Alkanediyl Bridged Calix[4]arenes: Synthesis, Conformational Analysis, and Rotational Barriers

Silvio E. Biali,[†] Volker Böhmer,*[,‡] Shmuel Cohen,[†] George Ferguson,[§] Cordula Grüttner,[‡] Flavio Grynszpan,[†] Erich F. Paulus,[⊥] Iris Thondorf,[∥] and Walter Vogt[‡]

Contribution from the Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem 91904, Israel, Institut für Organische Chemie, Johannes-Gutenberg-Universität, J.-J.-Becher-Weg 34, SB1, D-55099 Mainz, Germany, Department of Chemistry and Biochemistry, University of Guelph, Ontario, Canada N1G 2W1, Hoechst AG, D-65926 Frankfurt/Main, Germany, and Fachbereich Biochemie/Biotechnologie, Martin-Luther-Universität, D-06099 Halle, Germany

Received March 18, 1996[⊗]

Abstract: In calix[4]arenes when one methylene bridge carries an alkyl or aryl substituent, two diastereomeric *cone* conformations are possible in which this substituent assumes the equatorial or axial position. Two diastereomers with *cis* or *trans* arrangement of the substituents exist for the corresponding compounds with two substituted bridges, and diastereomeric *cone* conformations have to be considered additionally in most cases. Molecular mechanics calculations predict an energetical preference of the equatorial position of the substituents in both systems. This preference is markedly more pronounced for alkyl groups than for aryl groups. To test these predictions a series of calix[4]arenes in which one (**4**) or two opposite (**5**) methylene bridges are substituted by alkyl or aryl groups was synthesized by fragment condensation. For these calixarenes the solution conformations, the equatorial/axial conformational equilibria, and the energy barriers for the *cone* to *cone* ring inversion were determined by ^{1}H NMR spectroscopy. The experimental energy differences between the two *cone* conformations correlate well with the calculated ones. Free energies of activation $\Delta G^{\ddagger}$ for the *cone* to *cone* ring inversion of the monoalkyl substituted compounds **4** increase in the order methyl < *tert*-butyl < ethyl < isopropyl. For the bisalkyl substituted compounds (**5b**−**d**) only the *cis*-isomer could be isolated while *cis*- and *trans*-isomers were obtained for **5a** and for the bisaryl compounds **5e**−**g**. Among the *cis*-isomers **5a**−**d** exist exclusively as the equatorial conformers, while the conformational equilibrium is strongly solvent dependent for **5e**−**g**. Single crystal X-ray structures were obtained for several calixarenes with one (**4b**) or two substituted bridges (**5e**−**g**). Here the substituents are found exclusively in the equatorial position, and the molecular conformation is similar to the calculated one.

Introduction

Calixarenes are synthetic macrocycles readily available by condensation of *tert*-butylphenol with formaldehyde under alkaline conditions.[1] From these starting materials a large variety of more or less sophisticated compounds has been obtained.[2] Derivatization reactions usually involve the phenolic hydroxy groups (acylation, alkylation or even elimination or replacement), the *p*-positions (all kinds of electrophilic substitution, eventually after elimination of the *tert*-butyl groups), or the phenolic units as a whole (oxidation to *p*-quinones and subsequent reactions). Numerous selective procedures, involving certain phenolic units, are available not only in the calix[4]arene[3] series, but increasingly also for calix[6]arenes[4] and more recently even for calix[5]-[5] and calix[8]arenes.[6]

Another possible modification of the calixarene skeleton involves the methylene bridges, which however are not as easily amenable to chemical reactions. Oxidation to carbonyl groups and their subsequent reduction to alcohol functions have been reported for *tert*-butylcalix[4]arene,[7] but nothing is known about the stereochemistry of the last step. Recently, Sartori et al. described the first example of a calix[4]arene in which two distal methylene bridges are substituted by aryl rings.[8] Such substit-

[†] The Hebrew University of Jerusalem.
[‡] Johannes-Gutenberg-Universität.
[§] University of Guelph.
[⊥] Hoechst AG.
[∥] Martin-Luther-Universität.

[⊗] Abstract published in *Advance ACS Abstracts,* December 1, 1996.

(1) For optimized procedures see: Gutsche, C. D.; Iqbal, M. *Org. Synth.* **1990**, *68*, 234−237. Stewart, D. R.; Gutsche, C. D. *Org. Prep. Proc. Int.* **1993**, *25*, 137−139. Gutsche, C. D.; Dhawan, B.; Leonis, M.; Stewart, D. *Org. Synth.* **1990**, *68*, 238−242. Munch, J. H.; Gutsche, C. D. *Org. Synth.* **1990**, *68*, 243−246.

(2) For a recent review on calixarenes, see: Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713−745, and references cited there.

(3) For an early review, see: van Loon, J. D.; Verboom, W.; Reinhoudt, D. N. *Org. Prep. Proc. Int.* **1992**, *24*, 437−462.

(4) Janssen, R. G.; Verboom, W.; Harkema, S.; van Hummel, G. J.; Reinhoudt, D. N.; Pochini, A.; Ungaro, R.; Prados, P.; de Mendoza, J. *J. Chem. Soc., Chem. Comm.* **1993**, 506−508. Janssen, R. G.; Verboom, W.; Reinhoudt, D. N.; Casnati, A.; Freriks, M.; Pochini, A.; Uggozoli, F.; Ungaro, R.; Nieto, P. M.; Carramolino, M.; Cuevas, F.; Prados, P.; de Mendoza, J. *Synthesis* **1993**, 380−386. de Mendoza, J.; Carramolino, M.; Cuevas, F.; Nieto, P. M.; Prados, P.; Reinhoudt, D. N.; Verboom, W.; Ungaro, R.; Casnati, A. *Synthesis* **1994**, 47−50. Casnati, A.; Minari, P.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1991**, 1413−1414. Rogers, J. S.; Gutsche, C. D. *J. Org. Chem.* **1992**, *57*, 3152−3159. Kanamathareddy, S.; Gutsche, C. D. *J. Org. Chem.* **1992**, *57*, 3160−3166.

(5) Stewart, D. R.; Krawiec, M.; Kashyap, R. P.; Watson, W. H.; Gutsche, C. D. *J. Am. Chem. Soc.* **1995**, *117*, 586−601.

(6) Neri, P.; Geraci, C.; Piattelli, M. *Tetrahedron Lett.* **1993**, *34*, 3319−3322. Neri, P.; Battocolo, E.; Cunsolo, F.; Geraci, C.; Piattelli, M. *J. Org. Chem.* **1994**, *59*, 3880−3889. Cunsolo, F.; Piattelli, M.; Neri, P. *J. Chem. Soc., Chem. Commun.* **1994**, 1917−1918. Cunsolo, F.; Consoli, G. M. L.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* **1995**, *36*, 3751−3754. Geraci, C.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* **1995**, *36*, 5429−5432. Neri, P.; Geraci, C.; Piattelli, M. *J. Org. Chem.* **1995**, *60*, 4126−4135.

(7) Görmar, G.; Seiffarth, K.; Schulz, M.; Zimmermann, J.; Flämig, G. *Makromol. Chem.* **1990**, *191*, 81−87.

(8) Sartori, G.; Maggi, R.; Bigi, F.; Arduini, A.; Pastorio, A.; Porta, C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1657−1658; see, also ref. 22.

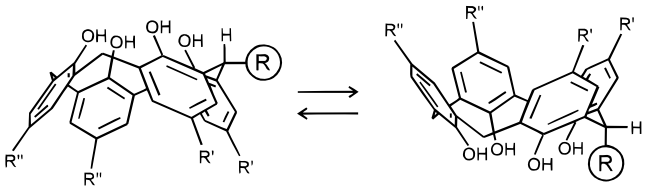
S0002-7863(96)00883-9 CCC: $12.00

uents not only offer an additional possibility to introduce further functionalities into the basic calixarene scaffold but also cause interesting stereochemical problems and possibilities. Here we report the synthesis of various calix[4]arenes in which one (**4**) or two opposite (**5**) methylene bridges are substituted by alkyl or aryl residues together with a comprehensive study of their conformational properties using molecular mechanics calculations, NMR-spectroscopy, and single crystal X-ray analysis.

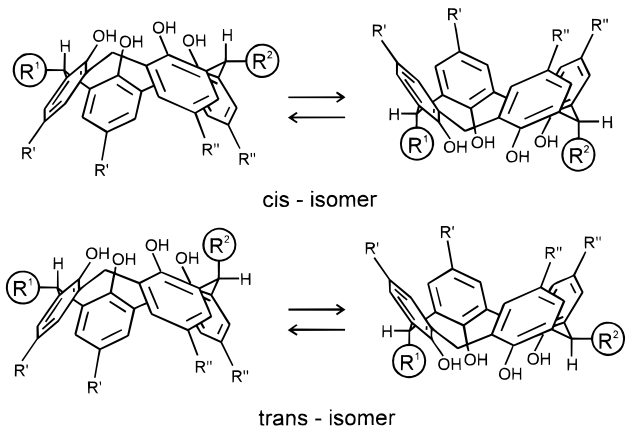
General Considerations

If in a calix[4]arene a methylene proton is replaced by a substituent R, the resulting molecule may still adopt a *cone* conformation. Since this substituent can be located either in an axial or an equatorial position, there exist two diastereomeric *cone* conformations, the axial and the equatorial conformer. These conformers can interconvert by the usual ring inversion process (Scheme 1).

Scheme 1



Scheme 2



The analogous introduction of an additional substituent at the distal methylene bridge results in *cis*- and *trans*-isomers.[9] Two distinct conformers exist for the *cis*-isomer in which both substituents (R^1, R^2) are located in axial or equatorial positions. Again these conformers should mutually interconvert by ring inversion (Scheme 2). In the *trans*-isomer, necessarily one substituent is in an axial position, while the second is equatorial. Thus, a single conformer exists for a *trans*-isomer when both substituents are identical, while two (mutually interconverting) diastereomeric *cone* conformations result, when the substituents at the methylene bridges (or/and the substituents R′/R″ in the *p*-position of the phenolic units) are nonidentical.

Computational Studies

In order to assess the influence of the nature of the substituent(s) R^1 (and R^2) on the relative stabilities and the geometries of the conformers, we performed molecular mechanics calculations using the TRIPOS force field. In addition to various substituents at the bridge(s), two different substituents at the upper rim (R′/R″ = Me/*t*-Bu) were considered.[10] Assuming that alkanediyl calix[4]arenes exist in the *cone* conformation the input geometries were constructed manually and subjected to energy minimization. Results for monosubstituted compounds are summarized in Table 1.

Table 1. Energy Differences (in kcal·mol^{-1}) for the Equatorial/Axial Position of the Substituent R^1 in Monoalkanediyl Calix[4]arenes **4** (Scheme 3) Obtained by Molecular Mechanics Calculations Using the TRIPOS Force Field

	R′	Me	Me	*t*-Bu	*t*-Bu
	R″	Me	*t*-Bu	Me	*t*-Bu
R^1		ΔE_{eq-ax}	ΔE_{eq-ax}	ΔE_{eq-ax}	ΔE_{eq-ax}
methyl		−2.14	−2.10	−2.29	−2.26
ethyl		−2.04	−1.99	−2.40	−2.25
isopropyl		−1.96	−1.88	−2.34	−2.23
tert-butyl		−2.52	−2.36	−3.10	−2.78
phenyl		−0.61	−0.29	−0.73	−0.43
p-tolyl		−0.59	−0.26	−0.70	−0.36
p-nitrophenyl		−0.47[a]	−0.25	−0.71	−0.52
2,4-dinitrophenyl		−0.10	0.05	−1.00	−0.83
2,6-dimethyl-4-nitrophenyl		−0.70	−0.45	−1.35	1.07

Notably, the calculations indicate that alkyl residues show a pronounced energetical preference for the equatorial position (ΔE_{eq-ax} ranging from −1.88 to −3.10 kcal·mol^{-1}), whereas for aryl residues this preference is considerably smaller (ΔE_{eq-ax} ranging from 0.05 to −1.35 kcal·mol^{-1}). Comparison of different aryl groups shows not only that the nature of their *p*-substituents has no influence, but also that a substituent in the *o*-position does not lead to a pronounced conformational preference. Within the series of alkyl calix[4]arenes the energy differences are in a similar range for R^1 = Me, Et, and *i*-Pr, whereas for the *tert*-butyl substituted derivatives a slight increase in ΔE_{eq-ax} is found which is due to the enhanced steric strain in the axial arrangement (see below). In general, the strong preference of aliphatic residues for the equatorial position results from the higher angle bending energy of the axial conformer. Here, the tetrahedral arrangement of the bridging methine carbon atom is distorted by the repulsion between the sp^3-carbon attached to the bridge and the adjacent hydroxyl groups. In the case of aryl substituents this repulsion is less pronounced as a result of their planar shape.

The substituents at the upper rim (R′, R″) have only little influence on the relative stabilities of the axial and equatorial conformers. The slightly larger energy gaps ΔE_{eq-ax} found for the calix[4]arenes with *p*-*tert*-butylphenol units adjacent to the substituted bridge (R′ = *t*-Bu) mainly originate from favorable van der Waals contacts between the substituents in the equatorial conformer.

The conformers of **4a**−**c** possess nearly C_{4v}-symmetry of their [14]-metacyclophane skeleton, and, in the case of R = Et and R = *i*-Pr, an *anti* arrangement of the hydrogen atoms at the CH−R bond. Such an arrangement is impossible for R = *t*-Bu, which leads to a strong distortion, especially in the axial conformer, due to repulsion between the *tert*-butyl and the hydroxyl groups. In the monoaryl substituted calix[4]arenes **4e**−**g** the aryl substituent is nearly coplanar with the reference plane (defined by the four bridging carbon atoms) in the equatorial conformer while in the axial conformer the plane of the aryl residue is almost normal to the methine C-H bond.

The calculations were extended to calix[4]arenes in which two opposite methylene bridges are replaced by identical or different alkanediyl bridges (Tables 2 and 3). As with the

(9) The same considerations are valid for two substituents at adjacent methylene bridges, where in addition the *trans*-isomer ($R^1 = R^2$) is chiral and exists as a pair of enantiomers. Additional pairs of enantiomers result for $R^1 \neq R^2$ and/or different substituents in *p*-position.

(10) For a preliminary report, see: Grüttner, C.; Böhmer, V.; Vogt, W.; Thondorf, I.; Biali, S. E.; Grynszpan, F. *Tetrahedron Lett.* **1994**, *35*, 6267−6270.

Table 2. Calculated (TRIPOS) Relative Steric Energies (in kcal·mol^{-1}) for the Bis-Alkanediyl Calix[4]arenes **5**

		R′ = R″ = Me			R′ = Me, R″ = *t*-Bu			
		cis isomers		*trans* isomers	*cis* isomers		*trans* isomers[a]	
R^1 = R^2		E_{total}	ΔE_{eq-ax}	E_{total}	E_{total}	ΔE_{eq-ax}	E_{total}	ΔE_{eq-ax}
methyl	*eq:*	−19.12	−4.25	−17.00	−25.20	−4.39	−23.10	−0.17
	ax:	−14.87	(−4.28)[b]	(−17.00)[c]	−20.81	(−4.39)[d]	−22.93	
ethyl	*eq:*	−21.19	−4.06	−19.15	−27.36	−4.28	−25.34	−0.26
	ax:	−17.13	(−4.08)[b]	(−19.16)[c]	−23.08	(−4.39)[d]	−25.08	
isopropyl	*eq:*	−24.37	−3.87	−22.42	−30.68	−4.16	−28.77	−0.34
	ax:	−20.50	(−3.92)[b]	(−22.44)[c]	−26.52	(−4.22)[d]	−28.43	
tert-butyl	*eq:*	−17.83	−3.39	−16.63	−24.32	−3.55	−23.49	−0.64
	ax:	−14.44	(−5.04)[b]	(−16.14)[c]	−20.77	(−5.46)[d]	−22.85	
phenyl	*eq:*	−20.27	−1.14	−19.71	−27.01	−0.95	−26.77	−0.46
	ax:	−19.13	(−1.21)[b]	(−19.70)[c]	−26.06	(−1.02)[d]	−26.31	
p-tolyl	*eq:*	−22.12	−1.12	−21.56	−29.08	−0.93	−28.83	−0.42
	ax:	−21.00	(−1.18)[b]	(−21.56)[c]	−28.15	(−0.96)[d]	−28.41	
p-nitrophenyl	*eq:*	−17.16	−0.85	−16.71	−23.84	−0.93	−23.60	−0.47
	ax:	−16.31	(−0.94)[b]	(−16.74)[c]	−22.91	(−0.96)[d]	−23.13	
2,4-dinitrophenyl	*eq:*	−12.67	0.09	−12.16	−19.78	−0.86	−19.39	−0.57
	ax:	−12.76	(−0.20)[b]	(−12.72)[c]	−18.92	(−0.95)[d]	−18.82	
2,6-dimethyl-4-nitrophenol	*eq:*	−16.29	−1.26	−15.62	−23.53	−1.58	−23.19	−0.94
	ax:	−15.03	(−1.4)[b]	(−15.66)[c]	−21.95	(−1.80)[d]	−22.25	

[a] Here *eq* (*ax*) denotes that the substituent adjacent to the *p-tert*-butyl phenol units is in an equatorial (axial) position. [b] Twofold value of ΔE_{eq-ax} of the corresponding monoalkanediyl calix[4]arene given in column 1 of Table 1. [c] Value calculated as average of E_{tot} of the equatorial and axial conformer of the *cis* isomer. [d] Values calculated as the sum of ΔE_{eq-ax} of the corresponding monoalkanediyl calix[4]arenes given in columns 2 and 3 of Table 1.

Table 3. Results of the Molecular Mechanics Calculations (TRIPOS) for the Bis-Alkanediyl Calix[4]arenes **5** (R′ = *t*-Bu, R″ = Me, R^2 = Me)[a]

		cis isomers		*trans* isomers[b]	
R^1		E_{total}	ΔE_{eq-ax}	E_{total}	ΔE_{eq-ax}
phenyl	*eq:*	−26.58	−2.85	−25.86	−1.38
	ax:	−23.73		−24.48	
p-chlorophenyl	*eq:*	−27.12	−2.90	−26.33	−1.31
	ax:	−24.22		−25.02	
p-nitrophenyl	*eq:*	−24.99	−2.83[c]	−24.27	−1.38[c]
	ax:	−22.16		−22.89	

[a] All energies are given in kcal·mol^{-1}. [b] Here *eq* (*ax*) denote that R^2 = Me is in an equatorial (axial) position.

monoalkanediyl calix[4]arenes the bis-equatorial position of the substituents is energetically favored in the *cis*-isomers. Moreover, the observed energy differences behave nearly additively, i.e., the equatorial/axial energy gaps ΔE_{eq-ax} of the *cis*-bis(alkanediyl) compounds are almost twice as large as ΔE_{eq-ax} of the corresponding monoalkanediyl calixarenes (Table 2). A strong deviation from this additivity is found, however, for the compounds bearing two bulky substituents (e.g., *tert*-butyl groups) at distal bridges.

The relative energies of the *trans*-isomers are nearly equal to the average of the relative energies found for the bis-equatorial and bis-axial conformer of the *cis*-isomer. Larger deviations are found again only for the calix[4]arenes substituted by two *tert*-butyl or 2,4-dinitrophenyl groups, the two substituents which cause rather strong deformations of the skeleton.

In the case of the bis(alkanediyl) calixarenes **5** with two different substituents at the upper rim (R′ = Me, R″ = *t*-Bu, Table 2) an equatorial position of the substituent adjacent to the *p-tert*-butylphenol units is preferred due to favorable van der Waals contacts, as observed for the monoalkanediyl systems **4.**

Calix[4]arenes bearing an alkyl (R^1) and an aryl substituent (R^2) at opposite methylene groups are of special interest. Calculations were carried out for three examples in which R^1 = Me is combined with different *p*-substituted phenyl groups. As expected for both stereoisomers (*cis* or *trans*) those conformers are energetically strongly favored in which the methyl group adopts the equatorial position (Table 3). Thus, the strong preference of an alkyl substituent for the equatorial position will direct in a *trans*-isomer a phenyl group into the axial position although the latter group has no pronounced conformational preference by itself.

From the variety of calix[4]arenes included in these calculations we have chosen the compounds **4a**−**d** and **5a**−**d** with alkyl substituents and **4e**−**g** and **5e**−**g** with aryl substituents as well as **5h** with an alkyl and an aryl substituent as models to test the computational predictions.

Synthesis of Calix[4]arenes with Alkane-1,1-diyl Bridges

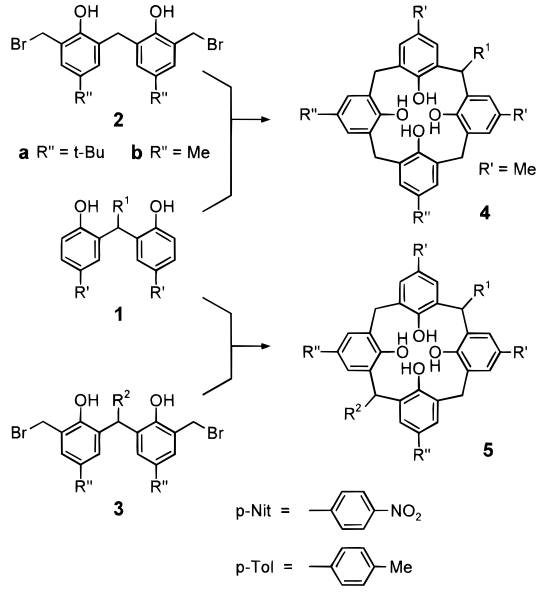
The direct functionalization of the methylene bridges in calixarenes is difficult. Therefore, the desired calix[4]arenes were synthesized by fragment condensation[11] (Scheme 3).

Alkanediyl diphenols **1** can be easily prepared in yields of 70−80% by condensation of the appropriate aldehyde with an excess of the corresponding phenol.[12] Condensation of the phenolic dimer **1** with the bisbromomethylated dimer **2** (in dioxane/$TiCl_4$) leads to the calix[4]arenes **4** with a single alkanediyl bridge. The two different substituents at the upper rim of **4a-f** (Me, *t*-Bu) were chosen to obtain more detailed information from the ^{1}H NMR spectra. Bisbromomethylation of **1** gives **3** in about 80% yield and its subsequent condensation with **1** results in the formation of the calix[4]arenes **5**, in which two opposite methylene bridges are substituted.

Yields of pure calix[4]arenes, easily isolated by column chromatography were in the range of 20 to 35% (not optimized) which makes these compounds available in reasonable quantities. For the bis-aryl substituted calix[4]arenes **5e**−**g** and for the aryl/alkyl substituted compound **5h** *cis*- and *trans*-isomers were formed and separated by column chromatography. The *cis*-isomer was obtained nearly exclusively for the bis-alkyl calix[4]arenes **5a**−**d** which is in accordance with the predicted relative stability of both isomers. Only in the case of **5a** traces (0.2%) of the *trans*-isomer could be isolated.

(11) Böhmer, V.; Merkel, L.; Kunz, U. *J. Chem. Soc., Chem. Commun.* **1987**, 896−897.
(12) Grüttner, C.; Böhmer, V.; Assmus, R.; Scherf, S. *J. Chem. Soc., Perkin Trans.1* **1995**, 93−94.

Scheme 3



1 / 3	a	b	c	d	e	f	g
R^1 / R^2	Me	Et	i-Pr	t-Bu	p-Tol	p-Nit	p-Nit
R' / R''	Me	Me	Me	Me	Me	Me	t-Bu

4	a	b	c	d	e	f	g
R^1	Me	Et	i-Pr	t-Bu	p-Tol	p-Nit	p-Nit
R''	t-Bu	t-Bu	t-Bu	t-Bu	t-Bu	t-Bu	Me

5	a	b	c	d	e	f	g
$R^1 = R^2$	Me	Et	i-Pr	t-Bu	p-Tol	p-Nit	p-Nit
R' = R''	Me	Me	Me	Me	Me	Me	t-Bu

5h	R^1 = p-Nit, R' = t-Bu, R^2 = R'' = Me

^{1}H NMR Studies

Solution Conformation of Calix[4]arenes with One Alkyl Substituent (4a−d). Compound **4a** displays in the ^{1}H NMR spectrum ($CDCl_3$, 400 MHz, rt) one *tert*-butyl and one *p*-methyl singlet at δ 1.20 and 2.15 ppm, respectively, one doublet at 1.67 ppm for the methyl group at the bridge, and two partially overlapping pairs of doublets at 3.44/4.20 ppm (4 protons) and at 3.47/4.24 ppm (2 protons), for the methylene protons adjacent and distal to the alkanediyl group. In addition, a quartet for the methine proton at 4.70 ppm, two broad signals (at 6.82 and 6.93 ppm) and one pair of doublets at 7.00 and 7.04 ppm for the aromatic protons, and a singlet at 10.20 ppm for the OH groups are found. The resemblance of the spectrum of **4a** (in particular the chemical shifts observed for the methylene protons) to that of *p-tert*-butylcalix[4]arene suggests that both compounds exist in similar *cone* conformations.

The signals in the ^{1}H NMR spectrum were assigned by a 2D NOESY spectrum. Cross peaks between the *tert*-butyl and methyl singlets and the aromatic doublets, and between two of these doublets allow the assignment of all aromatic protons. The methine signal displays a cross peak with the OH signal. Therefore, it should be located at the axial position while consequently the methyl group should be located equatorially. The methylene protons at higher field (3.44/3.47 ppm) give cross peaks with the aromatic protons at 6.82/6.93 and 7.04 ppm, respectively, while the methylene protons at lower field (4.20/4.24 ppm) display a cross peak with the OH signals. These NOEs establish in agreement with previous work[13] their equatorial and axial positions, since in the *cone* conformation the equatorial and axial methylene protons should be in steric proximity to the *meta* aromatic protons at neighboring rings and to the OH groups, respectively. All these NMR data suggest the presence of essentially a single *cone* conformation of C_s symmetry, in which the mirror plane bisects the alkanediyl and the opposite methylene bridge.

The ^{1}H NMR spectra of **4b** and **4c** are quite similar to that of **4a**, showing also a single *cone* conformer of C_s symmetry. In both cases NOEs were observed between the OH signal and the methine proton, indicating that the alkyl group at the bridge is located equatorially.

The ^{1}H NMR spectrum of **4d** displays a single signal for all *tert*-butyl groups, due to accidental isochrony. Interestingly, the aromatic protons vicinal to the substituent are downfield shifted (δ = 7.14 ppm) in comparison to **4a**−**c** where these protons are found in the 6.93−6.85 range. This shift may be caused by a distortion of the *cone* conformation or by a van der Waals effect between the *tert*-butyl group at the bridge and the aromatic protons, which is known to result in deshielding.[14] Since this downfield shift is exclusively observed for the protons adjacent to the substituent and not for the other protons located in the same ring, a van der Waals effect seems more probable.

Conformational Equilibria and Inversion Barriers in Calix[4]arenes 4a−d. The fact that only a single conformation is detected in the ^{1}H NMR spectra of the compounds **4a**−**d** may be rationalized by two explanations: (i) The mutual interconversion between the equatorial and axial conformer is fast on the NMR time scale, so that the observed spectra correspond to the weighted average of the signals of the two diastereomers. Since the NMR analysis indicates that the alkyl substituent is located in an equatorial position, the equatorial conformer must be the dominant form in the conformational equilibrium. (ii) The mutual interconversion is slow on the NMR time scale, with the population of the axial conformer being too low to be detected in the NMR spectrum. Both explanations necessarily require a strongly biased ("anancomeric") equilibrium toward the equatorial conformer.[15] Anancomeric systems display distinctive changes in the NMR spectrum when moving from slow to fast exchange on the NMR time scale. The signals broaden and then resharpen at chemical shifts which are similar to their initial values. This behavior is dubbed "exchange with a hidden partner".[16]

The maximum broadening of a given signal is defined as $\omega_{max} = \omega_{obs} - \omega_0$ where ω_{obs} is the measured maximal line width and ω_0 is the line width in the absence of exchange. The value of ω_{max} is a function of the chemical shift difference $\Delta\nu$ of a given group in the exchanging conformers and the mole fraction p of the less stable conformer (eq (1)).[16]

$$p\,\Delta\nu = \omega_{max} \qquad (1)$$

At the temperature of maximum broadening (T_m), the rate constant for the conversion of the more stable to the less stable conformer is given by eq (2).[16]

(13) See, for example: Böhmer, V.; Dörrenbächer, R.; Vogt, W.; Zetta, L. *Tetrahedron Lett.* **1992**, *33*, 769−772. Zetta, L.; Wolff, A. Vogt, W.; Platt, K.-L.; Böhmer, V. *Tetrahedron* **1991**, *47*, 1911−1924. Alfieri, C.; Dradi, E.; Pochini, A.; Ungaro, R. *Gazz. Chim. Ital.* **1989**, *119*, 335−338

(14) Günther, H. *NMR Spectroscopy*; Wiley: Chichester, 1980: p 86.

(15) See, for example: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; p 693.

(16) Anet, F. A. L.; Basus, V. J. *J. Mag. Res.* **1978**, *32*, 339−343. For papers using this method see, for example: Adams, S. P.; Whitlock, H. W. *J. Am. Chem. Soc.* **1982**, *104*, 1602−1611. Casarini, D.; Lunazzi, L.; Macciantelli, D. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1839−1844.

Table 4. Free Energy Differences and Rotational Barriers of the Conformers of Alkanediyl Calix[4]arenes in $CDCl_2CDCl_2$[a]

compd	conformation	$\Delta\nu$[b] (Hz)	T[c] (K)	ω[d] (Hz)	$K_{eq/ax}$	$\Delta G^{\ddagger}_{eq\rightarrow ax}$	$\Delta G^{\ddagger}_{ax\rightarrow eq}$
4a	eq	288[e]	343	3.6	79	18.0	15.0
4b	eq	294[e]	359	5.5	52	18.6	15.8
4c	eq	295[e]	390	25.9	10	19.0	17.2
4d	eq	299[e]	368	15.2	19	18.4	16.2
5h (*cis*)	Me eq, $NO_2C_6H_4$ eq	304[f]	330	11.7	25	16.5	14.4
5h (*trans*)	Me eq, $NO_2C_6H_4$ ax	304[f]	341	7.6	39	17.3	14.8

[a] ΔG values are given in kcal·mol^{-1}. [b] Estimated chemical shift difference between the bridging methine protons in the two conformations. [c] Temperature of maximum broadening. [d] Maximum width of the methine signal ($\omega_{max} - \omega_0$). [e] Estimated from the average chemical shift difference of the protons of the methylene bridges. [f] Estimated from the chemical shift difference between the benzylic methine protons of the *cis* and *trans* isomer of **5h**.

$$k = 2\pi\, p\, \Delta\nu \qquad (2)$$

For the calculation of the conformational equilibria and the rotational barriers we recorded the ^{1}H NMR spectra of the calix[4]arenes **4a**−**d** at different temperatures. The low and high temperature studies were carried out in $CDCl_3$ and $CDCl_2CDCl_2$ solutions, respectively. Characteristic hidden partner exchange patterns were observed at high temperatures. (e.g., Figure 1a). The value of ω_{max} was measured for the methine proton which gives the most convenient signal for monitoring the broadening since it is separated from the rest of the signals and displays (together with the methylene protons) the largest broadening effect of all signals.

For the monoalkanediyl calix[4]arenes studied, the equatorial/axial ratio is largest for **4a** (R′ = Me, $K_{eq/ax} = 79$), and smallest for **4c** (R′ = *i*-Pr, $K_{eq/ax} = 10.4$; see Table 4). Equatorial/axial equilibria of substituted cyclohexanes have been used to characterize the steric bulk of substituents (*A* values).[17] However, the equatorial/axial preferences of the substituents in the alkanediyl calix[4]arenes are obviously not a simple function of the bulk of the alkyl group at the bridge, since $K_{eq/ax}$ passes a minimum in the series **4a** → **4d** where the bulkiness of R′ increases continuously. This experimentally observed trend is reproduced by the calculations which predict the lowest $K_{eq/ax}$ for **4c** (Table 1).

The free energies of activation for the equatorial → axial inversion obtained for **4a**−**d** are higher than the barrier for the parent *p-tert*-butylcalix[4]arene ($\Delta G^{\ddagger} = 15.7$ kcal mol^{-1} in $CDCl_3$).[18] As observed for the equilibrium constant $K_{eq/ax}$, there is no monotonous change in $\Delta G^{\ddagger}$ as a function of the bulk of the substituent. Interestingly **4c**, the compound with the largest axial population of the series is the one with the largest diastereomerization barrier.

Solution Conformation and Inversion Barriers of Calix[4]arenes with One Aryl Substituent (4e−g). The slow exchange ^{1}H NMR spectrum of **4f** in $CDCl_3$ is in agreement with the presence of two equally populated diastereomeric *cone* conformers in which the *p*-nitrophenyl group is located at either an axial or equatorial position. At 230 K, two singlets in a nearly 1:1 ratio were found for the *tert*-butyl groups (1.17/1.18 ppm), for the methyl groups (2.04/2.19 ppm), and for the methine proton (5.27/6.11 ppm). The diastereomeric ratio in $CDCl_3$ is 1.1:1 at 230 K and 1.03:1 at 275 K. The assignment of pairs of mutually coupled methylene and *o*- and *m*-nitrophenyl protons[19] was made on the basis of a 2D DQF COSY spectrum. The diastereomerization process was monitored in $CDCl_3$ by following the coalescence of *p-tert*-butyl, *p*-methyl, and various aromatic protons (Table 5). From all these coalescence processes a diastereomerization barrier of 15.3 ± 0.1 kcal mol^{-1} was obtained.[20]

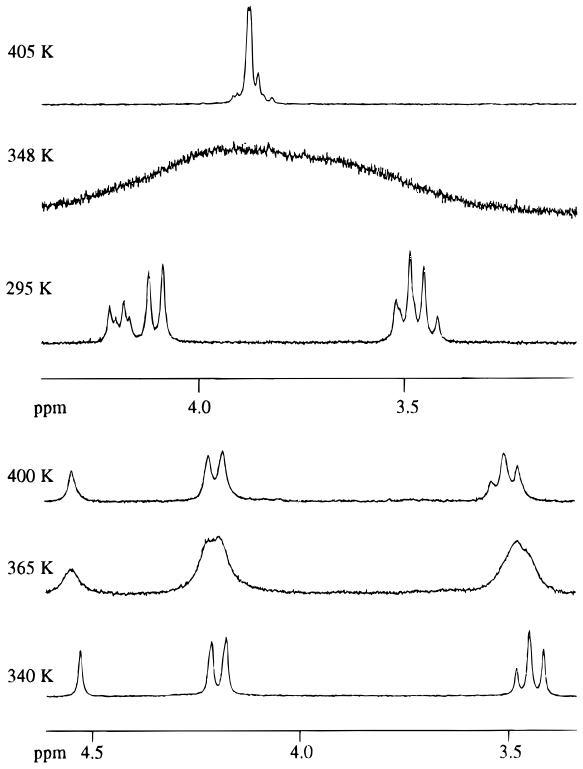


Figure 1. Variable temperature ^{1}H NMR spectra (400 MHz, $CDCl_2$-$CDCl_2$): Lower part (a): methylene and methine region of **4d**; temperatures from top to bottom: 400 K (fast exchange), 365 K (maximum broadening of the methine signal), and 340 K (slow exchange). Upper part (b): methylene region of **4f**; temperatures from top to bottom: 405 K, 348 K, and 295 K. The pattern at 405 K is the result of the superimposition of two closely spaced AB systems in a 2:1 ratio.

It should be noted that the protons within a given methylene group remain diastereotopic under fast exchange conditions, and two pairs of doublets should be expected for these groups. However, since each proton spends almost equal time at an equatorial or axial position (due to the near identical equatorial/axial conformational ratio) the chemical shift of these protons should not be markedly different (see Figure 1b).[21]

The low temperature ^{1}H NMR spectrum of the corresponding calix[4]arene **4g** in $CDCl_2CDCl_2$ indicates that similar to **4f**, the axial and equatorial conformers are almost equally populated. In the fast exchange spectrum at 400 K, the methylene region

(17) For a recent compilation of "*A*" values see ref. 15, p 697.

(18) Gutsche, C. D.; Bauer, L. J. *J. Am. Chem. Soc*. **1985**, *107*, 6052−6059.

(19) Pairs of signals related by COSY belong to the same diastereomer (otherwise they will not be mutually coupled) and cannot mutually exchange by the diastereomerization process.

(20) Exchange rates (k_C) at the coalescence temperatures were calculated by either the Gutowsky−Holm's (Gutowsky, H. S.; Holm, C. H. *J. Chem. Phys*. **1956**, *25*, 1228−1234) or Kurland's equations (Kurland, R. J.; Rubin, M. B.; Wise, W. B. *J. Chem. Phys*. **1964**, *40*, 2426−2427).

(21) The chemical shifts under fast exchange conditions are 3.90 and 3.88 ppm ($J = 13.9$ Hz) for the methylene groups adjacent to the alkanediyl group, and 3.89 and 3.85 ppm ($J = 13.6$ Hz) for the distal methylene groups.

has the appearance of an asymmetric quintet, due to the partial overlap of the transitions of the AB systems expected for these protons.

The slow exchange NMR spectra of the calixarenes **4f** and **4g** indicate in agreement with the calculations that in contrast to an alkyl group, a *p*-nitrophenyl group does not have any distinct conformational preference in $CDCl_3$. In order to test whether the dipole of the *p*-nitrophenyl ring plays a role in the conformational preference of this substituent, we examined also the NMR spectrum of the corresponding calix[4]arene **4e** with a *p*-tolyl substituent in $CDCl_3$ under slow exchange conditions (270 K). The integration ratio of the methine proton signals indicates that the ratio between the equatorial and axial conformers is 1.3:1. This corresponds to a free energy difference of 0.14 kcal mol^{-1} (at 270 K) favoring the equatorial conformer. Clearly, the dipole moment of the aryl group has only a minor effect on the conformational equilibrium in calix[4]arenes with an aryl substituent at **one** methylene bridge.

Solution Conformation and Conformational Equilibria of Calix[4]arenes with Two Alkyl Substituents at Opposite Methylene Bridges (5a−d). The ^{1}H NMR spectra of **5a−d** are in agreement with a *cone* conformation with C_{2v} symmetry which shows also that we are dealing with the *cis*-isomer (for *trans*-**5a** see below). The chemical shifts of the methine protons are very similar to those of their corresponding monoalkanediyl calixarenes indicating that the alkyl groups are located in equatorial positions. This was corroborated for **5b−d** by NOESY spectra.

The NMR spectra of the calixarenes *cis*-**5a−d** were studied in the 295−400 K temperature range in $CDCl_2CDCl_2$ and in the 220−295 K range in $CDCl_3$. No line shape changes corresponding to the exchange with a "hidden" partner could be observed. Since a broadening as low as 3.6 Hz could be distinguished under our experimental conditions (cf., **4a**), the maximum broadening of the systems will be less than this value, provided that T_m is within the range of temperatures studied. Using equations (1) and (2) one can estimate a lower limit of $\Delta G^\circ = 3.0$ kcal mol^{-1} for the conformational equilibria between diequatorial and diaxial forms at 343 K. The formal introduction of a second alkanediyl group into the system in a *cis* relationship to the first one seems to further increase the equatorial/axial energy gap as predicted by the calculations.

Only in the case of **5a** traces of the *trans*-isomer could be isolated. It displays in the NMR under slow exchange conditions ($CDCl_2CDCl_2$, 255 K) a pair of doublets for the methylene protons and two quartets for the equatorial and axial methine protons, in agreement with a frozen *cone* conformation of C_s symmetry. The ring inversion process was studied by following the coalescence of the pair of doublets of the methylene groups, yielding a barrier of 14.6 kcal mol^{-1} (Table 5). A comparison of this value with the barrier of **4a** (18.0 kcal mol^{-1}) indicates that the introduction of a second alkanediyl group in a *trans* relationship to the first one lowers the *cone* to *cone* inversion barrier.

Conformation and Inversion Barriers of Calix[4]arenes with Aryl Substituents at Opposite Methylene Bridges (5e,f).[22] The ^{1}H NMR spectrum of *trans*-**5f** in $CDCl_2CDCl_2$ (275 K) displays two methyl singlets, one pair of doublets for the methylene protons, two singlets for the methine protons, and four singlets as well as four doublets for the aromatic protons (Figure 2a). The ring inversion process (leading to homomerization) was followed by the coalescence of the methylene (Figure 2a) and methine signals (Table 5) giving a barrier of 15.6 kcal mol^{-1}.

Table 5. Coalescence Data for Alkanediyl Calix[4]arenes in $CDCl_2CDCl_2$

compd	conformation	$\Delta\nu^a$ (Hz)	J (Hz)	$T_C{}^a$ (K)	$\Delta G^\ddagger$ (kcal·mol^{-1})
5a (*trans*)	ax-eq	290	13.6	318	14.6
5f (*trans*)	ax-eq	256 (CH_2)	13.8	338	15.6
		283 (CH-Ar)		341	15.7 (15.6)[k]
5f (*cis*)	eq-eq/ax-ax[b]	32.2 (*p*-Me)		315	15.8
		308 (CH_2)	14.0	337	15.4 (15.6)[k]
		202 (CH_2)	13.7	337	15.7
5e (*cis*)	eq-eq/ax-ax[c]	320 (CH_2)		342	15.6[e]
		233 (CH_2)		342	15.8[e] (15.5)[k]
		333 (CH)		335	15.3[e]
4g	eq + ax[d]	257.7 (CH_2)	13.3	340	15.6
		43.1 (Ar-NO_2)[i]	8.4	305	15.1[f] (15.0)[k]
		42.6 (*p*-Me)[g]		299	14.8[f]
4f	eq + ax[d]	257.4 (CH_2)	13.9	348	16.1
		309.4 (CH_2)	14.0	332	15.2[f]
		245.7 (CH_2)	13.7	332	15.4[f]
		7.1 (*t*-Bu)		286	15.1[f]
		21.7 (ArOH)		302	15.4[f] (15.2)[k]
		15.9 (Ar-NO_2)[h]	8.8	298	15.3[f]
		48.8 (Ar-NO_2)[i]	8.8	310	15.2[f]
		42.5 (*p*-Me)		307	15.2[f]

[a] At 400 MHz. [b] Two conformers present in a 1.2:1.0 ratio. [c] Two conformers present in a 4.0:1.0 ratio (by integration of the methine protons), $\Delta G^\circ = 0.97$ kcal·mol^{-1}. [d] Two conformers present in a 1:1 ratio. [e] Barrier from the equatorial to the axial conformer. [f] In $CDCl_3$. [g] *p*-Me groups proximal to the *p*-nitrophenyl group. [h] Aromatic protons *ortho* to the nitro group. [i] Aromatic protons *meta* to the nitro group. [k] Average $\Delta G^\ddagger$ value.

In the slow exchange NMR spectra of *cis*-**5f** in $CDCl_2CDCl_2$ the ratio between the methine proton signal at δ 6.05 (axial) to the signal at δ 5.20 (equatorial) is 0.85:1 indicating that the diaxial form is slightly favored (Figure 2b). From the coalescence of the *p*-methyl and the methylene protons follows a barrier of 15.6 kcal mol^{-1}. The fast exchange spectrum displays in the methylene region a closely spaced AB system (Figure 2b) as expected, since the two protons within a methylene group remain diastereotopic also under fast exchange conditions.

Condensation of **1e** with **3e** gives **5e,** the *p*-tolyl analog of **5f**. The ^{1}H NMR spectrum of its *cis*-isomer ($CDCl_2CDCl_2$) is shown in Figure 2c for comparison. Here the diequatorial and diaxial conformer exist at equilibrium in a 4:1 ratio ($\Delta G^\circ =$ 0.97 kcal mol^{-1} at 295 K), and a barrier of 15.5 kcal mol^{-1} was determined for the conversion of the diequatorial into the diaxial form. The pair of doublets found for the methylene protons under fast exchange conditions (Figure 2c) shows a chemical shift difference which is larger than the one observed for *cis*-**5f**, indicating that the equilibrium is more strongly biased toward the diequatorial conformation in **5e**.

In general, the introduction of aryl substituents at opposite methylene bridges of a calix[4]arene does not affect the rigidity of the system, as indicated by the values in Table 5.

Conformation and Diastereomerization Barrier of a "Mixed" Calix[4]arene with an Alkyl and an Aryl Substituent at Opposite Methylene Bridges (5h). The methine quartets of the *cis*- and *trans*-isomers of **5h** resonate at about 4.6 ppm. This chemical shift is similar to those observed for the methine quartets of **4a** and the *cis*-isomer of **5a** (4.70 and 4.68 ppm, respectively) which suggests that the methyl group in both isomers of **5h** is located in an equatorial position. In contrast, the singlet of the methine proton adjacent to the *p*-nitrophenyl ring resonates at very different chemical shifts in the *trans* and the *cis*-isomer of **5h** (5.34 and 6.10 ppm) indicating that the *p*-nitrophenyl ring is located in axial and equatorial position,

(22) Variable temperature ^{1}H NMR studies for two bishomooxacalix[4]arenes substituted by phenyl at two opposite methylene bridges were recently reported by Sartori, G.; Bigi, F.; Porta, C.; Maggi, R.; Peri, F. *Tetrahedron Lett.* **1995**, *35*, 8323−8326

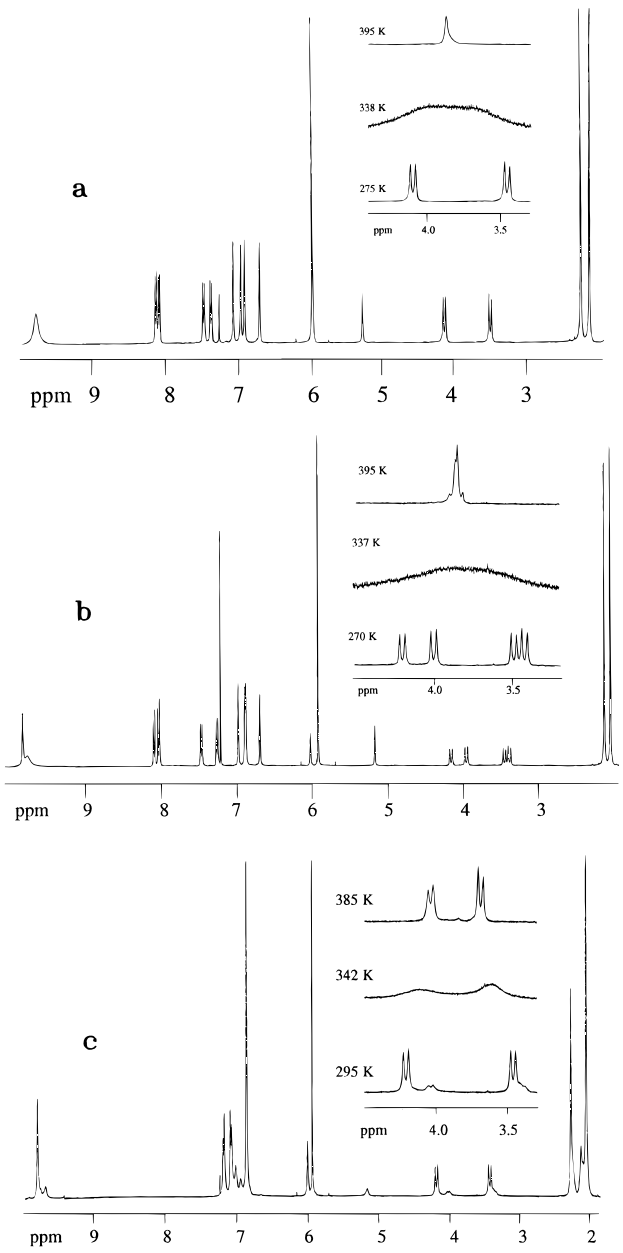


Figure 2. ^{1}H NMR spectra (400 MHz, $CDCl_2CDCl_2$) of (a) **5f** (*trans*-isomer) at 275 K. Right: (from top to bottom) expansion of the methylene region at 395 K, 338 K (coalescence), and 275 K. (b) **5f** (*cis*-isomer) at 270 K. Right: (from top to bottom) expansion of the methylene region at 395 K, 337 K (coalescence), and 270 K. (c) **5e** (*cis*-isomer) at 270 K. Two conformers can be detected, diequatorial and diaxial in a 4:1 ratio. Right: (from top to bottom) expansion of the methylene region at 385 K, 342 K (coalescence), and 295 K.

respectively. As observed for the systems **4a**−**d** and **5a**−**d** the alkyl substituent has a strong preference for the equatorial position, thus forcing the aryl substituent into the equatorial (*cis*) or axial (*trans*) position, which again is in accordance with the calculations.

Upon raising the temperature, line shape changes characteristic of exchange with hidden partners were observed for both isomers. The values obtained for $\Delta G°$ and $\Delta G^{‡}$ (see Table 4) are both reduced by similar amounts as compared to **4a**. However, since the *p* value derived from the maximal broadening (eq 1) affects both $\Delta G°$ and $\Delta G^{‡}$ the difference obtained may be simply an artifact.

Solvent Effects on the Equatorial/Axial Equilibria. For several compounds the equatorial/axial equilibrium ratio was determined in solvents of different polarity by integration of the methine signals in the ^{1}H NMR spectra.[23] Not all samples could be studied at the same temperature due to experimental limitations (e.g., viscosity and solubility effects). However, we found experimentally that a change in temperature has only a minor effect on the conformational equilibria, so that a comparison of the values collected in Table 6 is justified.

Table 6. Conformational Equilibria Axial ⇌ Equatorial for Selected Calix[4]arenes of Types **4** or *cis*-**5**[f]

compd	solvent	$K_{eq/ax}$	ΔG (kcal·mol^{-1})
4e	$CDCl_3$[a]	1.3	0.14
	THF-d_8	3.0	0.58
4f	$CDCl_3$	1.13	0.06
	THF-d_8	2.0	0.36
5e	$CDCl_2CDCl_2$[b]	4.2	0.84
	toluene-d_8	4.4	0.80
	$CDCl_3$[a]	5.3	0.90
	THF-d_8	11.7	1.28
	pyridine-d_5	>20[e]	>1.6
5f	$CDCl_2CDCl_2$[a]	0.85	−0.09
	toluene-d_8[c]	1.0	0.00
	$CDCl_3$	1.18	0.09
	THF-d_8[d]	2.2	0.4
	pyridine-d_5	>20[e]	>1.6
5g	toluene-d_8	0.32	−0.59
	$CDCl_3$[c]	0.40	−0.49
	THF-d_8	0.24	−0.74
	pyridine-d_5	14.5	1.28

[a] 270 K. [b] 295 K. [c] 265 K. [d] 255 K. [e] Estimated lowest value, since no axial conformer could be detected by ^{1}H NMR. [f] Temperature 260 K unless otherwise indicated.

For all compounds a pronounced solvent effect can be observed. $K_{eq/ax}$ increases in the series $CDCl_3$, toluene-d_8, $CDCl_2CDCl_2$, THF-d_8, and pyridine-d_5. This relative stabilization of the equatorial conformer in the more polar solvents can be explained in terms of steric hindrance to solvation of the hydroxyl groups which are shielded in the axial conformer by the (two) phenyl residue(s), while they are exposed to solvation in the equatorial conformer. Especially the strong effect of pyridine can be understood in this way, since OH···N hydrogen bond interactions must be assumed here.

There is not only an effect of the number but also of the kind of phenyl substituents, since the axial conformer is more favored in **5f** (with *p*-nitrophenyl groups) than in **5e** (with *p*-tolyl residues), and this effect is less well understood at present. In addition to solvation effects dipole−dipole interactions of the residues at the bridge (among themselves and with the calixarene *cone*) must be considered.

Finally, there is a steric effect of the substituents in the *p*-position, since in the *tert*-butyl substituted **5g** the axial conformer is more favored than in the methyl substituted **5f**. Steric hindrance to solvation of the substituents at the bridge and in *p*-position may be taken as a tentative explanation again.

In conclusion, strongly solvent dependent conformational changes may be achieved with suitably substituted calixarenes with alkanediyl bridges, since a strong decrease of the axial conformer from 80% to 6% is observed already for **5g** when THF is replaced by pyridine.

(23) The examination of strongly biased systems by integration of the NMR signals is difficult, since the peak(s) of the minor conformer must be both detected and positively identified. In the case of **5f** and **5e**, no signal corresponding to the axial conformer could be detected in pyridine. In these cases the reported value is an estimation of the lower limit of the equilibrium constant. The small signal of the methine proton of the axial conformer of **5h** (at 5.79 ppm) was identified by a NOESY spectrum which displayed a magnetization transfer cross peak between this signal and the methine proton of the major (axial) conformer at 7.35 ppm.

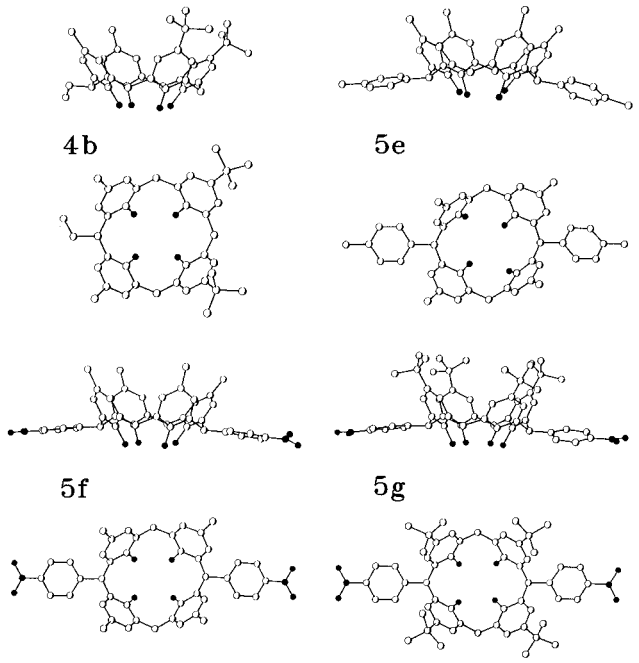


Figure 3. Molecular conformation (seen from two different directions) of the monoalkanediyl calixarene **4b** and the bis-alkanediyl calixarenes **5e**−**g** as determined by single crystal X-ray analysis.

Crystal Structures

Single crystals suitable for X-ray analysis were obtained for **4b** (from methanol/chloroform) and for the *cis*-isomers **5e** (from pyridine), **5f** (from acetonitrile), and **5g** (from acetone), see Table 7. In all cases the molecule is found in the *cone* conformation, and the substituent(s) at the bridge(s) assume the equatorial position (see Figure 3). For the alkyl substituted **4b** this is entirely in agreement with the preferred conformation in solution. The same is true for **5e** which in all solvents and especially in pyridine, from which the single crystals were grown, exists predominantly as the bis-equatorial conformer (compare Table 6), while for **5f** and especially for **5g** comparable amounts of the bisaxial conformer are found in other solvents. Unfortunately, we could neither get single crystals for **5g** from toluene or THF, solvents where the bisaxial conformer is dominant, nor single crystals for any of the *trans*-isomers, where necessarily one of the substituents must assume the axial position.

Compound **5e** has an interesting layered structure in the crystal lattice which is shown in Figure 4. The asymmetric unit contains one calixarene and four pyridine molecules. Two pyridines are hydrogen bonded to the calixarene (O(2)−N(1) = 2.652 Å, O(4)−N(2) = 2.721 Å) the first one being partially included in the cavity of a neighboring calixarene. The ring planes of the two non-hydrogen bonded pyridines are oriented nearly perpendicular to the hydrogen bonded ones. The four pyridines are located near the $(1\bar{0}\bar{1})$ plane. The calixarene molecules are arranged in two layers from both sides of these pyridine molecules. Therefore, pyridine and calixarene molecules form alternate layers in the crystal parallel to the $(\bar{1}0\bar{1})$ plane.

In **5f** an acetonitrile of solvation lies asymmetrically in the calix cup with the methyl group directed toward the base of the *cone*. Pairs of such calix-acetonitrile moieties pack about an inversion center to form a globular cavity in which the two acetonitrile molecules are enclosed. Intermolecular O−H···O hydrogen bonds (O···O 2.893 Å) link molecules of **5f** to form dimers about an inversion center. In this way infinite columns are developed in the crystal lattice.

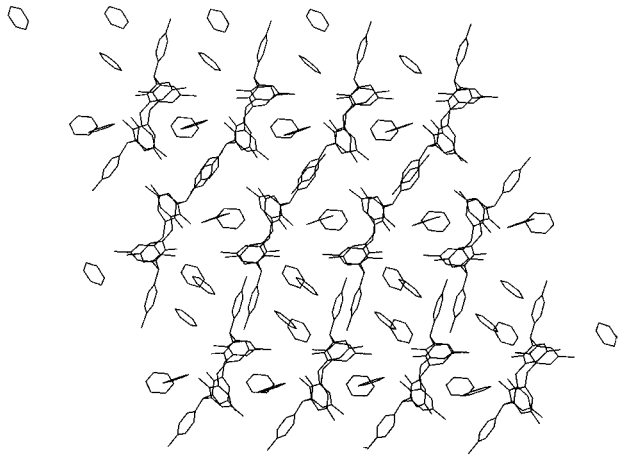


Figure 4. Section of the crystal lattice of **5e** showing the alternating layers of calixarene and pyridine molecules.

Two different positions are found for the acetone molecules in the structure of **5g**. One molecule resides in the cavity, with one methyl group pointing toward the bottom. Small temperature coefficients indicate, that this molecule is almost fixed without any disorder. The two other acetone molecules having large temperature coefficients are disordered outside the calixarene cavity. The calixarene molecules are located between glide planes. They are arranged "head-to-head" and "tail-to-tail" in columns parallel to the crystallographic *c*-axis with the *p*-nitrophenyl residues pointing outwards.

Comparison of the Calculated Molecular Conformations with the X-ray Structures

The *cone* conformation of a calix[4]arene can be described more in detail, for instance, by the geometrical parameters collected in Table 8. For comparison the corresponding values are given for the minimum energy conformation calculated for **4b** and **5e**−**5g.**

The experimental values in Table 8 show that there are slight deviations from an ideal fourfold symmetry of the basic calixarene skeleton (without the different substituents), presumably resulting on the one hand from a distortion which can be attributed to the substitution of the methine group and on the other hand from intermolecular forces due to packing interactions. The examination of the O···O distances reveals that the molecules **4b**, **5f**, and **5g** show the usual circular hydrogen bonding pattern characteristic for calix[4]arenes. In contrast, the X-ray structure of **5e** is strongly distorted from an ideal C_{4v} and even C_{2v} *cone* conformation as indicated by the dihedral angles between the reference plane through the four methylene carbons and the planes through the phenolic rings which vary between 118.8 and 132.7°. This is most probably caused by intermolecular interactions between the calixarene and pyridine molecules, two of which are hydrogen bonded to the phenolic hydroxyl groups. Additionally, the aromatic rings of the substituents at the bridges are remarkably tilted relative to the calixarene reference plane by 30.7 and 25.2°, respectively, an effect which is much less pronounced in **5f** and **5g** (see below).

The comparison of the X-ray structures and the calculated structures (Table 8) shows that the conformations observed in the crystal are well reproduced by the force field calculations. In cases where there are no strong packing interactions the agreement with the minimized structures is surprisingly close. The extent of distortion resulting from the introduction of the alkanediyl substituent(s) at one hand and from the packing interactions at the other hand can be estimated by comparing the geometrical parameters of the crystal structure and the

Table 7. Summary of Cell Parameters, Data Collection, Structure Solution, and Refinement Details

	4b	**5e**	**5f**	**5g**
	(a) Crystal Data			
formula	$C_{40}H_{48}O_4$	$C_{46}H_{44}O_4 \cdot 4C_5H_5N$	$C_{44}H_{38}N_2O_8 \cdot CH_3CN$	$C_{56}H_{62}N_2O_8 \cdot 3C_3H_6O$
formula weight	592.78	977.27	763.82	1065.31
color, habit	colorless	colorless	pale yellow octahedron	light yellow
crystal size (mm)	0.62 × 0.35 × 0.2	0.8 × 0.4 × 0.2	0.39 × 0.30 × 0.30	0.8 × 0.4 × 0.2
crystal system	monoclinic	monoclinic	monoclinic	monoclinic
a (Å)	15.798(3)	26.172(7)	13.1598(12)	31.808(8)
b (Å)	17.551(3)	11.307(3)	14.0173(6)	21.826(5)
c (Å)	12.897(2)	19.456(2)	20.7809(15)	17.223(5)
β (deg)	108.83(1)	107.18(2)	90.208(9)	92.37(2)
V (Å^3)	3384.5(10)	5501(1)	3833.3(5)	11947(5)
space group	$P2_1/c$	$P2_1/c$	$P2_1/c$	$C2/c$
Z	4	4	4	8
F(000)	1280	2080	1608	4576
ρ_{calc} (g cm^{-3})	1.163	1.18	1.324	1.185
μ (cm^{-1})	0.73	5.40	0.91	0.8
	(b) Data Acquisition, Solution and Refinement			
temp (K)	193(2)	293	294	193(2)
radiation	Mo Kα	Cu Kα	Mo Kα	Mo Kα
data collect. method	2Θ/Θ-scan	2Θ/Θ-scan	2Θ/Θ-scan	ϖ-scan
unit-cell refl. (Θ-range)	25 (3−11.8)	24 (11.5−14.5)	25 (8.0−12.2)	25 (5−15)
max. 2Θ for refl.	56.1	50	54	47
hkl range of refl.	−20 20;−23 2;−17 1	−26 26; 0 11; 0 19	−16 16; 0 17; 0 26	−34 35;−6 24;−19 19
variat. in *n* stand. refl.	2.5% ($n = 1$)	23.7% ($n = 3$)[a]	0.7% ($n = 3$)	3% ($n = 1$)
reflect. measured	8901	5618[a]	8696	10143
unique reflect.	8207	5608	8349	8845
R_{int}	0.032	0.061	0.011	0.035
refinement on	F^2 (with all data)	F (with all data)	F^2 (with all data)	F^2 (with all data)
solution method	direct methods	direct methods	direct methods	direct methods
H-atom treatment	isotrop. ref	riding	riding	riding
no. of variabl. in L.S.	569	667	537	725
R, reflect. $I > 2\sigma(I)$	0.058, 4015	0.061, 3985	0.054, 3318	0.065, 2048
R, R_w	0.1319,[b] 0.1672[b]	0.084,[b] 0.084[b]	0.163,[b] 0.141[b]	0.262,[b] 0.1753[b]
density range in final Δ-map (e Å^{-3})	−0.471, 0.652	−0.233, 0.34	−0.213, 0.255	−0.202, 0.328
final maximum shift/error ratio	0.02	0.0077	−0.019	0.003
sec. extinct. type			SHELXL	
sec. extinct. corr.			0.0014(3)	

[a] The crystal decayed during acquisition, due to the loss of solvent molecules. [b] For all unique reflections.

Table 8. Geometric Parameters of the Molecular Conformations Found by X-ray Analysis and Comparison with the Calculated Structures

	distances between oxygen atoms (in Å)		bond angles (deg) at the bridging carbon atom		torsion angles (deg) of the Ar−C−Ar bonds				inclination (deg) of the phenolic rings	
compd	proximal (O1···O2, to O4···O1)	distal (O1···O3 and O2···O4)	Ar−C−Ar	Ar−C−R or Ar−C−R^1 Ar−C−R^2	ϕ_1 χ_1	ϕ_2 χ_2	ϕ_3 χ_3	ϕ_4 χ_4	I III	II IV
4b										
X-ray	2.68, 2.64, 2.67, 2.66	3.65, 3.87	109.8	113.7, 111.5	−89.3 91.6	−91.4 82.2	−83.5 94.3	−92.8 84.4	127.3 132.7	122.0 118.8
Calcd (0.24)[a]	2.67, 2.69, 2.68, 2.63	3.72, 3.82	106.9	112.0, 113.2	−90.9 94.2	−92.6 90.2	−91.0 92.2	−93.1 88.2	123.4 119.5	119.0 119.2
5e										
X-ray	3.18, 2.70, 3.09, 2.71	3.46, 4.68	107.7 108.7	113.9, 114.7, 113.2, 116.1	−88.1 107.5	−96.4 74.4	−111.7 109.1	−97.4 80.8	128.7 134.4	108.3 108.0
Calcd (0.45)[a]	2.69, 2.66, 2.69, 2.66	3.78, 3.79	104.3, 104.3	113.8, 113.8, 113.8, 113.8	−93.0 94.6	−91.0 91.0	−93.0 94.6	−91.0 91.0	124.7 120.7	119.8 119.8
5f										
X-ray	2.74, 2.76, 2.75, 2.76	3.80, 3.92	107.7, 107.7	115.3, 113.7, 114.4, 114.3	−85.4 99.3	−93.6 89.0	−92.7 93.4	−93.7 84.4	128.3 120.0	113.4 118.4
Calcd (0.20)[a]	2.69, 2.66, 2.69, 2.66	3.78, 3.79	104.3, 104.4	113.8, 113.8, 113.8, 113.8	−93.0 94.6	−91.0 90.9	−93.0 94.6	−91.0 90.9	120.7 120.7	119.8 119.8
5g										
X-ray	2.66, 2.63, 2.76, 2.70	3.67, 3.91	108.4, 108.6	114.4, 114.9. 115.8, 112.0	−98.0 87.0	−83.0 93.5	−94.0 91.7	−87.0 91.1	119.5 129.6	118.8 116.7
Calcd (0.20)[a]	2.71, 2.68, 2.71, 2.68	3.81, 3.81	103.1, 103.1	113.4, 113.5, 113.4, 113.5	−93.6 94.8	−91.3 91.8	−93.6 94.8	−91.3 91.8	118.7 118.7	118.9 118.9

[a] Fit between the calculated structure and the X-ray structure for the heavy atoms of the calixarene framework, the phenolic oxygens and the *para*-carbon atoms (rms value/Å).

computed conformations. It is obvious, e.g., from the O···O distances that monosubstitution leads to a stronger deviation of the *cone* from the fourfold symmetry than disubstitution. In the latter case the calculated structures reveal that the steric strain induced by the two distal substituents is compensated by forcing the molecule into a C_{2v} symmetrical shape. The crystal structures show the same trend being somewhat irregular due to the packing interactions. A measure for the steric strain caused by the substituents are the values of the Ar−C−Ar bond angles of the methine bridges which are substantially lower than those of the parent *p-tert*-butylcalix[4]arene (112.5°). However, this effect is overestimated by the TRIPOS force field.

Conclusions

Calix[4]arenes bearing substituents at the methylene bridges are available from the corresponding alkanediyl diphenols by fragment condensation procedures. Like unsubstituted calix[4]arenes they adopt (exclusively) a *cone* conformation in which these substituents assume an axial or equatorial position. Aliphatic residues show a strong preference for the equatorial position, as predicted by the calculation and may be used to control the position of aromatic residues which have by themselves no definite preference. Substituents at the methylene bridges can be used to attach various additional functionalities to the calix[4]arene skeleton, thus extending its utility as a building block for the construction of larger molecular assemblies up to polymers. The knowledge of the conformational preferences of these substituents may enable the design of calix[4]arenes with predefined stereochemistry and the construction of molecular hosts with a tailor made orientation of functional groups.

Experimental Section

Calculations. The computational studies were done with the SYBYL 6.0 software[27] including the TRIPOS force field[28] using some modified parameters.[29] The optimizations were performed using a distance-dependent dielectric with $\epsilon = 1$ until the rms energy gradient was less than 0.001 kcal·mol^{-1}·Å^{-1} with the Powell minimizer included in the SYBYL/MAXIMIN2 routine. The Gasteiger−Hückel method[30,31] was used for the calculation of the partial charge distribution of the molecules.

Syntheses. Melting points were determined on a Thomas Hoover apparatus and are uncorrected. ^{1}H NMR spectra were recorded at room temperature, if not otherwise indicated, using a Bruker AC 200 (200 MHz) or a Bruker AMX 400 (400 MHz) FT spectrometer with Me_4Si as internal standard. Coupling constants *J* are given in Hz. FD and EI mass spectra were performed on a Finnigan MAT 8230 spectrometer.

Dioxane was dried over sodium. Preparative column chromatography separations were carried out on Merck silica gel 60 (230−400 mesh). 6,6′-Dibromomethyl-4,4′-di-*tert*-butyl-2,2′-(methanediyl)diphenol **2a** and 6,6′-dibromomethyl-4,4′-dimethyl-2,2′-(methanediyl)diphenol **2b** were be prepared as described for similar examples[32] or according to the bisbromomethylated alkanediyl diphenols **3** (see below). The crude products of **2a** (white solid, mp 153−154 °C (ether)) and of **2b** (beige solid after precipitation from acetic acid/ice water) were used for the fragment condensations.

Alkanediyl diphenols 1 were prepared as already described.[12] Analytical data of **1b** and **1d** are given in reference 12.

4,4′-Dimethyl-2,2′-(ethane-1,1-diyl)diphenol (1a): From *p*-cresol and acetaldehyde; yield 78%, mp 144−145 °C ($CHCl_3$/light petroleum) (lit. 141 °C[33]); ^{1}H NMR ($CDCl_3$) δ 7.11 (s, 2H, ArH), 6.86 (dd, 2H, J = 8.4, J = 1.8, ArH), 6.70 (s, 2H, OH), 6.68 (d, 2H, J = 8.1, ArH), 4.69 (q, 1H, J = 7.1, CH), 2.27 (s, 6H, CH_3), 1.64 (d, 3H, J = 7.1, CH_3); MS (EI) 242.2 (M^+, calcd 242.1). Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.1; H, 7.6.

4,4′-Dimethyl-2,2′-(2-methylpropane-1,1-diyl)diphenol (1c): From *p*-cresol and isobutyraldehyde; yield 75%, mp 172−173 °C ($CHCl_3$/light petroleum); ^{1}H NMR ($CDCl_3$) δ 7.08 (d, 2H, J = 1.3, ArH), 6.81 (dd, 2H, J = 8.2, J = 1.8, ArH), 6.67 (d, 2H, J = 8.1, ArH), 6.46 (s, 2H, OH), 3.97 (d, 1H, J = 11.2, CH), 2.64 (m, 1H, CH), 2.25 (s, 6H, CH_3), 0.91 (d, 6H, J = 6.4, CH_3); MS (EI) 270.3 (M^+, calcd 270.2). Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.7; H, 8.2.

4,4′-Dimethyl-2,2′-(4-tolylmethanediyl)diphenol (1e): From *p*-cresol and *p*-tolylaldehyde; yield 75%, mp 163−165 °C ($CHCl_3$/light petroleum) [lit. 139−140 °C (light petroleum)[34]]; ^{1}H NMR ($CDCl_3$) δ 7.13, 7.05 (2xd, 2H each, J = 8.2, 9.2, ArH), 6.95 (dd, 2H, J = 8.1, J = 1.8, ArH), 6.72 (d, 2H, J = 7.9, ArH), 6.71 (s, 2H, ArH), 5.79 (s, 1H, CH), 4.95 (s, 2H, OH), 2.35, 2.20 (2xs, 3H, 6H, CH_3); MS (EI) 318.2 (M^+, calcd 318.2). Anal. Calcd for $C_{22}H_{22}O_2$: C, 82.98; H, 6.97. Found: C, 82.7; H, 6.9.

4,4′-Dimethyl-2,2′-(4-nitrophenylmethanediyl)diphenol (1f): From *p*-cresol and *p*-nitrobenzaldehyde; yield 71%, mp 237−239 °C (glacial acetic acid) [lit. 230−232 °C (benzene)[34]]; ^{1}H NMR (acetone-d_6) δ 8.14 (s, 2H, OH), 8.13, 7.33 (2xd, 2H each, J = 8.7, Ar(NO_2)H), 6.92 (dd, 2H, J = 8.3, J = 2.3, ArH), 6.78 (d, 2H, J = 8.4, ArH), 6.66 (d, 2H, J = 2.4, ArH), 6.30 (s, 1H, CH), 2.14 (s, 6H, CH_3); MS (EI) 349.2 (M^+, calcd 349.4). Anal. Calcd for $C_{21}H_{19}O_4N$: C, 72.19; H, 5.48; N, 4.01. Found: C, 71.8; H, 5.6; N, 4.2.

4,4′-Di-*tert*-butyl-2,2′-(4-nitrophenylmethanediyl)diphenol (1g): From *p-tert*-butyl phenol and *p*-nitrobenzaldehyde; yield 74%, mp 174−175 °C (glacial acetic acid or benzene) [lit. 239−240 °C (benzene/hexane)[34]]; ^{1}H NMR ($CDCl_3$) δ 8.14, 7.31 (2xd, 2H each, J = 8.7, Ar(NO_2)H), 7.16 (dd, 2H, J = 8.4, J = 2.4, ArH), 6.93 (d, 2H, J = 2.4, ArH), 6.75 (d, 2H, J = 8.4, ArH), 6.08 (s, 1H, CH), 5.22 (s, 2H, OH), 1.17 (s, 18H, C(CH_3)$_3$); MS (EI) 433.4 (M^+, calcd 433.5). Anal. Calcd for $C_{27}H_{31}O_4N$: C, 74.80; H, 7.21; N, 3.23. Found: C, 74.8; H, 7.0; N, 3.2.

Bisbromomethylation of Alkanediyl Diphenols. A suspension of the corresponding alkanediyl diphenol **1** (0.08 mol) and paraformaldehyde (0.18 mol, 5.4 g) in 20 mL of glacial acetic acid was treated with 33% HBr in acetic acid (0.26 mol, 44 mL). The reaction mixture was stirred for 1 h and cooled in the refrigerator for 12 h. In the case of **3a**−**d** a white precipitate was formed, which was separated by filtration and recrystallized from chloroform/*n*-hexane. The reaction mixture of **3e**−**g** was dropwise added to ice water under stirring. The white precipitate was separated by filtration and dried 48 h over P_2O_5 in vacuo. The crude products were used for the fragment condensations. For analytical characterization small amounts of **3e**−**g** could be recrystallized from chloroform/*n*-pentane.

6,6′-Dibromomethyl-4,4′-dimethyl-2,2′-(ethane-1,1-diyl)diphenol (3a): yield 27.9 g (82%), mp 131−134 °C ($CHCl_3$/*n*-hexane); ^{1}H NMR ($CDCl_3$) δ 7.09, 6.94 (2xd, 2H each, J = 1.8, ArH), 6.13 (s, 2H, OH), 4.63 (q, 1H, J = 7.2, CH), 4.57, 4.45 (2xd, 2H each, J = 10.1, CH_2), 2.27 (s, 6H, CH_3), 1.64 (d, 3H, J = 7.1, CH_3); MS (EI) 428.0

(24) Single crystals of **5f**·3C_6H_5N·H_2O obtained from pyridine also showed the molecule in the bis-equatorial conformation. The structure could not be sufficiently refined, however.

(25) For a similar intercalation-type bilayer arrangement, see: Goldberg, I. *J. Incl. Phenom.* **1984**, *1*, 349−364; compare also Davies, J. E. D. *J. Mol. Struct.* **1981**, *75*, 1−12. For layered structures of calixarenes, see: Atwood, J. L., Bott, S. L. in *Calixarenes, A Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer: 1991.

(26) Acetonitrile is often found in the cavity of calix[4]arenes or calix[4]arene derivatives, but usually favoring fourfold symmetry. For an early example see: McKervey, M. A., Seward, E. M., Ferguson, G.; Ruhl, B. L. *J. Org. Chem.* **1986**, *51*, 3581−3584; for a very recent one: Böhmer, V.; Dörrenbächer, R.; Frings, M.; Heydenreich, M.; de Paoli, D.; Vogt, W.; Ferguson, G.; Thondorf, I. *J. Org. Chem.* **1996**, *61*, 549−559.

(27) SYBYL 6.0, TRIPOS Ass., Inc.

(28) Clark, M.; Cramer, R. D.; van Opdenbusch, N. *J. Comput. Chem.* **1989**, *10*, 982−1012.

(29) Thondorf, I.; Hillig, G.; Brandt, W.; Brenn, J.; Barth, A.; Böhmer, V. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2259−2267.

(30) Gasteiger, J.; Marsili, M. *Tetrahedron* **1980**, *36*, 3219−3226.

(31) Marsili, M.; Gasteiger, J. *J. Croat. Chem. Acta* **1980**, *53*, 601−614.

(32) Zetta, L.; Wolff, A.; Vogt, W.; Platt, K.-L.; Böhmer, V. *Tetrahedron* **1991**, *47*, 1911−1924.

(33) Adler, E.; von Euler, H.; Gie, G. J. *Arkiv Kemi Mineral. Geol.* **1943**, *12*, 1−20.

(34) Casiraghi, G.; Casnati, G.; Cornia, M.; Sartori, G.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2077−2079.

(M^+, calcd 426.0). Anal. Calcd for $C_{18}H_{20}O_2Br_2$: C, 50.71; H, 4.73. Found: C, 50.5; H, 4.7.

6,6′-Dibromomethyl-4,4′-dimethyl-2,2′-(propane-1,1-diyl)diphenol (3b): yield 28.2 g (80%), mp 141−143 °C ($CHCl_3$/*n*-hexane); ^{1}H NMR ($CDCl_3$) δ 7.06, 6.91 (2xd, 2H each, J = 1.8, ArH), 6.71 (s, 2H, OH), 4.57, 4.45 (2xd, 2H each, J = 10.1, CH_2), 4.30 (t, 1H, J = 7.9, CH), 2.25 (s, 6H, CH_3), 2.09 (m, 2H, CH_2), 0.88 (t, 3H, J = 7.3, CH_3); MS (EI) 442.2 (M^+, calcd 440.0). Anal. Calcd for $C_{19}H_{22}O_2Br_2$: C, 51.82; H, 5.04. Found: C, 51.4; H, 5.0.

6,6′-Dibromomethyl-4,4′-dimethyl-2,2′-(2-methylpropane-1,1-diyl)diphenol (3c): yield 30.5 g (84%), mp 149−152 °C ($CHCl_3$/*n*-hexane); ^{1}H NMR ($CDCl_3$) δ 7.06, 6.87 (2xd, 2H each, J = 1.7, ArH), 6.36 (s, 2H, OH),), 4.53, 4.45 (2xd, 2H each, J = 10.1, CH_2), 4.04 (d, 1H, J = 11.1, CH), 2.55 (m, 1H, CH), 2.23 (s, 6H, CH_3), 0.89 (d, 6H, J = 6.3, CH_3); MS (EI) 456.0 (M^+, calcd 454.0). Anal. Calcd for $C_{20}H_{24}O_2Br_2$: C, 52.86; H, 5.33. Found: C, 52.7; H, 5.6.

6,6′-Dibromomethyl-4,4′-dimethyl-2,2′-(2,2-dimethylpropane-1,1-diyl)diphenol (3d): yield 30.3 g (81%), mp 128−131 °C ($CHCl_3$/*n*-hexane); ^{1}H NMR ($CDCl_3$) δ 7.25, 6.90 (2xd, 2H each, J = 1.6, ArH), 5.75 (s, 2H, OH), 4.53 (d, 2H, J = 10.2, CH_2), 4.52 (s, 1H, CH), 4.45 (d, 2H, J = 10.1, CH_2), 2.24 (s, 6H, CH_3), 1.12 (s, 9H, $C(CH_3)_3$); MS (EI) 470.0 (M^+, calcd 468.0). Anal. Calcd for $C_{21}H_{26}O_2Br_2$: C, 53.84; H, 5.60. Found: C, 53.6; H, 5.6.

6,6′-Dibromomethyl-4,4′-dimethyl-2,2′-(4-tolylmethanediyl)diphenol (3e): yield 30.1 g (75%), mp 111−114 °C ($CHCl_3$/*n*-pentane); ^{1}H NMR ($CDCl_3$) δ 7.10, 7.03 (d, 2H, J = 7.3, ArH), 6.97, 6.64 (2xs, 2H each, ArH), 5.78 (s, 1H, CH), 5.13 (d, 2H, J = 11.4, CH_2), 4.86 (s, 2H, OH), 4.62 (d, 2H, J = 11.1, CH_2), 2.34, 2.17 (2xs, 3H, 6H, CH_3); MS (EI) 504.2 (M^+, calcd 502.0). Anal. Calcd for $C_{24}H_{24}O_2Br_2$: C, 57.37; H, 4.82. Found: C, 57.8; H, 5.2.

6,6′-Dibromomethyl-4,4′-dimethyl-2,2′-(4-nitrophenylmethanediyl)-diphenol (3f): yield 34.1 g (80%), mp 119−120 °C ($CHCl_3$/*n*-pentane); ^{1}H NMR ($CDCl_3$). δ 8.12, 7.27 (2xd, 2H each, J = 8.5, Ar(NO_2)H), 7.02 (s, 2H, OH), 6.76, 6.60 (2xd, 2H each, J = 2.3, ArH), 5.08 (s, 1H, CH), 4.84, 4.66 (2xd, 2H each, J = 9.9, CH_2), 2.16 (s, 6H, CH_3); MS (EI) 533.1 (M^+, calcd 533.0). Anal. Calcd for $C_{23}H_{21}O_4NBr_2$: C, 51.78; H, 3.97. Found: C, 52.0; H, 4.1.

6,6′-Dibromomethyl-4,4′-di-*tert*-butyl-2,2′-(4-nitrophenylmethanediyl)diphenol (3g): yield 34.1 g (69%), mp 97−100 °C ($CHCl_3$/*n*-pentane); ^{1}H NMR ($CDCl_3$). δ 8.12, 7.27 (2xd, 2H each, J = 8.5, Ar(NO_2)H), 7.02 (s, 2H, OH), 6.76, 6.60 (2xd, 2H each, J = 2.3, ArH), 6.11 (d, 2H, J = 13.2, CH_2), 5.51 (s, 2H, OH), 5.16 (d, 2H, J = 12.2, CH_2), 4.90 (s, 1H, CH), 1.17 (s, 18H, $C(CH_3)_3$); MS (EI) 620.8 (M^+, calcd 619.0). Anal. Calcd for $C_{29}H_{33}O_4NBr_2$: C, 56.22; H, 5.37. Found: C, 57.1; H, 5.8.

General Procedure for the Fragment Condensations. In a three necked flask equipped with a condenser and a nitrogen inlet were treated 300 mL of dry dioxane with 3.3 mL of $TiCl_4$ under vigorous stirring. At a temperature of 60 °C a solution of 5 mmol of the alkanediyl diphenol **1** and 5.5 mmol of the corresponding bisbromomethylated diphenol **2** or **3** in 200 mL of dry dioxane was added dropwise over 4 h, and the mixture was refluxed for 70 h. The solvent was evaporated, and the solid residue dissolved in $CHCl_3$. Silica gel (40 g) was added, and the solvent was evaporated again. The residue was extracted with $CHCl_3$ (Soxhlet apparatus), the extract was concentrated, and the products were isolated by column chromatography (silica gel) with $CHCl_3$/CCl_4 mixtures and finally recrystallized as indicated.

11,17-Di-*tert*-butyl-25,26,27,28-tetrahydroxy-2,5,23-trimethylcalix[4]arene (4a): yield 1.04 g (36%), mp 330 °C ($CHCl_3$/MeOH); ^{1}H NMR ($CDCl_3$) δ 10.20 (s, 4H, OH), 7.04, 7.00 (2xd, 2H each, J = 2.3, ArH), 6.93, 6.82 (2xs, 2H each, ArH), 4.70 (q, 1H, J = 7.2, CH), 4.24, 4.20, 3.47, 3.44 (4xd, 1H, 2H, 1H, 2H, J = 13.8, CH_2), 2.15 (s, 6H, CH_3), 1.67 (d, 3H, J = 7.2, CH_3), 1.20 (s, 18H, $C(CH_3)_3$); MS (EI) 578.3 (M^+, calcd 578.3). Anal. Calcd for $C_{39}H_{46}O_4$·$CHCl_3$: C, 68.81; H, 6.79. Found: C, 69.6; H, 6.8.

11,17-Di-*tert*-butyl-2-ethyl-25,26,27,28-tetrahydroxy-5,23-dimethylcalix[4]arene (4b): yield 890 mg (30%), mp 333−334 °C ($CHCl_3$/MeOH); ^{1}H NMR ($CDCl_3$) δ 10.16 (s, 4H, OH), 7.04, 7.00 (2xd, 2H each, J = 2.3, ArH), 6.86, 6.81 (2xs, 2H each, ArH), 4.35 (t, 1H, J = 7.7, CH), 4.24, 4.20, 3.47, 3.44 (4xd, 1H, 2H, 1H, 2H, J = 13.8, CH_2), 2.17 (m, 2H, CH_2), 2.15 (s, 6H, CH_3), 1.20 (s, 18H, $C(CH_3)_3$), 0.94 (t, 3H, J = 7.2, CH_3); MS (EI) 592.4 (M^+, calcd 592.4). Anal. Calcd for $C_{40}H_{48}O_4$: C, 81.03; H, 8.17. Found: C, 80.8; H, 7.9.

11,17-Di-*tert*-butyl-25,26,27,28-tetrahydroxy-5,23-dimethyl-2-isopropylcalix[4]arene (4c): yield 940 mg (31%), mp 332−334 °C ($CHCl_3$/MeOH); ^{1}H NMR ($CDCl_3$) δ 10.09 (s, 4H, OH), 7.04, 7.00 (2xd, 2H each, J = 2.3, ArH), 6.85, 6.78 (2xs, 2H each, ArH), 4.23, 4.20 (2xd, 1H, 2H, J = 13.8, CH_2), 4.03 (d, 1H, J = 11.2, CH), 3.46, 3.43 (2xd, 1H, 2H, J = 13.9, CH_2), 2.68 (m, 1H, $CH(CH_3)_2$), 2.15 (s, 6H, CH_3), 1.20 (s, 18H, $C(CH_3)_3$), 0.95 (d, 6H, J = 6.4, $CH(CH_3)_2$); MS (EI) 606.5 (M^+, calcd 606.4). Anal. Calcd for $C_{41}H_{50}O_4$·0.5 CH_3-OH: C, 80.03; H, 8.41. Found: C, 79.7; H, 8.3.

2,11,17-Tri-*tert*-butyl-25,26,27,28-tetrahydroxy-5,23-dimethylcalix[4]arene (4d): yield 870 mg (28%), mp 332−334 °C ($CHCl_3$/MeOH); ^{1}H NMR ($CDCl_3$) δ 9.88 (s, 4H, OH), 7.14, 7.02, 7.01, 6.78 (4xs, 2H each, ArH), 4.53 (s, 1H, CH), 4.22, 4.21, 3.46, 3.43 (4xd, 1H, 2H, 1H, 2H, J = 13.9, CH_2), 2.14 (s, 6H, CH_3), 1.12 (s, 27H, $C(CH_3)_3$); MS (EI) 620.5 (M^+, calcd 620.4). Anal. Calcd for $C_{42}H_{52}O_4$: C, 81.24; H, 8.45. Found: C, 81.0; H, 8.2.

11,17-Di-*tert*-butyl-25,26,27,28-tetrahydroxy-5,23-dimethyl-2-(4-tolyl)-calix[4]arene (4e): yield 753 mg (23%), mp 332−334 °C ($CHCl_3$/MeOH); ^{1}H NMR ($CDCl_3$, 270 K) (two diastereomeric *cone* conformations) δ 10.09 (br s, 8H, OH), 7.22/7.16, 7.12/7.11 (4xd, 2H each, J = 8.5, ArH), 7.06/7.03, 7.02/6.99 (4xd, 2H each, J = 2.3, ArH), 6.98/6.92, 6.86/6.83 (4xd, 2H each, J = 1.9, ArH), 6.07/5.24 (2xs, 1H each, CH), 4.24, 4.22, 4.18, 4.15 (4xd, 2H, 2H, 1H, 1H, J = 12.7−13.0, CH_2), 3.49, 3.48, 3.45, 3.42 (4xd, 1H, 2H, 2H, 1H, J = 12.5−13.5, CH_2), 2.37/2.35 (2xs, 3H each, CH_3), 2.17/2.05 (2xs, 6H each, CH_3), 1.22/1.20 (2xs, 18H each, $C(CH_3)_3$); MS (FD) 654.8 (M^+, calcd 654.4). Anal. Calcd for $C_{45}H_{50}O_4$: C, 82.52; H, 7.70. Found: C, 82.8; H, 7.2.

11,17-Di-*tert*-butyl-25,26,27,28-tetrahydroxy-5,23-dimethyl-2-(4-nitrophenyl)calix[4]arene (4f): yield 754 mg (22%), mp 337−339 °C ($CHCl_3$/*n*-hexane); ^{1}H NMR ($CDCl_3$, 230 K) (two diastereomeric *cone* conformations) δ 10.21/10.16 (2xs, 4H each, OH), 8.20/8.15, 7.50/ 7.38 (4xd, 2H each, J = 8.8, Ar(NO_2)H), 7.02 (m, 8H, ArH), 7.07, 6.95, 6.89, 6.71 (4xs, 2H each, ArH), 6.11/5.27 (2xs, 1H each, CH), 4.22, 4.21, 4.13 (3xd, 1H, 2H, 3H, J = 13.5−13.9, CH_2), 3.52, 3.51, 3.48, 3.45 (4xd, 1H, 2H, 2H, 1H, J = 13.6−14.1, CH_2), 2.19/2.04 (2xs, 6H each, CH_3), 1.18/1.17 (2xs, 18H each, $C(CH_3)_3$); MS (EI) 685.4 (M^+, calcd 685.3). Anal. Calcd for $C_{44}H_{47}O_6N$: C, 77.04; H, 6.91. Found: C, 77.2; H, 6.8.

25,26,27,28-Tetrahydroxy-5,11,17,23-tetramethyl-2-(4-nitrophenyl)-calix[4]arene (4g): yield 366 mg (12%), mp 333−335 °C ($CHCl_3$/*n*-hexane); ^{1}H NMR ($CDCl_3$, 250 K) (two diastereomeric *cone* conformations) δ 10.05/10.00 (2xs, 4H each, OH), 8.18/8.14, 7.48/7.37 (4xd, 2H each, J = 7.9−9.0, Ar(NO_2)H), 6.97, 6.91 (2xd, 2H each, J = 1.8, ArH), 6.85 (m, 8H, ArH), 6.82 (s, 2H, ArH), 6.68 (d, 2H, J = 1.6, ArH), 6.08/5.25 (2xs, 1H each, CH), 4.19, 4.17, 4.11, 4.09 (4xd, 2H, 1H, 2H, 1H, J = 13.8, CH_2), 3.45, 3.42, 3.41, 3.36 (4xd, 2H, 2H, 1H, 1H, J = 13.9, CH_2), 2.19, 2.14, 2.13, 2.08 (4xs, 6H each, CH_3); MS (EI) 601.2 (M^+, calcd 601.7). Anal. Calcd for $C_{38}H_{35}O_6N$: C, 75.87; H, 5.81. Found: C, 75.6; H, 5.9.

25,26,27,28-Tetrahydroxy-2,5,11,14,17,23-hexamethylcalix[4]-arene (5a) (*cis*-isomer): yield 560 mg (22%), mp 378−380 °C ($CHCl_3$/MeOH); ^{1}H NMR ($CDCl_3$) δ 10.08 (s, 4H, OH), 6.91, 6.80 (2xd, 4H each, J = 1.8, ArH), 4.68 (q, 2H, J = 7.2, CH), 4.17, 3.40 (2xd, 2H each, J = 13.8, CH_2), 2.16 (s, 12H, CH_3), 1.66 (d, 6H, J = 7.2, CH_3); MS (EI) 508.3 (M^+, calcd 508.3). Anal. Calcd for $C_{34}H_{36}O_4$: C, 80.27; H, 7.14. Found: C, 80.4; H, 7.0.

25,26,27,28-Tetrahydroxy-2,5,11,14,17,23-hexamethylcalix[4]-arene (5a) (*trans*-isomer): yield 5 mg (0.2%), mp 364−366 °C ($CHCl_3$/MeOH); ^{1}H NMR ($C_2D_2Cl_4$, 255 K) δ 10.20 (br s, 4H, OH), 6.89, 6.85, 6.77, 6.74 (4xs, 2H each, ArH), 4.56 (q, 1H, J = 7.1, CH), 4.07 (d, 2H, J = 13.6, CH_2), 3.91 (q, 1H, J = 7.9, CH), 3.34 (d, 2H, J = 13.9, CH_2), 2.11, 2.09 (2xs, 6H each, CH_3), 1.85 (d, 3H, J = 7.6, CH_3), 1.61 (d, 3H, J = 7.0, CH_3); MS (EI) 508.2 (M^+, calcd 508.3).

2,14-Diethyl-25,26,27,28-tetrahydroxy-5,11,17,23-tetramethylcalix-[4]arene (5b) (*cis*-isomer): yield 644 mg (24%), mp 375−377 °C ($CHCl_3$/MeOH); ^{1}H NMR ($CDCl_3$) δ 10.00 (s, 4H, OH), 6.83, 6.78 (2xs, 4H each, ArH), 4.32 (t, 2H, J = 7.8, CH), 4.17, 3.39 (2d, 2H each, J = 13.8, CH_2), 2.14 (m, 4H, CH_2), 2.14 (s, 12H, CH_3), 0.93 (t,

6H, J = 7.2, CH_3); MS (EI) 536.4 (M^+, calcd 536.3). Anal. Calcd for $C_{36}H_{40}O_4 \cdot CH_3OH$: C, 78.14; H, 7.80. Found: C, 78.9; H, 8.0.

25,26,27,28-Tetrahydroxy-5,11,17,23-tetramethyl-2,14-diisopropylcalix[4]arene (5c) (*cis*-isomer): yield 790 mg (28%), decomposition 410 °C ($CHCl_3$/MeOH); ^{1}H NMR ($CDCl_3$) δ 9.87 (s, 4H, OH), 6.83, 6.77 (2xs, 4H each, ArH), 4.17 (d, 1H, J = 13.8, CH_2), 3.99 (d, 2H, J = 11.2, CH), 3.38 (d, 2H, J = 13.9, CH_2), 2.67 (m, 2H, CH-$(CH_3)_2$), 2.14 (s, 12H, CH_3), 0.94 (d, 12H, J = 6.3, $CH(CH_3)_2$); MS (EI) 564.4 (M^+, calcd 564.3). Anal. Calcd for $C_{38}H_{44}O_4$: C, 80.80; H, 7.86. Found: C, 80.6; H, 8.0.

2,14-Di-*tert*-butyl-25,26,27,28-tetrahydroxy-5,11,17,23-tetramethylcalix[4]arene (5d) (*cis*-isomer): yield 563 mg (19%), mp 325−327 °C ($CHCl_3$/MeOH); ^{1}H NMR ($CDCl_3$) δ 9.35 (s, 4H, OH), 7.09, 6.74 (2xd, 4H each, J = 1.7, ArH), 4.46 (s, 2H, CH), 4.15, 3.35 (2xd, 2H each, J = 13.9, CH_2), 2.13 (s, 12H, CH_3), 1.18 (s, 18H, $C(CH_3)_3$); MS (EI) 592.5 (M^+, calcd 592.4). Anal. Calcd for $C_{40}H_{48}O_4$: C, 81.03; H, 8.17. Found: C, 80.9; H, 8.4.

25,26,27,28-Tetrahydroxy-5,11,17,23-tetramethyl-2,14-di-(4-tolyl)-calix[4]arene (5e) (*cis*-isomer): yield 330 mg (10%), decomposition 382 °C ($CHCl_3$/MeOH); ^{1}H NMR ($CDCl_3$, 270 K) (major *cone* conformer) δ 9.86 (s, 4H, OH), 7.20, 7.10 (2xd, 4H each, J = 7.9, ArH), 6.84 (br s, 8H, ArH), 6.04 (s, 2H, CH), 4.23, 3.47 (2xd, 2H each, J = 13.8, CH_2), 2.34, 2.08 (2xs, 6H, 12 H, CH_3); MS (FD) 660.2 (M^+, calcd 660.3). Anal. Calcd for $C_{46}H_{44}O_4 \cdot CH_3OH$: C, 81.47; H, 6.98. Found: C, 80.9; H, 7.0.

25,26,27,28-Tetrahydroxy-5,11,17,23-tetramethyl-2,14-di-(4-tolyl)-calix[4]arene (5e) (*trans*-isomer): yield 165 mg (5%), mp 305−306 °C ($CHCl_3$/MeOH); ^{1}H NMR ($CDCl_3$, 270 K) δ 9.86 (br s, 4H, OH), 7.15, 7.14, 7.13, 7.08 (4xd, 2H each, J = 7.7, ArH), 6.98, 6.91, 6.83, 6.82 (4xbr s, 2H each, ArH), 5.94, 5.23 (2xs, 1H each, CH), 4.17, 3.45 (2xd, 2H each, J = 13.9, CH_2), 2.36, 2.32, 2.19, 2.07 (4xs, 3H, 3H, 6H, 6H, CH_3), MS (FD) 660.4 (M^+, calcd 660.3). Anal. Calcd for $C_{46}H_{44}O_4 \cdot CH_3OH$: C, 81.47; H, 6.98. Found: C, 81.1; H, 6.9.

25,26,27,28-Tetrahydroxy-5,11,17,23-tetramethyl-2,14-di-(4-nitrophenyl)calix[4]arene (5f) (*cis*-isomer): yield 433 mg (12%), decomposition 306 °C ($CHCl_3$/MeOH); ^{1}H NMR ($C_2D_2Cl_4$, 270 K) (two diastereomeric *cone* conformations) δ 9.83, 9.76 (2xbr s, 4H each, OH), 8.10/8.04, 7.48/7.27 (4xd, 4H each, J = 8.7, Ar(NO_2)H), 7.00, 6.91, 6.90, 6.71 (4xs, 4H each, ArH), 6.04/5.20 (2xs, 2H each, CH), 4.20/4.00 (2xd, 2H each, J = 13.9, CH_2), 3.49/3.42 (2xd, 2H each , J = 13.8/14.1, CH_2), 2.18/2.11 (2xs, 12H each, CH_3); MS (FD) 723.0 (M^+, calcd 722.3). Anal. Calcd for $C_{44}H_{38}O_8N_2$: C, 73.10; H, 5.30. Found: C, 73.4; H, 5.1.

25,26,27,28-Tetrahydroxy-5,11,17,23-tetramethyl-2,14-di-(4-nitrophenyl)calix[4]arene (5f) (*trans*-isomer): yield 325 mg (9%), decomposition 359 °C ($CHCl_3$/MeOH); ^{1}H NMR ($C_2D_2Cl_4$, 275 K) δ 9.78 (s, 4H, OH), 8.12, 8.07, 7.45, 7.35 (4xd, 2H each, J = 8.5, Ar(NO_2)H), 7.03, 6.94, 6.88, 6.67 (4xs, 2H each, ArH), 5.95, 5.24 (2xs, 1H each, CH), 4.10, 3.46 (2xd, 2H each, J = 13.9, CH_2), 2.20, 2.08 (2xs, 6H each, CH_3); MS (FD) 722.2 (M^+, calcd 722.3). Anal. Calcd for $C_{44}H_{38}O_8N_2$: C, 73.10; H, 5.30. Found: C, 72.9; H, 5.4.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrahydroxy-2,14-di-(4-nitrophenyl)calix[4]arene (5g) (*cis*-isomer): yield 800 mg (18%), mp 337−339 °C (acetone); ^{1}H NMR ($CDCl_3$, 265 K) (two diastereomeric *cone* conformations) δ 10.10/9.96 (2xbr s, 4H each, OH), 8.17/8.08, 7.52/7.31 (4xd, 4H each, J = 8.4−8.8, Ar(NO_2)H), 7.21, 7.10, 6.96 (3xd, 4H, 8H, 4H, J = 2.0, ArH), 6.16/5.33 (2xs, 2H each, CH), 4.29/4.12 (2xd, 2H, J = 14.0, CH_2), 3.61/3.56 (2xd, 2H each J = 14.1, CH_2), 1.23/1.13 (2xs, 36H each, $C(CH_3)_3$); MS (FD) 890.2 (M^+, calcd 890.5). Anal. Calcd for $C_{56}H_{62}O_8N_2$: C, 75.47; H, 7.23. Found: C, 74.9; H, 7.2.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrahydroxy-2,14-di-(4-nitrophenyl)calix[4]arene (5g) (*trans*-isomer): yield 128 mg (3%). The analytical data of the *trans*-isomer of **5g** are in agreement with those published by Sartori et al.[8]

5,23-Di-*tert*-butyl-25,26,27,28-tetrahydroxy-11,14,17-trimethyl-2-(4-nitrophenyl)calix[4]arene (5h) (*cis*-isomer): yield 525 mg (15%), mp 322−324 °C ($CHCl_3$/MeOH); ^{1}H NMR ($CDCl_3$) δ 10.03 (s, 4H, OH), 8.15, 7.52 (2xd, 2H each, J = 8.0, 8.6, Ar(NO_2)H), 7.01, 6.96, 6.93, 6.87 (4xs, 2H each, ArH), 6.14 (s, 1H, CH), 4.72 (q, 1H, J = 6.9, CH), 4.23, 3.50 (2xd, 2H, J = 13.4, 13.0, CH_2), 2.18 (s, 6H, CH_3), 1.69 (d, 3H, J = 7.1, CH_3), 1.12 (s, 18H, $C(CH_3)_3$); MS (FD) 699.7 (M^+, calcd 699.4). Anal. Calcd for $C_{44}H_{49}O_6N \cdot CH_3OH$: C, 75.47; H, 7.30. Found: C, 75.6; H, 7.2.

5,23-Di-*tert*-butyl-25,26,27,28-tetrahydroxy-11,14,17-trimethyl-2-(4-nitrophenyl)calix[4]arene (5h) (*trans*-isomer): yield 490 mg (14%), mp 303−305 °C ($CHCl_3$/MeOH); ^{1}H NMR ($CDCl_3$) δ 10.03 (s, 4H, OH), 8.17, 7.41 (2xd, 2H each, J = 8.5, Ar(NO_2)H), 7.15, 7.10 (2xd, 2H each, J = 1.9, ArH), 6.91, 6.83 (2xs, 2H each, ArH), 5.35 (s, 1H, CH), 4.61 (q, 1H, J = 7.1, CH), 4.14, 3.47 (2xd, 2H each, J = 13.9, CH_2), 2.16 (s, 6H, CH_3), 1.64 (d, 3H, J = 7.1, CH_3), 1.24 (s, 18H, $C(CH_3)_3$); MS (FD) 699.3 (M^+, calcd 699.4). Anal. Calcd $C_{45}H_{49}O_6N$: C, 77.21; H, 7.06. Found: C, 77.1; H, 7.2.

Acknowledgment. This work was supported by the Commission of the European Communities, the German Israeli Foundation for Scientific Research & Development, and the Deutsche Forschungsgemeinschaft.

Supporting Information Available: Tables of atomic coordinates, isotropic and anisotropic displacement parameters, and bond lengths and angles of all structures reported in this paper and of details of the molecular mechanics calculations (65 pages). See any current masthead page for ordering and Internet access instructions.

JA960883N