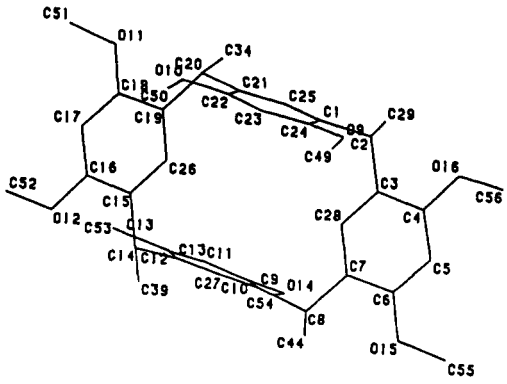
Relevant crystal data for **6a** and **6b** are summarized in Table 10. The structures were both solved by direct methods and have been fully refined by routine procedures. For **6b** the hydrogen atoms were found experimentally from difference Fourier maps, while for **6a** the atomic positions of the hydrogen atoms were calculated according to the stereochemistry of the carrier atoms. In both cases the contribution of hydrogen atoms was added to the structure factor calculations without refinement. The final *R* factor indexes for **6b** and **6a** were 0.050 and 0.073, respectively. The final difference Fourier maps in both cases revealed no missing or misplaced electron density. The numbering of the atoms is shown in Figure 1. The fully refined structures of **6b** and **6a** are shown by stereo drawings in Figures 2 and 3, respectively. Details of both structures will be published elsewhere.

Structure and Conformation of the 6b conformer. With the exclusion of the isopropyl ester side chain substituents attached to atoms C(2), C(8), C(14), and C(20) (Figure 2), the macrocyclic molecule can be described as having a flattened-cone conformation with an approximate C_{2v} symmetry. This is clearly shown by the values of the torsion angles around the four pairs of bonds C(1)–C(2) and C(2)–C(3), C(7)–C(8) and C(8)–C(9), C(13)–C(14) and C(14)–(15), and C(19)–C(20) and C(20)-C(21). These pairs of angles have nearly the same absolute values but opposite signs (with a deviation never greater than 15.9°),due to the presence of two nearly orthogonal planes of symmetry roughly defined by atoms C(11), C(27), C(23), and C(25) and C(5), C(28), C(26), and C(17), respectively. In fact, the torsion angle around C(1)–C(2) is related by a plane of symmetry to that around C(8)–C(9) (112.5° and −108.5°), and so the torsion angle around C(13)–C(14) is similarly related to that around C(20)–C(21) (98.1° and −109.0°, respectively). Analogously, the angle around C(2)–C(3) is symmetry related to that around C(19)–C(20) (31.5° and 19.2°, respectively), as is the angle around C(7)–C(8) which is symmetry related to that around C(14)–C(15) (32.5° and −16.6°, respectively). The observed distortions are to be ascribed to crystal forces which influence locally the conformation of the macrocyclic system.

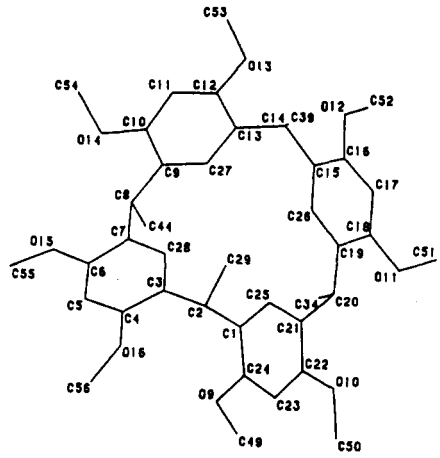
In this conformation opposite benzene rings are almost coplanar (small angles of 11° and 9° occur between opposite rings), while successive benzene rings are almost orthogonal to each other: the angles that each benzene ring forms with the adjacent rings are either 100° or 89°.

In all instances, the two methoxy group substituents of each benzene ring lie nearly in the same plane as the ring, and all of them point away from the core of the macrocycle. In particular, the four methoxy groups on the two opposite benzene rings run parallel to one of the pseudobinary axes of the macrocycle, while the remaining four methoxy groups run perpendicular to this axis. The C_{2v} symmetry is broken by the four side chain isopropyl ester groups which assume, in the solid state, a different conformation. This is most likely the result of crystal forces, and it is due to the need to achieve the most favorable intramolecular interactions between these groups of substituents of symmetry-related macrocyclic molecules. All four groups stick out on one side of the macrocycle: their configuration can be described as *cis-cis-cis* relative to C(2).

The conformation of $-CHCH_2COOCH(CH_3)_2$ is defined by the angles χ_1, χ_2, χ_3, and χ_4 as shown in Figure 2. The first angle χ_1 determines the orientation of the group with respect to the macrocycle, while the χ_2 angle determines the orientation of the ester group with respect to the rest of the chain. The χ_3 and χ_4 angles characterize the conformation of the ester group. The χ_1 and χ_2 angles show the larger variability with χ_1 assuming values of −68.7°, −87.5°, −53.6°, and −169.5° (or 164.9°, 144.2°, 178.0°, 63.8°) and χ_2 assuming values of 175.8°, 122.3°,



6b



6a

Figure 1. Numbering of C-alkylcalix[4]resorcinarenes 6a and 6b.

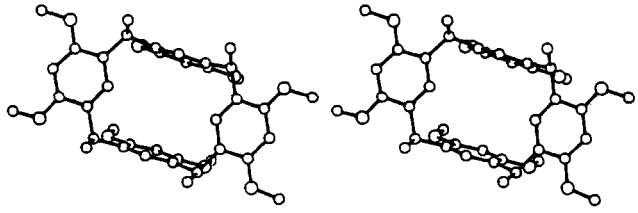


Figure 2. Stereo drawing of compound 6b.

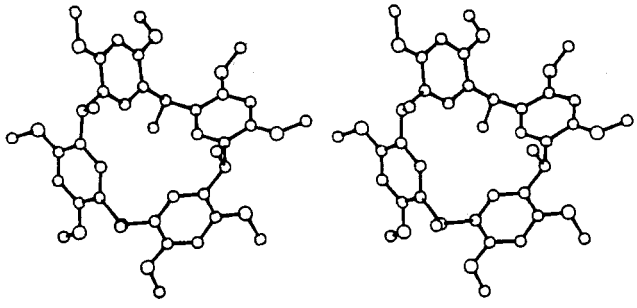


Figure 3. Stereo drawing of compound 6a.

−56.3°, and 44.2° for the four substituents of the macrocyclic system. The χ_3 angle instead shows approximately the same values (within 9°) in the four chains: the χ_3 angle is always in the *trans* conformation, with the values around the single C–O bond being −176.2°, 175.0°, and 177.4°. On the contrary, the χ_4 angle assumes values corresponding to both the (g^-, t) and (t, g^+) conformations of the methyl groups of the isopropyl moiety with respect to the O–C bond. In this conformation the C–H bond of the isopropyl moiety tends to be nearly coplanar (synplanar) to the carboxylic acid moiety.

Structure and Conformation of the 6a conformer. If the (carbomethylisopropyl)oxy side chain substituents of atoms C(2), C(8), C(14), and C(20) are not considered, the macrocycle of the 6a conformer can be grossly described as having a 1,2-alternate conformation with an approximate C_s symmetry. As shown in the stereo drawing in Figure 3 the plane of symmetry passing through atoms C(2) and C(14) generates two halves for which the torsion angles have opposite values. In fact, the torsion angles around the C(2)–C(3), C(7)–C(8), C(8)–C(9), and C(13)–C(14) bonds (67°, 39°, −96°, and 66°, respectively) have grossly the same absolute value (within 20°), but opposite signs with respect to the torsion angles around the C(1)–C(2), C(20)–C(21), C(19)–C(20), and C(14)–C(15) (−79°, −20°, 92°, and −76°, respectively).

In this conformation the benzene rings, related by the symmetry plane, make angles of 111° and 121°, while successive benzene rings not related by symmetry make angles of 91° and 101° (the angles between opposite benzene rings are 40° and 61°).

The configuration of the four isopropyl ester side chain groups is *cis-trans-cis* relative to C(2). As in the case of 6b the larger variability in the conformational angles for 6a is shown by the χ_1 and χ_2 torsion angles, while the χ_3 angle always shows values corresponding to a *trans* conformation and the χ_4 angle presents values appropriate for a staggered conformation of the methyl substituents, such that the C–H bond results nearly eclipsed with the C=O of the ester group, as found in the case of the 6a conformer.

Molecular Modeling Studies

Gutsche[1] has suggested that calix[4]arenes adopt conformations that can be categorized in four classes: the cone, the partial cone, the 1,2-alternate, and the 1,3-alternate conformations. Later, Reinhoudt[8] reported data about the relative energetics of such conformations for calix[4]arenes without substituents at the methylene bridges, showing that the preferred conformation of these molecules depends on the number and the positions of the alkoxy substituents on the aromatic rings and that, in some cases, the conformation with the lowest calculated energy can be different from the conformation found in solution and in the solid state. Therefore, due to the novelty of our C-alkylcalix[4]resorcinarenes we have undertaken a computational study in order to elucidate the conformational properties of compounds 2, 4, 6, and 8. We were interested in gaining an insight into the energetic profile of the conformations of calix[4]-resorcinarenes bearing different side chains at the CH_2 bridges and in comparing the computer-generated lowest energy 3D-structures of compounds 2, 4, 6, and 8 with those obtained by ^1H NMR spectroscopy in solution, and with those obtained by X-ray diffraction in the solid state.

Three types of molecular manipulations were carried

(8) Grootenhuis, P. D. J.; Kollman, P. A.; Groenen, L. C.; Reinhoudt, D. N.; van Hummmel, G. J.; Ugozzoli, F.; Andreetti, G. D. *J. Am. Chem. Soc.* **1990**, *112*, 4165.

Table 11. Energies of MM2 (MODEL)-Minimized Conformations of Calix[4]resorcinarenes

conformn	E (kcal/mol)	calcd equilibrium mixture (%)
flattened cone	86.7	71.6
flattened partial cone 1	87.6	15.7
1,3-alternate	87.8	11.2
flattened partial cone 2	89.1	1.2
1,2-alternate	90.0	0.3

out in this computational study: interactive structure building, geometry optimization, and conformational searching.

The SYBYL[9] program equipped with the TRIPOS force field was employed for the first two tasks in order to get the 3D-structure of a relative minimum-energy calixarene ring bearing no side chains.

Because of the high number of rotatable bonds present in compounds 2, 4, 6, and 8, even a rough conformational analysis (120° increment of each rotatable bond) of these structures endowed with side chains was a computationally unfeasible task. Likewise, it is a reasonable assumption to consider the conformational possibilities of the calixarene ring to be to some extent independent of the presence of aliphatic side chains at the methylene bridges. For these reasons the conformational search on 2, 4, 6, and 8 was divided in two steps. In the first one, the analysis of the calix[4]resorcinarene structure with methylene bridges was carried out. Secondly, the work was completed and refined by adding the four side chains to each minimum-energy structure calculated in the first step and by performing a further search and a final minimization procedure operating on the whole structures.

The RANDOMSEARCH module within SYBYL was employed to perform the conformational analysis of the calixarene ring. The eight nonaromatic C–C bonds were selected as being capable of free rotation and randomly varied. An energy cutoff of 70 kcal/mol (default value) was imposed to the search output conformations. This calculation yielded 33 structures with different geometries, which were further minimized with the SYBYL MAXIMIN2 submode, setting the convergence criterion RMS GRADIENT to the value 1.0×10^{-3} kcal/mol Å^2. Atomic partial charges were computed with the GAST–HUCK method. This procedure reduced the initial 33 to five conformers, which with slight distortion of the macrocyclic ring could be described as the flattened cone, two types of flattened partial cones, the 1,3-alternate, and the 1,2-alternate conformations.

We considered the observed distortion of the calixarene ring to probably be due to the torsional energy parameterization of the TRIPOS force field which is not sufficiently accurate to model such flexible macrocyclic structures.

A further optimization of the geometries of these five structures thus seemed necessary in order to obtain the symmetries of calix[4]resorcinarenes reported in the literature.[1] The MODEL[10] program (generalized MM2 force field) was employed for this task. In this program the dipole–dipole electrostatic energy calculation was preferred to the charge–charge-based one. By this further minimization, four conformations with the expected symmetries C_{2v} (flattened cone), C_{2h} type and C_s type

(9) SYBYL (Version 5.4); Tripos Associates, Inc., St. Louis, MO 63144.
(10) Steliou, K. MODEL (Version K.S.2.96); University of Montreal, Canada.

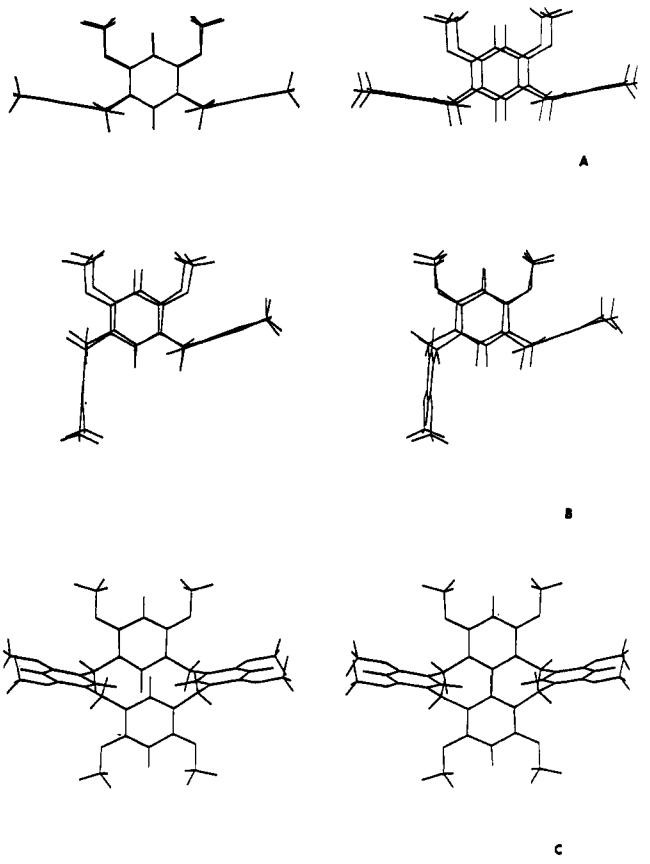


Figure 4. Stereoview of flattened cone (A), flattened partial cone 1 (B), and flattened partial cone 2 (C) conformations of unsubstituted calix[4]resorcinarene.

(flattened partial cones), and D_{2d} (1,3-alternate) were obtained. The 1,2-alternate conformation was derived from the fifth structure, which showed a very high strain energy, by adjusting the coordinates of half of the molecule as to obtain a C_s symmetry. The resulting geometry was optimized by the block-diagonal Newton-Raphson procedure in MODEL. In Table 11 the energies of the five final minimized conformations are reported, while in Figures 4 and 5 the corresponding 3D-stuctures are represented.

It can be seen in Table 11 that the flattened cone and the 1,2-alternate conformation have, respectively, the lowest and the highest steric energy, while the 1,3-alternate conformation possesses an intermediate steric energy. The Boltzmann distribution of these conformers indicates that the cone conformation corresponds to 71.6% of the equilibrium mixture calculated at 298 °K (see Table 11).

The analysis of each contibution to the global steric energy, as calculated by MODEL, revealed that the van der Waals energy contribution is the factor determining the energy difference among the studied conformations. A careful observation of Figure 4 reveals that the calculated geometries of the two types of flattened partial-cone conformations, which we reported in a previous paper[5] as belonging to the symmetry point groups C_{2h} and C_s, respectively, indeed show lower symmetries. The flattened partial cone 2 shows actually a C_s instead of the previously assigned C_{2h} symmetry. In fact, opposite benzene rings related by the mirror plane defined by atoms C(11), C(27), and C(25) are not coplanar, forming an angle of 116°. On the other hand, a point group C_s was assigned to the

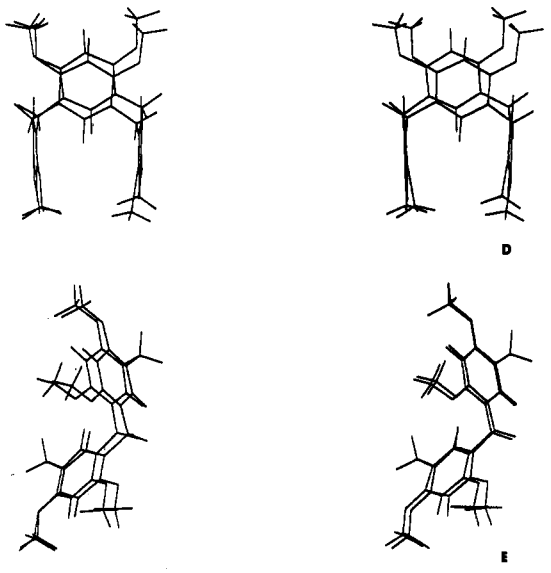


Figure 5. Stereoview of 1,3-alternate (D) and 1,2-alternate (E) conformations of unsubstituted calix[4]resorcinarene.

Table 12. Energies of MM2 (MODEL)-Minimized Conformations of *C*-Alkylcalix[4]resorcinarenes (kcal/mol)

conformn	methyl ester	ethyl ester	isopropyl ester	alcohol
flattened cone	109.4	107.9	107.1	99.8
1,2-alternate	111.6	108.9	107.3	103.9
1,3-alternate	116.1	112.9	113.7	106.9

flattened partial cone 1 conformation, due to the presence of a plane of symmetry defined by atoms C(5), C(28), C(26), and C(17).

At this stage, we turned our attention to the molecules bearing the various types of substituents. Four aliphatic side chains, namely CH_2COOR (R = Me, Et, i-Pr) and CH_2CH_2OH, were added to each of the five conformations previously described. In the case of the 1,2-alternate conformation, the substituents were drawn in the *cis-trans-cis* configuration relative to C(2), in accordance with the ^1H NMR data. Conversely, in the remaining four conformations, the side chains were added so that the *all-cis* relative configuration experimentally observed in the partial cone structure was maintained. The resulting five structures for each type of compound were minimized with MODEL until convergence was obtained. A final statistical search was then carried out on the side chains with the program BAKMDL[11] to find their preferred spatial orientations.

The sp^3–sp^3 and the sp^3–sp^2 rotatable bonds of the side chains were randomly varied through 120° and 60° increments, respectively. Conversely, the ester groups were kept in a *trans* conformation. Because of the high number of theoretical conformations, the analysis on bonds was not run to completion according to BAKMDL stopping criterion. Every search was thus stopped when a new lower energy conformer was not located after 24 CPU hours of searching from the last located one. Even if the procedure gives no absolute guarantee that the global minimum has been located, the following reasons give us confidence about the reliability of the values obtained. First, the statistic-search procedure[12] favors the low-energy regions of conformational space; second, the energy difference between the latest two conformers found was always less than 1 kcal/mol. Moreover, the energy difference between two calixarene-ring conformations (see Table 12) is much greater than this value.

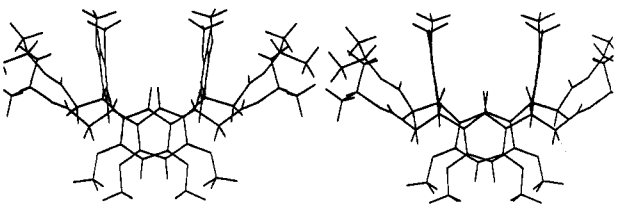


Figure 6. Stereoview of compound **6c**.

The results of the molecular mechanics calculations on the flattened-cone and the 1,2- and the 1,3-alternate geometries for each compound **2**, **4**, **6**, and **8** are summarized in Table 12, which shows that the flattened-cone conformation is always the lowest energy structure. The 1,2-alternate conformation, with the *cis-trans-cis* side chain relative configuration, now presents a very low steric energy. These results explain well the achievement of the calix[4]arenes with these geometries during the cyclization reaction. It is interesting to note also that ΔE between the flattened-cone and the 1,2-alternate conformations (Table 12) decreases with the increasing bulkiness of the R groups in the side chains.

The substitution on the CH_2 bridges brings about a small distortion of the macrocycle ring, mainly in 1,2- and 1,3-alternate conformations with slight influence on the symmetry.

The inversion in the energy between the 1,3- and the 1,2-alternate conformations, as shown in Tables 11 and 12, must be attributed to the presence of the side chains on the methylene bridges. These theoretical observations are supported by the experimental results (Tables 6–8).

Since the theoretical structures of both the isopropyl substituted flattened-cone and 1,2-alternate conformations are the same as those described in the X-ray Diffraction Analyses section (vide supra), we report here a description of the calculated 1,3-alternate conformation shown in Figure 6.

The macrocyclic system, with the exclusion of the isopropyl ester side chains, presents an approximate D_{2d} symmetry, as shown by the values of the torsion angles around the four pairs of bonds C(1)–C(2) and C(2)–C(3), C(7)–C(8) and C(8)–C(9), C(13)–C(14) and C(14)–C(15), and C(19)–C(20) and C(20)–C(21). These pairs of angles have nearly the same absolute values, but opposite signs (with a deviation never greater than 19.5°), due to the presence of two nearly orthogonal planes of symmetry roughly defined by the following atoms: the first pair, C(11), C(27), C(23), and C(25); and the second pair, C(5), C(28), C(26), and C(17). In fact, the torsion angles around C(1)–C(2) are related by a plane of symmetry to that around C(8)–C(9) (60.4° and −78.5°, respectively) while the torsion angle around C(13)–C(14) is similarly related to that around C(20)–C(21) (60.9 and −78.6, respectively). Analogously, the angle around C(2)–C(3) is symmetry related to that around C(19)–C(20) (59.0° and −44.7°, respectively), and similarly around C(7)–C(8), which is symmetry related to that around C(14)–C(15) (−44.3° and 59.1°, respectively). The observed distortions can be ascribed to the optimization of the van der Waals interactions among the bulky side chains on the methylene

(11) Steliou, K. BAKMDL-MM2 (Version K.S.2.94); University of Montreal, Canada.
(12) Steliou, K. 1989 International Chemical Congress of Pacific Basin Societes, Honolulu, HI, Dec 1989.

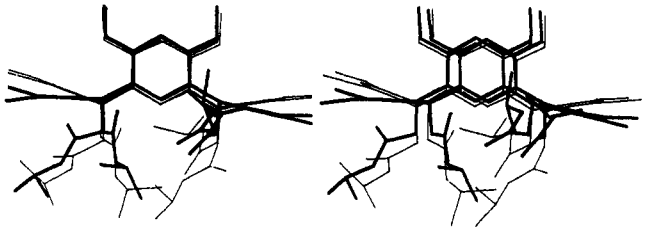


Figure 7. Stereoview of the superimposition between X-ray-determined (bold) and computer-calculated geometries of compound **6b**.

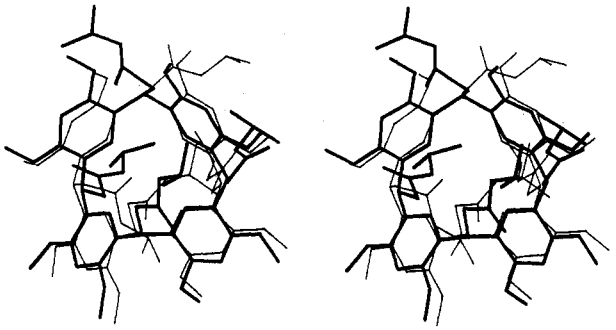


Figure 8. Stereoview of the superimposition between X-ray-determined (bold) and computer-calculated geometries of compound **6a**.

bridges, this phenomenon being much less evident when no side chains are present.

In the 1,3-alternate conformation the opposite benzene rings are almost coplanar (small angles of 11.1° and 11.9° occur between opposite rings), whereas successive benzene rings are almost orthogonal to each other with an angle ranging between 87° and 88°.

A comparison between the X-ray and the calculated structures of **6a** and **6b** led to the following conclusions.

A least-squares fit between the X-ray and the calculated structures of both the flattened-cone and the 1,2-alternate conformations was performed by the SYBYL root mean square (rms)-fitting procedure. All the calix[4]arene ring C-atoms (28 atoms per molecule) were selected and superimposed. An rms value of 0.34 Å was computed for the flattened-cone **6b**. A very good superimposition (see Figure 7) was found for the two opposite aromatic rings parallel to the symmetry plane, whereas the two rings perpendicular to this plane show a minor superimposition differing by about 15–20° (the X-ray structure being more flattened than the calculated one). In the case of **6a** (see Figure 8), a slightly worse rms value (0.52 Å) was obtained. However, a better superimposition between the calculated and the X-ray structure (rms value of 0.17 Å) can be obtained with the unsubstituted 1,2-alternate structure (Figure 9). The decrease of the matching can be ascribed to a slight deformation of the macrocyclic ring operated by the bulkiness of the side chains.

Since the results of the computational studies on **6a** and **6b** are in accord with the X-ray analysis results, we can conclude that the parameterization of the MODEL generalized MM2 force field makes the program suitable for studies on calix[4]resorcinarenes. Consequently, the geometries calculated for calix[4]resorcinarenes bearing different ester functions should be considered reliable.

Conclusion

In conclusion, the results of the present study show that the stereoselectivity of the cyclization appears to be dependent on the reaction conditions and the nature of the side chains at the bridging carbon atoms.

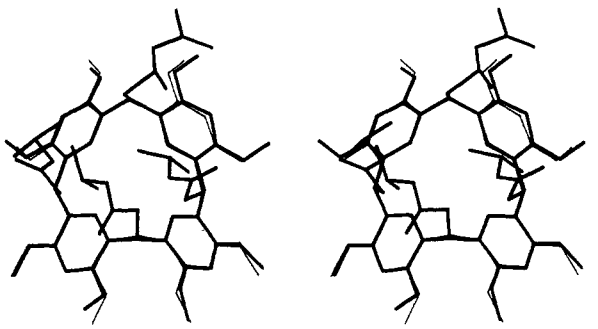


Figure 9.

Furthermore, the synthetic route outlined above affords considerable versatility in extending functionality at the "outside periphery" of the calixarene skeleton. For example, conversion of the ester functions to primary alcohols allows further elaborations at this site so as to provide more binding possibilities. Studies on the elongation, the functionalization, and the introduction of chirality by adding stereocenters in the side chains are in progress.

Experimental Section

General Procedure for the Preparation of *C*-Alkylcalix[4]resorcinarenes. To a solution of the cinnamic acid ester (1 mmol) in $CHCl_3$ (5 mL) was added $BF_3{\cdot}Et_2O$ (0.2 mL, 1.5 mmol), and the mixture was stirred at room temperature for 15 h, diluted with MeOH, and dried.

Reaction with (*E*)-2,4-Dimethoxycinnamic Acid Methyl Ester (1). Silica gel chromatography (hexane/EtOAc, (3:2)) of the residue afforded a 2:3 mixture (167 mg, 75% overall yield) of **2a** and **2b**, which were separated by preparative TLC ($CHCl_3$/MeOH, (98:2)).

***r*-2,*c*-8,*t*-14,*t*-20-Tetra(carbomethoxymethyl)pentacyclo[19.3.1.1^{3,7}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-4,6,10,12,16,18,22,24-octol, octamethyl ether (2a)**: vitreous solid; UV λ_{max} ($CHCl_3$) nm (log ϵ) 284 (4.6), 241.5 (4.7); ^{1}H- and ^{13}C-NMR in Table 3; high-resolution EIMS [M]$^+$ found 888.3568, calcd for $C_{48}H_{56}O_{16}$ 888.3572; FAB MS *m*/*z* (rel int) 889 (MH^+, 58), 888 (63), 815 ($M - CH_2COOCH_3^+$, 100), 755 (815 – $HCOOMe^+$, 22), 719 (50), 371 ($M - 2CH_2COOMe/2^{2+}$; M* 748.0 (888 → 815). Anal. Calcd for $C_{48}H_{56}O_{16}$: C, 64.9; H, 6.3. Found: C, 64.6; H, 6.5.

***r*-2,*c*-8,*c*-14,*c*-20-Tetra(carbomethoxymethyl)pentacyclo[19.3.1.1^{3,7}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-4,6,10,12,16,18,22,24-octol, octamethyl ether (2b)**: mp 255–6 °C; UV λ_{max} ($CHCl_3$) nm (log ϵ) 281 (4.4), 240.5 (4.4); ^{1}H- and ^{13}C-NMR in Table 4; high-resolution EIMS [M]$^+$ found 888.3546, calcd for $C_{48}H_{56}O_{16}$ 888.3572; FAB MS (rel int) 889 (MH^+, 22), 888 (39), 815 ($M - CH_2COOMe^+$, 100), 755 (815 – $HCOOMe^+$, 9), 719 (12), 445 (18), 371 ($(M - 2 \times CH_2COOMe/2^{2+}$, 307 (55), 223 (60); M* 748.0 (888 → 815). Anal. Calcd for $C_{48}H_{56}O_{16}$: C, 64.9; H, 6.3. Found: C, 64.6; H, 6.6.

Reaction with (*E*)-2,4-Dimethoxycinnamic Acid Ethyl Ester (3). Silica gel chromatography (hexane/CH_2Cl_2/EtOAc (3:4:3)) of the residue afforded a 1:1 mixture of **4a** and **4c** (108 mg), which were separated by preparative TLC ($CHCl_3$/MeOH, (98:2)), and **4b** (53 mg, overall yield 68%).

***r*-2,*c*-8,*t*-14,*t*-20-Tetra(carbethoxymethyl)pentacyclo[19.3.1.1^{3,7}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(25),15,17,19(26),21,23-dodecaen-4,6,10,12,16,18,22,24-octol, octamethyl ether (4a)**: mp 241–2 °C; UV λ_{max} ($CHCl_3$) nm (log ϵ) 282 (4.5), 241 (4.6); ^{1}H- and ^{13}C-NMR in Table 3; FAB MS *m*/*z* (rel int) 945 (MH^+, 37), 857 ($M - CH_2COOEt^+$, 100), 783 (857 – $HCOOEt^+$, 11), 385 ($M - 2CH_2COOEt/2^{2+}$, 9); M* 778.0 (944 → 857). Anal. Calcd for $C_{52}H_{64}O_{16}$: C, 66.1; H, 6.8. Found: C, 65.8; H, 6.9.

r-2,c-8,c-14,c-20-Tetra(carbethoxyethyl)pentacyclo-[19.3.1.1^{3,7}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19-(26),21, 23-dodecaen-4,6,10,12,16,18,22,24-octol, octamethyl ether (4b): mp 199–200 °C; UV λ_{max} ($CHCl_3$) nm (log ϵ) 283 (4.6), 241 (4.7); ^{1}H- and ^{13}C-NMR in Table 4; FAB MS *m/z* (rel int) 945 (MH^+, 6), 857 (M – CH_2COOEt^+, 100), 783 (857 – $HCOOEt^+$, 9), 385 (M – $2CH_2COOEt/2^{2+}$, 8); M* 778.0 (944 → 857). Anal. Calcd for $C_{52}H_{64}O_{16}$: C, 66.1; H, 6.8. Found: C, 65.8; H, 6.6.

r-2,t-8,c-14,t-20-Tetra(carbethoxyethyl)pentacyclo-[19.3.1.1^{3,7}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19-(26),21, 23-dodecaen-4,6,10,12,16,18,22,24-octol, octamethyl ether (4c): mp 249–50 °C; UV λ_{max} ($CHCl_3$) nm (log ϵ) 282 (4.4), 2.41 (4.7); ^{1}H- and ^{13}C-NMR in Table 5; FAB MS *m/z* (rel int) 945 (MH^+, 35), 857 (M – CH_2COOEt^+, 100), 783 (857 – $HCOOEt^+$, 10), 385 (M – $2CH_2COOEt/2^+$, 9); M* 778.0 (944 → 857). Anal. Calcd for $C_{52}H_{64}O_{16}$: C, 66.1; H, 6.8. Found: C, 65.9; H, 6.9.

Reaction with (*E*)-2,4-Dimethoxycinnamic Acid Isopropyl Ester (5). Silica gel chromatography (hexane/CH_2Cl_2/EtOAc (2:7:1)) of the residue afforded **6a** (67 mg), **6c** (64 mg), and **6b** (69 mg, overall yield 80%).

r-2,c-8,t-14,t-20-Tetra(carbisopropoxymethyl)pentacyclo-[19.3.1.1^{3,7}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19-(26), 21,23-dodecaen-4,8,10,12,16,18,22,24-octol, octamethyl ether (6a): mp 213–5 °C; UV λ_{max} ($CHCl_3$) nm (log ϵ) 283 (4.5), 242 (4.5); ^{1}H- and ^{13}C-NMR in Table 3; FAB MS *m/z* (rel int) 1001 (MH^+, 48), 899 (M – CH_2COOiP^+, 100), 811 (899 – $HCOOiP^+$, 6), 399 (M – $2CH_2COOiP/2^{2+}$, 7); M* 808.2 (1000 → 899). Anal. Calcd for $C_{56}H_{72}O_{16}$: C, 67.2; H, 7.2. Found: C, 67.0; H, 7.4.

r-2,c-8,c-14,c-20-Tetra(carbisopropoxymethyl)pentacyclo-[19.3.1.1^{3,7}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19-(26), 21,23-dodecaen-4,6,10,12,16,18,22,24-octol, octamethyl ether (6b): mp 165–7 °C; UV λ_{max} ($CHCl_3$) nm (log ϵ) 282 (4.4), 242 (4.4); ^{1}H- and ^{13}C-NMR in Table 4; FAB MS *m/z* (rel int) 1001 (MH^+, 46), 899 (M – CH_2COOiP^+, 100), 811 (899 – $HCOOiP^+$, 5), 399 (M – $2CH_2COOiP/2^{2+}$, 19); M* 808.2 (1000 → 899). Anal. Calcd for $C_{56}H_{72}O_{16}$: C, 67.2; H, 7.2. Found: C, 66.9; H, 7.5.

r-2,t-8,c-14,t-20-Tetra(carbisopropoxymethyl)pentacyclo-[19.3.1.1^{3,7}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19-(26), 21,23-dodecaen-4,6,10,12,16,18,22,24-octol, octamethyl ether (6c): mp 274–5 °C; UV λ_{max} ($CHCl_3$) nm (log ϵ) 282 (4.5), 242 (4.5); ^{1} H- and ^{13}C- NMR in Table 4; high-resolution EIMS $[M]^+$ found 1000.4828, calcd for $C_{56}H_{72}O_{16}$ 1000.4820; FAB MS *m/z* (rel int) 1001 (MH^+, 39), 899 (M – CH_2COOiP^+, 100), 811 (899 – $HCOOiP^+$, 17), 399 (M – $2CH_2COOiP^{2+}$, 9); M* 808.2 (1000 → 899). Anal. Calcd for $C_{56}H_{72}O_{16}$: C, 67.2; H, 7.2. Found: C, 66.8; H, 7.3.

Synthesis of Compound 7. To a solution of (*E*)-2,4-dimethoxycinnamic acid methyl ester (1, 222 mg, 1 mmol) in $CHCl_3$ (5 mL) was added BF_3·Et_2O (0.13 mL, 1 mmol), and the mixture was stirred at room temperature for 7 h, added with MeOH, and evaporated. Silica gel chromatography ($CHCl_3$) of the resulting residue gave the starting material 1 (150 mg), compound 7 (16 mg), and a mixture of **2a** and **2b** (22 mg).

(*E*)-2,4-Dimethoxy-5-[2-(methoxycarbonyl)-1-(2,4-dimethoxyphenyl)ethyl]cinnamic acid methyl ester (7): oil; [α] = 0; UV λ_{max} ($CHCl_3$) nm (log ϵ) 335 (4.16), 295 sh (4.09), 285 (4.13), 245 (4.17); EIMS *m/z* (rel int) 444 (M^+, 13), 371 (M – CH_2COOMe^+, 83), 235 (371 – A ring$^+$, 42), 222 (M – B ring$^+$, 38), 191 (21), 190 (18), 151 (235 – CH=CHCOOMe$^+$, 100), 121 (40), 91 (40); M* 310.0 (444 → 371), 148.9 (371 → 235), 97.0 (235 → 151).

General Reduction Procedure. Calixarene ester (**2a, 4a, 6a** or **2b, 4b, 6b**; 1 mmol) in THF (30 mL) was added dropwise to a stirred solution of $LiAlH_4$ (6 mmol, 227 mg) under N_2 and left under reflux for 48 h. The cooled reaction mixture was added with EtOAc and successively with H_2O. Standard workup gave a residue that by column chromatography with $CHCl_3$–MeOH (95:5) gave the corresponding calixarene alcohol **8a** or **8b** (0.50–0.58 mmol).

When the reaction was carried out with the esters **4c** and **6c**, in the 1,3-alternate conformation, mainly the alcohol **8a** (0.32–0.45 mmol) was obtained

r-2,c-8,t-14,t-20-Tetra(hydroxyethyl)pentacyclo-[19.3.1.1^{3,7}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19-(26),21,23-dodecaen-4,6,10,12,16,18,22,24-octol, octamethyl ether (8a): mp 234–5°; ^{1}H- and ^{13}C-NMR in Table 3; EIMS *m/z* (rel int) 776 (M^+, 19), 731 (M – $CH_2CH_2OH^+$, 100), 343 (M – $2CH_2CH_2OH/2^{2+}$, 38). Anal. Calcd for $C_{44}H_{56}O_{12}$: C, 68.0; H, 7.2. Found: C, 67.9; H, 7.4.

r-2,c-8,c-14,c-20-Tetra(hydroxyethyl)pentacyclo-[19.3.1.1^{3,7}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19-(26),21,23-dodecaen-4,6,10,12,16,18,22,24-octol, octamethyl ether (8b): mp 295–6 °C; ^{1}H- and ^{13}C- NMR in Table 4; EIMS *m/z* (rel int) 776 (M^+, 31), 731 (M – $CH_2CH_2OH^+$, 100), 343 (M – $2CH_2CH_2OH/2^{2+}$, 57). Anal. Calcd for $C_{44}H_{56}O_{12}$: C, 68.0; H, 7.2. Found: 67.7; H, 7.4.

General Optimization Reactions Procedure. Reactions were carried out according to the general procedure on approximately 0.2 mmol of substrate at the temperatures and the substrate/BF_3 ratios listed in Tables 6–9. The reactions were monitored by TLC and stopped when the starting material disappeared. Standard workup and rough purification by silica gel chromatography with the above-reported eluent system were performed. The approximate percentage of each component was established by the integration of appropriate isolated signal in the ^{1}H NMR spectra of the crude mixtures of tetramers.

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Supplementary Material Available: ^{1}H- and ^{13}C-NMR signal assignments for 7 and for alkyl chains of **2a,b, 4a–c, 6a–c,** and **8a,b** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.