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CONFORMATIONAL ANALYSIS OF CALIX[*n*]ARENES WITH CHIRAL SUBSTITUENTS BY USING CIRCULAR DICHROISM

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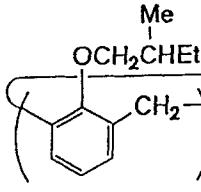
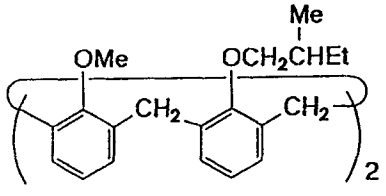
Calix[*n*]arenes ($n = 4$ and 6) bearing chiral substituents (R^*) on the lower rim (1_n) or on the upper rim (4_n) were synthesized. The isomers derived from 1_4 were conformationally immobile and showed different circular dichroism (CD) spectra. In the ^1H NMR spectra the proton signals in R^* shifted to higher magnetic field when the lower rim is sterically crowded and in the CD spectra a strong CD band appeared. Therefore, the change in the CD spectra is rationalized in terms of $R^*\cdots\pi$ interactions. In contrast, compound 4_4 was not conformationally immobilized and the CD spectra changed in response to the metal binding to the methoxy oxygens arranged on the lower rim. The specific metal interaction enabled the metal binding event to be detected by the CD technique.

INTRODUCTION

It is known that four different conformational isomers exist in calix[4]arene-25,26,27,28-tetrol derivatives: cone, partial cone, 1,2-alternate and 1,3-alternate.[1] Unmodified calix[4]arene-25,26,27,28-tetrols adopt a cone conformation because of strong intramolecular hydrogen-bonding interactions whereas *O*-alkylated derivatives can adopt conformations other than cone because of the loss of such strong intramolecular hydrogen-bonding interactions.[1–7] We previously reported the synthesis of all possible conformational isomers derived from calix[4]arene-25,26,27,28-tetrols.[6] In that work we experienced continuous problems because the conformer distribution can be determined only by ^1H or ^{13}C NMR spectroscopy.[1–8] Because of this limitation, it is difficult to monitor the progress of the reaction. It occurred to us that if the conformer distribution can be determined by some other easier methods, one could conveniently monitor the time dependence of the conformer distribution or estimate the conformational isomerism in non-deuterated solvents. More recently, we noticed that in water-soluble calix[*n*]arenes bearing chiral substituents the circular dichroism (CD) spectra change sensitively on guest binding.[9] The spectral change was reasonably explained by the conformational change in the host calixarene induced by inclusion of guest molecules. This finding suggesed the idea that conformational isomers bearing chiral substituents would afford different CD spectra, from which one could assign the structure of conformational isomers. With these objects in mind, we synthesized the calix[*n*]arenes **1–5** and their non-cyclic reference compounds bearing chiral substituents.



1_n



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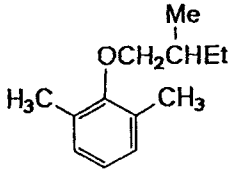

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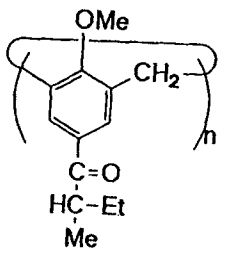
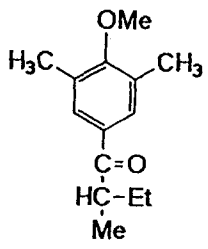


4_n



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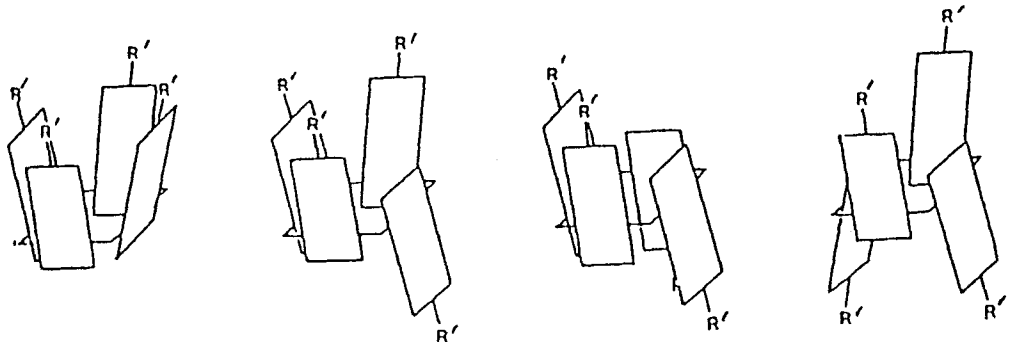


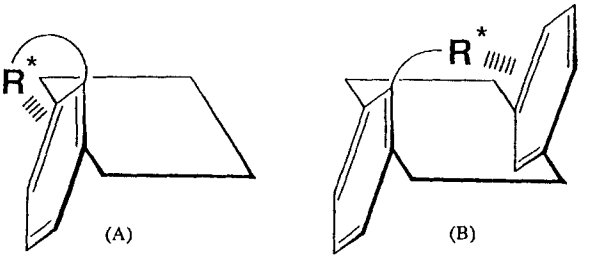
Cone Partial cone 1,2-Alternate 1,3-Alternate

RESULTS AND DISCUSSION

CD spectra of conformational isomers of 1_n

It has been established that the oxygen-through-the-annulus rotation is inhibited by *O*-substituents larger than Et.[3,5] We therefore chose the (*S*)-2-methylbutyl group as a chiral *O*-substituent. We could synthesize three different conformational isomers of 1_4, that is, cone, partial cone and 1,3-alternate. The ^{1}H NMR spectra of these compounds were unaffected by temperature change ($C_2D_2Cl_4$, 25–80 °C), indicating that these compounds are conformationally immobilized. In **2**, on the other hand, two OH groups are substituted with the (*S*)-2-methylbutyl group but two residual OH groups are substituted with a methyl group. Hence two 1,3-anisole units can still rotate through the annulus. In 1_6 the $ArCH_2Ar$ protons appear as a singlet resonance at 3·82 ppm ($C_2D_2Cl_4$, 130 °C). This implies that the phenyl units are conformationally mobile. Compound **3** was synthesized as a reference compound.

When the CD band is observed for 1_n, two possible interactions exist between the chiral centre (R*) and the chromophoric π-system. Type A is the interaction of R* with its own π-system whereas type B is the interaction of R* with the neighbouring π-system distal or proximal to its own π-system. Typical CD spectra are illustrated in Figure 1.



The results of spectral measurements are summarized in Table 1. No perceptible CD band was detected for monomeric **3**. This means that, apparently, the contribution of type A is negligibly small. In contrast, a strong, negative CD band appeared in cone-1_4 (Figure 1). When the conformation is immobilized to cone, the contribution of type B is sterically disregarded. Therefore, one has to take the contribution of type A into account. Then, why is cone-1_4 CD active and **3** CD inactive? In *O*-alkylation of calix[4]arene-25,26,27,28-tetrols the reactions frequently stop at the disubstituted stage.[6,10–15] This is due to the steric crowding on the narrow lower rim of calix[4]arene. Examination of molecular models of cone-1_4 reveals that (*S*)-2-methylbutyl groups diverge like a skirt below the calix[4]arene ring in order to reduce the steric crowding and the chiral centre can exist on its own benzene ring

Table 1. Absorption and CD spectra of $\mathbf{1}_n$, **2** and **3** in chloroform at 25 °C

Compound[a]	absorption spectrum λ_{max} (nm)	absorption spectrum ε (cm^{-1} mol^{-1} dm^3)	CD spectrum λ_{max} (nm)	CD spectrum $[\theta]$ (deg cm^2 $dmol^{-1}$)
Cone-$\mathbf{1}_4$	276·6	2330	286·0	−1370
Partial-cone-$\mathbf{1}_4$	278·6	2010	283·5	−2250
1,3-Alternate-$\mathbf{1}_4$	272·0	2230	276·0	−455
$\mathbf{1}_6$	288·0	3340	281·5	370
2	270·8	2220	280·5	240
3	266·2	387	—[b]	—[b]

[a] 5·00 mmol dm^{-3}.
[b] The CD band was not detected ($\theta < 10$).

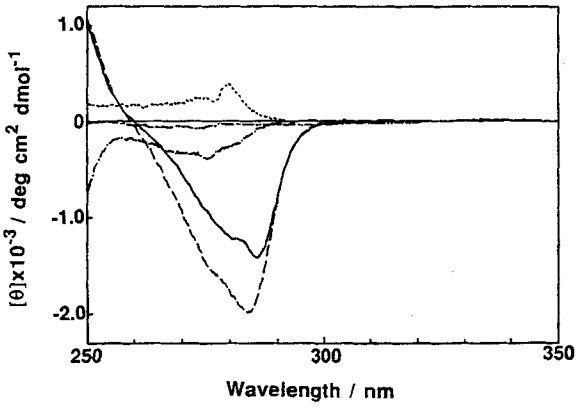
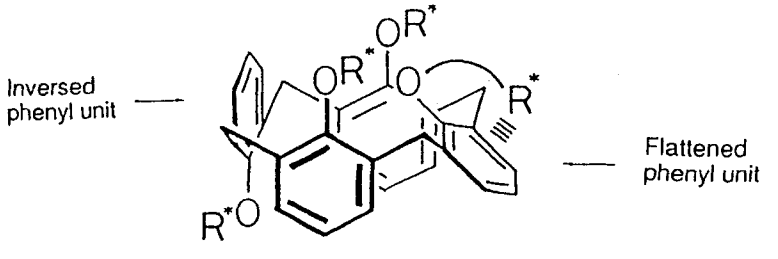


Figure 1. CD spectra of $\mathbf{1}_n$, **2** and **3** in chloroform at 25 °C: [$\mathbf{1}_n$ or **2**] = 5·00 mmol dm^{-3}. ——, Cone-$\mathbf{1}_4$; -----, partial-cone-$\mathbf{1}_4$; -·-·-, 1,3-alternate-$\mathbf{1}_4$; ····· **2**; -··- **3**

with some probability. This is the origin of the CD activity in cone-$\mathbf{1}_4$. In contrast, monomeric **3** can adopt many different conformations because of the absence of such steric crowding and the chiral-centre-on-the-benzene conformation like type A is rather classified as an energetically unfavourable conformation. It is certain, therefore, that the difference in the steric crowding leads to the difference in the CD activity. The above explanation is supported by the ^{1}H NMR spectra. As illustrated in Figure 2, the 2-methyl protons and 3-CH_2 methylene protons in cone-$\mathbf{1}_4$ shift to higher magnetic field (compared with those in **3**). This is due to the shielding effect of the benzene ring current; hence these protons exist exactly on the benzene ring with high probability.

Partial-cone-$\mathbf{1}_4$ showed the strongest CD band among three conformers of $\mathbf{1}_4$. As the CD spectrum is very similar to that of cone-$\mathbf{1}_4$, the CD activity should arise from a type A interaction. Through examination of the ^{1}H NMR spectrum we noticed that the (*S*)-2-methylbutyl protons in the phenyl unit (C in Figure 2) distal to the inverse phenyl unit (A in Figure 2) distinctly shift to higher magnetic field (for the assignment, see Experimental); for example, $\delta_H = 0·75$ ppm for $CH_3(CH)$ and 0·83–0·93 ppm for $CH_3(CH_2)$. Examination of x-ray crystallographic studies on partial-cone-calix[4]arenes reveals that this phenyl unit is significantly 'flattened,' producing serious steric crowding on the *O*-substituent. It is therefore reasonable to consider that the space around the (*S*)-2-methylbutyl group in the 'flattened' phenyl unit is more crowed than that in cone-$\mathbf{1}_4$ and the (*S*)-2-methylbutyl group exists predominantly on its own benzene ring to reduce the high steric crowding. This conformational requirement would induce the upfield shift of the (*S*)-2-methylbutyl protons and afford a strong type A CD band. It is also reasonable to consider, therefore, that three residual phenyl units (that is, one inverse phenyl unit and two phenyl units proximal to the inverse phenyl unit) scarcely contribute to the CD activity. The



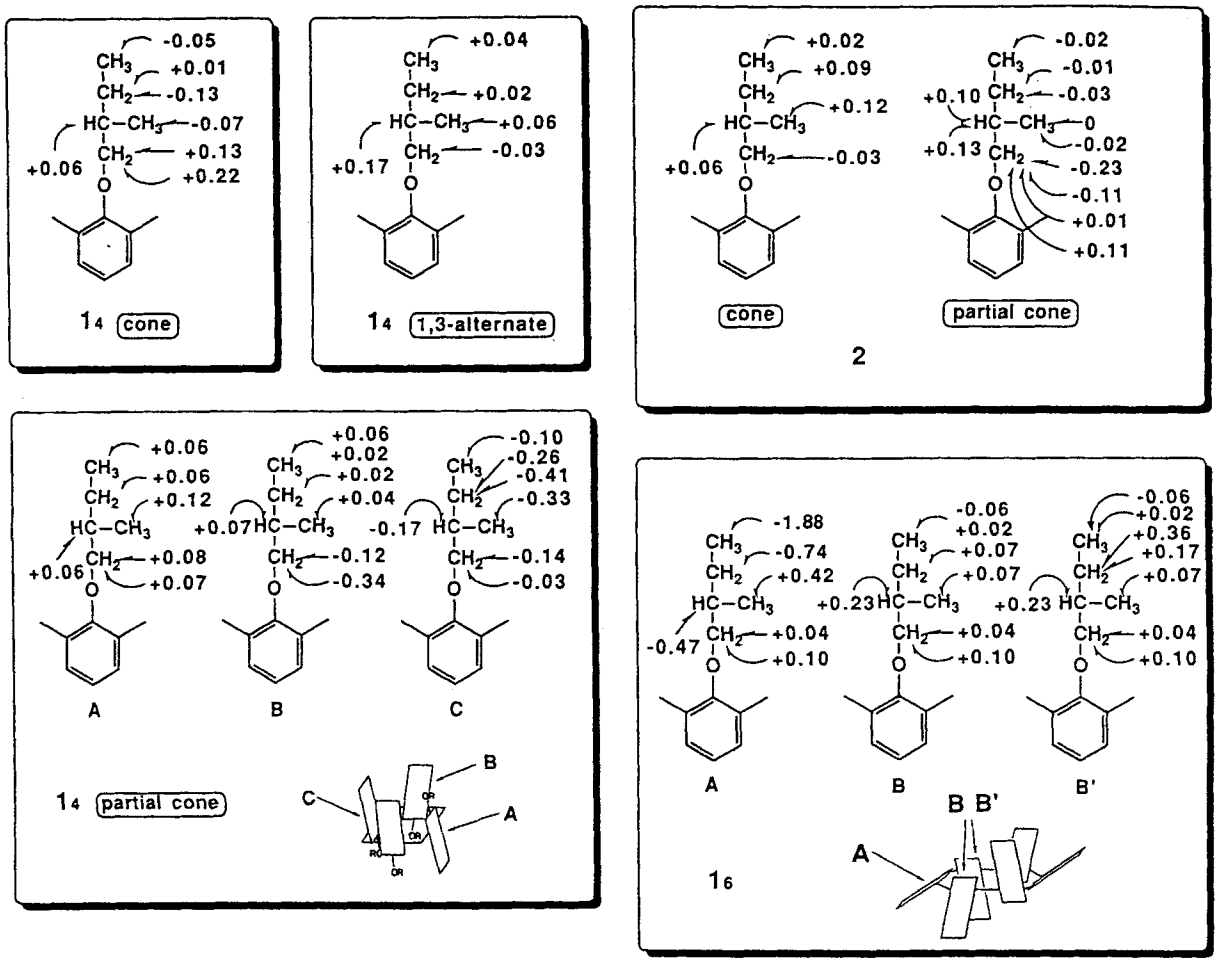
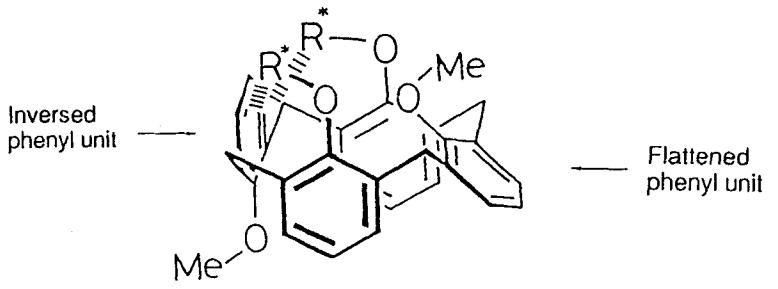


Figure 2. Shifts of the (*S*)-2-methylbutyl protons (in ppm) from those in monomeric **3** in $CDCl_3$ at 25 °C: + denotes the downfield shift and − denotes the upfield shift

fact that the (*S*)-2-methylbutyl protons in these three phenyl units scarcely shift to higher magnetic field (Figure 2) is compatible with this explanation.

1,3-Alternate-**1**$_4$ showed a relatively weak, negative CD band. As mentioned above for partial-cone-**1**$_4$, three phenyl units other than the 'flattened' phenyl unit scarcely contribute to the CD activity. The structure of 1,3-alternate-**1**$_4$ is basically similar to the combination of these three phenyl units. X-ray crystallographic studies on 1,3-alternate calix[4]arene derivatives indicate that four phenyl units are more or less parallel to each other and ample space exists around the *O*-substituents.[16,17] This steric situation would not force the (*S*)-2-methylbutyl group to be expelled from the cavity onto the benzene ring. In ^{1}H NMR, in fact, a significant upfield shift was not observed for the protons near the chiral centre in the (*S*)-2-methylbutyl substituent. Therefore, 1,3-alternate-**1**$_4$ is classified as a conformation with weak CD activity.

The foregoing considerations indicate that the CD activity in cone-, partial-cone- and 1,3-alternate-**1**$_4$ is reasonably explained according to the route, steric crowding on the narrow lower rim → expulsion of the (*S*)-2-methylbutyl group onto the benzene ring → appearance of the CD band. In other words, the intensity in the CD band is associated with the contribution of the type A interaction. From careful comparison of $[\theta]$ with λ_{max} in the absorption spectra, we found that the order of the intensity in $[\theta]$ (partial-cone-**1**$_4$ > cone-**1**$_4$ > 1,3-alternate-**1**$_4$ > **3**) shows good agreement with the order of λ_{max} values in the absorption spectra (from longer to shorter wavelength; see Table 1). The trend suggests that the sterically distorted calix[4]arene has the narrow HOMO–LUMO barrier.



In contrast to **1**$_4$, **2** resulted in a weak, positive CD band. This implies that the CD-active origin is different from that for **1**$_4$, that is, the CD activity is not attributable to a type A interaction. The absence of type A interaction is related to reduced steric crowding because in **2** two of four bulky (*S*)-2-methylbutyl groups are replaced with a methyl group. The reduced steric crowding is also supported by the absorption spectrum: λ_{max} appears at a wavelength shorter than those for **1**$_4$ (Table 1). ^{1}H NMR measurements in $CDCl_3$ indicated that **2** exists as a mixture of cone and partial cone (66 : 34) (see Experimental). As described above, the

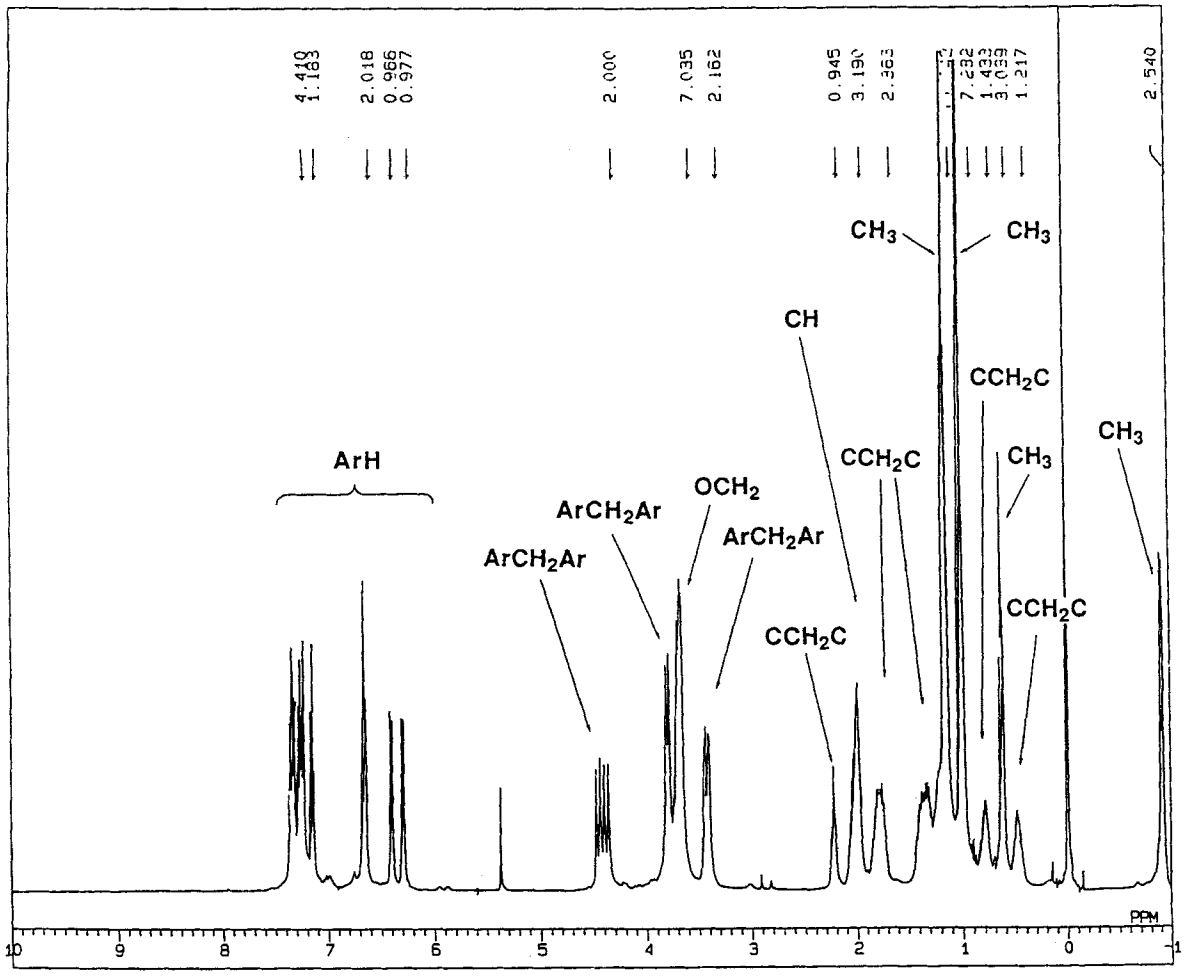


Figure 3. ^{1}H NMR spectrum of **1**$_6$ (400 MHz, CD_2Cl_2, −70 °C)

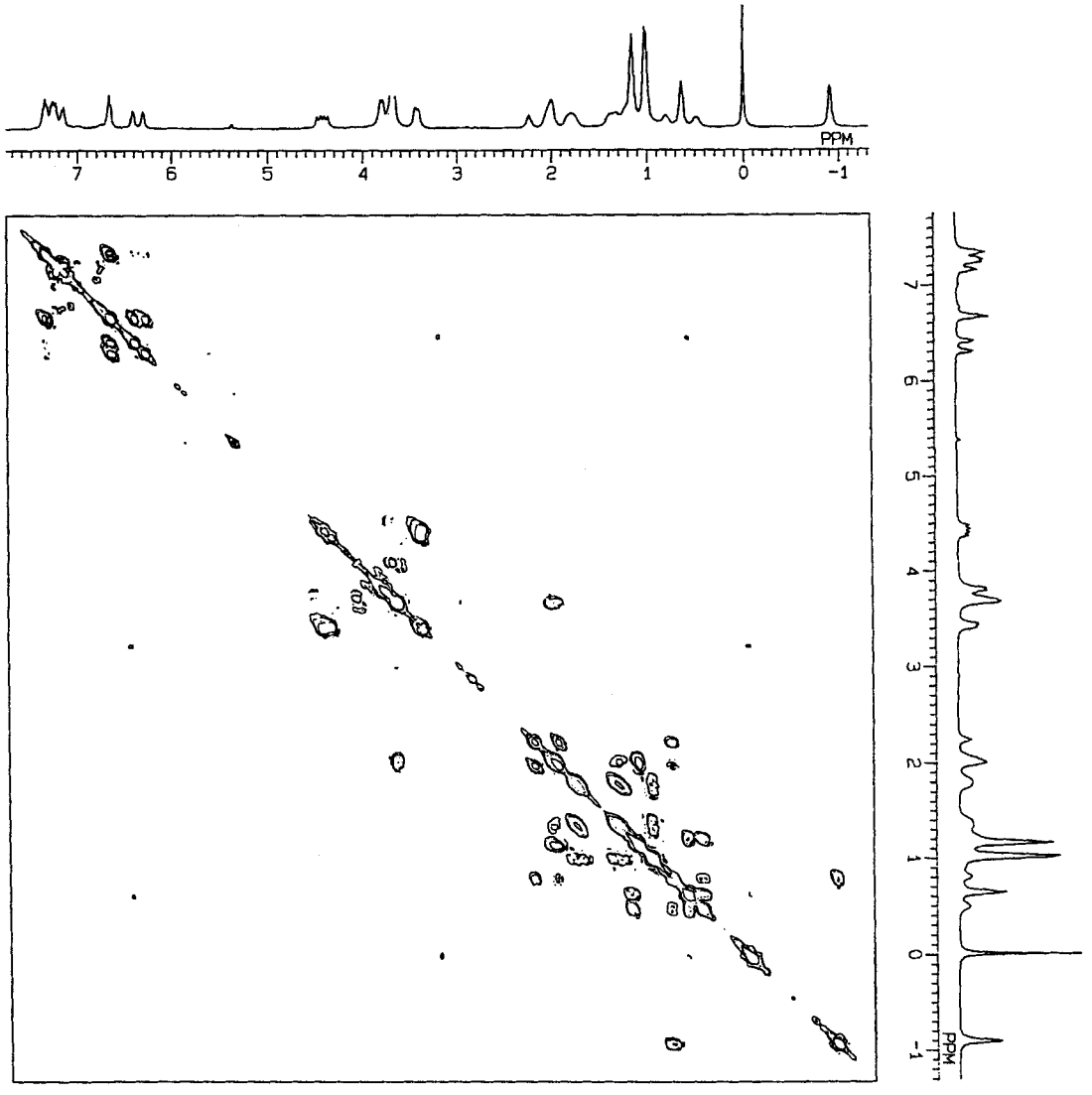


Figure 4. ^1H–^1HCOSY spectrum of $\mathbf{1}_6$ (400 MHz, CD_2Cl_2, −70 °C)

cone conformation includes only the type A interaction for steric reasons. Hence the appearance of the positive CD implies that the CD activity cannot be attributed to cone-**2**. These considerations allow us to conclude that the weak, positive CD band arises from partial-cone-**2**. The possible $R^*\cdots\pi$ interaction is expected for two R^* groups and the π-system of the reversed phenyl unit. This interaction is classified as type B. We consider that this type B interaction also exists in partial-cone-$\mathbf{1}_4$ but is offset by the stronger type A interaction in the flattened phenyl unit.

Compound $\mathbf{1}_6$ is conformationally mobile but may adopt some favourable conformation over others under an equilibrium. The ^1H NMR spectrum and ^1H–^1H COSY spectrum (400 MHz, CD_2Cl_2, −70 °C) are shown in Figures 3 and 4, respectively. It is clearly seen from these spectra that there are three inequivalent $ArCH_2Ar$ methylene protons and each peak corresponds to two $ArCH_2Ar$ groups (i.e. integral intensity 4H: δ_H, 3·38–3·48, 3·80 and 4·34–4·50 ppm). Also interesting is the chemical shift of the terminal methyl group: two of six methyl groups shift to unusually high

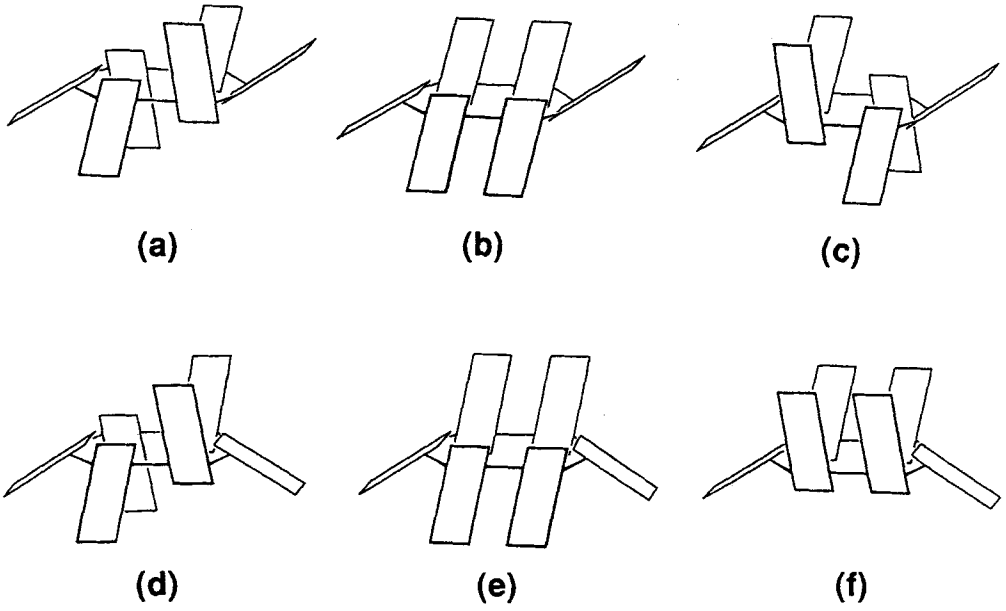


Figure 5. Six candidate conformations for $\mathbf{1}_6$

magnetic field ($\delta_H = -0{\cdot}91$ ppm in contrast to $\delta_H = 0{\cdot}97$ ppm for CH_3 in **3**: $\Delta\delta_H = -1{\cdot}88$ ppm). This supports the view that two of six phenyl units are significantly flattened, throwing the (*S*)-2-methylbutyl group into the cavity. We can suggest six possible conformations which are apparently compatible with the above-mentioned observations (Figure 5). Examination of CPK molecular models suggests that it is sterically impossible (because of serious steric crowding) for two flattened (*S*)-2-methylbutyl groups to occupy the same side of the calix[6]arene ring (see Figure 5). Hence, conformations (d), (e) and (f) are excluded. If the flattened phenyl unit A and the proximal phenyl unit B were to adopt an *anti* conformation, the OCH_2 methylene protons in A would be strongly shielded by the benzene π-system in B. As shown in Figure 2, this is not the case. Hence, conformations (b) and (c) are inconceivable. We therefore conclude that the conformation (a) (i.e. 1,2,3-alternate) is most energetically stable and most reasonable. A similar 1,2,3-alternate conformation was proposed for calix[6]arene esters and ethers by Kanamathareddy and Gutsche.[18] The CPK molecular model for conformation (a) indicates that the two terminal methyl groups in A and A′ are strongly shielded by the benzene π-systems of inverse B and B′ at the 3- and 5-positions.

The above conformational inspection allows to predict that the CD activity for $\mathbf{1}_6$, if any, arises from a type B interaction which features a positive CD band. As shown in Table 1, in fact, $\mathbf{1}_6$ gives a positive CD band although the $[\theta]$ value is relatively small. We consider that the small $[\theta]$ is due to the conformational mobility.

The foregoing results consistently indicate that the CD activity in $\mathbf{1}_n$ is caused by the $R^* \cdots \pi$ interaction and an intra-phenyl-unit interaction (type A) gives a negative CD band whereas an inter-phenyl-unit interaction (type B) gives a positive CD band.

CD spectra of $\mathbf{4}_n$

In contrast to **3**, compound **5** was CD active. This is because the chiral centre is situated at the α-carbon to the benzoyl conjugate system. We noticed that in a chloroform–acetonitrile mixed solvent the addition of $MClO_4$ (M = Li or Na) enhances the $[\theta]$ value 1·2–1·3-fold (Table 2). Since **5** scarcely interacts with these metal ions (confirmed by ^1H NMR spectroscopy), this change is ascribed to the solvent polarity enhanced by these salts. This view is also supported by the solvent effect: the $[\theta]$ value in chloroform is smaller than that in chloroform–acetonitrile mixed solvent.

The $ArCH_2Ar$ methylene protons in $\mathbf{4}_6$ give a singlet resonance at 4·00 ppm ($CDCl_3$, room temperature), indicating that the phenyl units are conformationally mobile. The ^1H NMR spectrum was hardly changed even in the presence of saturated $LiClO_4$ or $NaClO_4$. One can therefore consider that $\mathbf{4}_6$ is classified as a poor ionophore. In the CD spectral measurement the $[\theta]$ value was slightly increased on adding $LiClO_4$ or

Table 2. Absorption and CD spectra of 4_n and **5** in a chloroform–acetonitrile (1 : 1, v/v) mixed solvent at 25 °C

Compound	Additive (mol dm^{-3})	Absorption spectrum $\lambda_{max}(1)$ (nm)	$\varepsilon(1)$ (cm^{-1} mol^{-1} dm^{-3})	$\lambda_{max}(2)$ (nm)	$\varepsilon(2)$ (cm^{-1} mol^{-1} dm^{-3})	CD spectrum λ^{max} (nm)	$[\theta]$ (deg cm^2 dmol^{-1})
4_4	None	263·5	44400	238·5	24400	259	13000
	$LiClO_4$ (0·20)	264·0	41700	238·5	24600	257	11500
	$LiClO_4$ (0·40)	264·0	40400	238·5	25800	257	9200
	$NaClO_4$ (0·20)	264·0	42800	238·5	23000	259	13000
4_6	None	261·5	67700	—	—	255	15100
	$LiClO_4$ (0·40)	262·5	66200	—	—	255	15600
	$NaClO_4$ (0·20)	261·5	66400	—	—	255	17700
5	None	260·5	6200	—	—	259	2200
	None[a]	261·5	7200	239·5	5900	259	2050
	$LiClO_4$ (0·40)	263·0	6300	—	—	259	2790
	$NaClO_4$ (0·20)	261·0	6500	—	—	259	2570

[a] Solvent 100% chloroform.

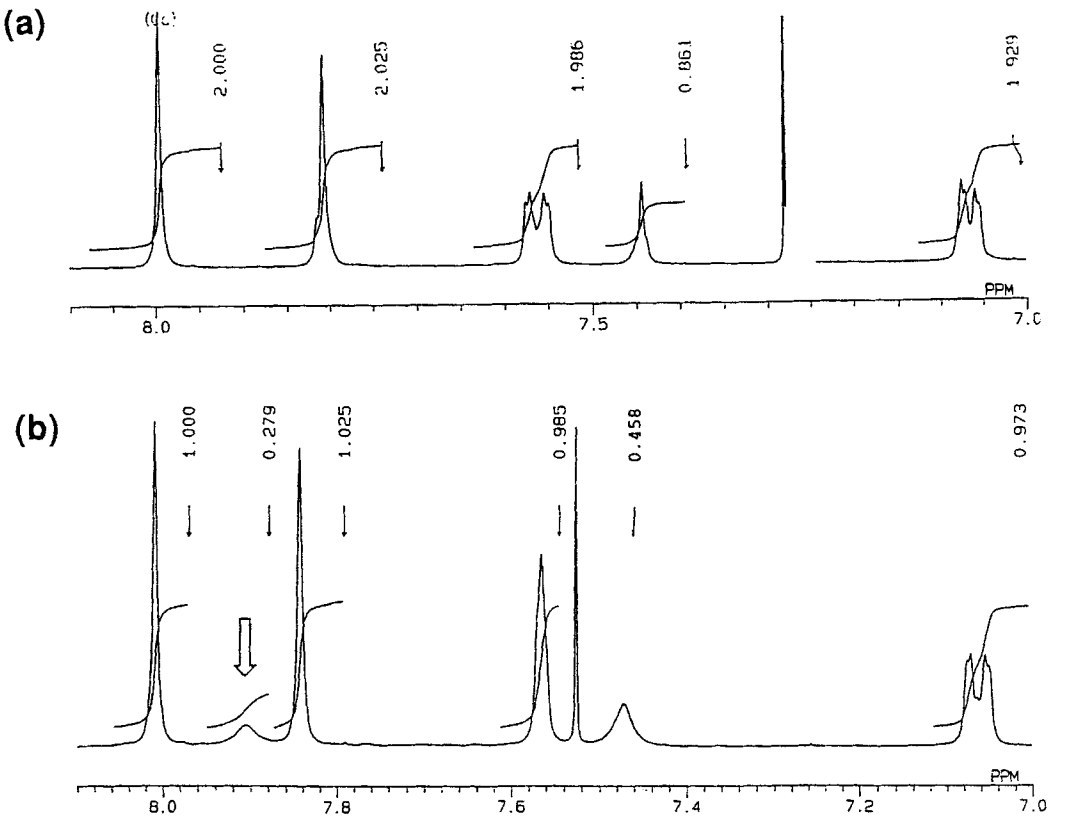


Figure 6. Partial ^{1}H NMR spectra of 4_4 (20 mmol dm^{-3}), (a) in the absence and (b) the presence of $LiClO_4$ (200 mmol dm^{-3}): 400 MHz, 0 °C, $CDCl_3$–CD_3CN (1 : 1, v/v). The line indicated by the large arrow is ascribable to the aromatic protons in the Li^+ · cone-4_4 complex

$NaClO_2$ (Table 2). The slight increase is therefore ascribable to the salt-induced change in the solvent polarity.

We previously found that the conformational isomerism in 5,11,17,23-tetra-*p-tert*-butyl-25,26,27,28-tetramethoxycalix[4]arene is affected by the solvent effect.[19] In particular, the ratio of cone vs partial-cone conformer is very sensitive: in polar solvents the cone conformer increases while the partial-cone conformer decreases.[14] We estimated the conformational isomerism in 4_4 in several solvents by ^1H NMR spectroscopy, but the conformer distribution was not very sensitive to changes in the solvent polarity: at 0 °C, cone-4_4/partial-cone-4_4 = 0·138 in $CDCl_3$, 0·137 in $CDCl_3$-CD_3CN (1:9, v/v), 0·122 in $CDCl_3$–CD_3OD (9:1, v/v) and 0·143 in $CDCl_3$–DMSO-d_6 (1:1, v/v). Compound 4_4 has a dipole moment arising from the intramolecular charge-transfer band from MeO to COR, which is much stronger than that in 5,11,17,23-tetra-*p-tert*-butyl-25,26,27,28-tetramethoxycalix[4]arene. The above finding suggests that if the dipole moment in each phenyl unit is too strong, the conformational isomerism becomes less sensitive to the change in the solvent polarity.

It is known that 25,26,27,28-tetramethoxycalix[4]arene derivatives bind Li^+ and the cone–partial-cone equilibrium is inclined to the cone conformation so that four methoxy oxygens can coordinate to Li^+.[19] ^1H NMR measurements established that 4_4 exists as a mixture of cone and partial cone in an 11:89 ratio in chloroform–acetonitrile (1:1, v/v) mixed solvent at 0 °C. Figure 6 shows the partial ^1H NMR spectra for the aromatic protons. In the presence of $LiClO_4$ a new peak appeared at 7·91 ppm, which was assignable to the Li^+ · cone-4_4 complex. Assuming the formation of a 1:1 complex, the binding constant ([Li^+ · cone-4_4]/[Li^+][cone-4_4]) was estimated to be 3·17 $dm^3 mol^{-1}$. On the other hand, the ^1H NMR spectrum of 4_4 was hardly affected by added $NaClO_4$. This indicates that the ionophoric cavity in 4_4, composed of four ethereal oxygens, shows high selectivity toward Li^+.

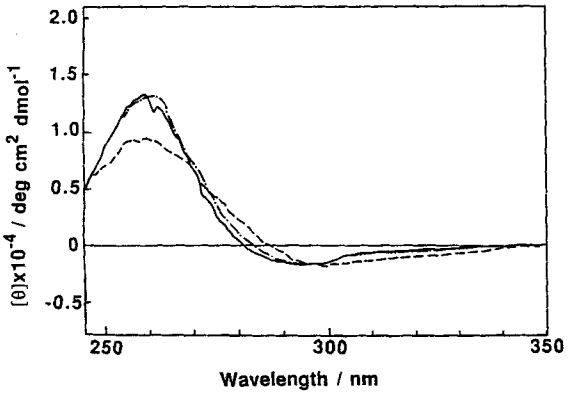


Figure 7. CD spectra of 4_4 (4·00 mmol dm^{-3}) in $CHCl_3$–CH_3CN (1:1, v/v) at 25 °C: ··, no additive; ----, 400 mmol dm^{-3} $LiClO_4$; -·-·, 200 mmol dm^{-3} $NaClO_4$

As shown in Table 2, the [θ] value is significantly decreased by added $LiClO_4$ but not by added $NaClO_4$ (Figure 7). This implies that the Li^+ · cone-4_4 complex has a smaller [θ] than cone-4_4 (and probably than partial-cone-4_4). As described for **5**, the CD band is strengthened when the intramolecular charge transfer is facilitated in polar solvents. In the Li^+ · cone-4_4 complex, the electron-donating ability of MeO is suppressed through the Li^+···OMe interaction and therefore [θ] is decreased. This specific situation permits the detection of the metal binding by the change in the CD spectrum.

CONCLUSIONS

This study on chiral calixarenes has demonstrated that the CD spectra are sensitively affected by the conformer structures. Although the CD spectra did not change so dramatically as observed for chromogenic calixarenes,[20,21] we believe that the present method will become potentially important in chiral guest recognition by chiral calixarenes.

EXPERIMENTAL

Materials. The methods for the synthesis of conformational isomers from calix[4]arene-25,26,27,28-tetrols were described previously.[5,6] We applied these procedures to the synthesis of 1_4.

25,26,27,28-Tetrakis[(S)-2-methylbutoxy]calix[4]arene (cone-1_4). Calix[4]arene-25,26,27,28-tetrol (0·70 g, 1·65 mmol) was dissolved in DMF (20 ml) and treated with oil-dispersed NaH (net 60%; 1·06 g, 26·4 mmol). After the addition of (*S*)-2-methylbutyl bromide (5·0 g, 33·1 mmol), the reaction mixture was heated at 60 °C for 8 h. NaH was decomposed by the addition of methanol. The mixture was diluted with 1·0 mol dm^{-3} HCl and the solution was extracted with chloroform. The chloroform layer was separated, washed three times with water and dried over $MgSO_4$. The solution was evaporated to dryness and the residue was purifed by column chromatography [silica gel, chloroform–hexane (1:5, v/v)] m.p. 116–117 °C, yield 58%; ^1H NMR ($CDCl_3$, room temperature), δ_H = 0·92 and 1·01 (CH_3, t and d, 3H each), 1·09–1·22 and 1·58–1·79 (CCH_2C, m, 1H each), 1·86–1·99 (CH, m 1H), 3·64–3·74 and 3·78–3·88 (OCH_2, m, 1H each), 3·17 and 4·49 ($ArCH_2Ar$, d, 1H each), 6·50–6·60 (ArH, m, 3H). Analysis: found, C 81·70, H 9·24; calculated for $C_{40}H_{48}O_4$, C 81·77, H 9·15%.

*Partial-cone-***1**$_4$ *and 1,3-alternate-***1**$_4$. Calix[4]arene-25,26,27,28-tetrol (0·70 g, 1·65 mmol) and (*S*)-2-methylbutyl bromide (5·0 g, 33·1 mmol) were allowed to react at 70 °C in DMF (40 ml) in the presence of Cs_2CO_3 (21·6 g, 66·2 mmol). After 24 h, (*S*)-2-methylbutyl bromide (5·0 g, 33·1 mmol) was added and the reaction was continued for a further 24 h. After cooling, the reaction mixture was diluted with 1·0 mol dm^{-3} HCl and extracted with chloroform. The organic layer was washed once with 10% sodium thiosulphate and twice with water and dried over $MgSO_4$. The solution was concentrated to dryness, the residue being recrystallized from chloroform–methanol. 1,3-Alternate-**1**$_4$ was isolated from this solution whereas partial-cone-**1**$_4$ was obtained by concentration of the filtrate and cooling. 1,3-Alternate-**1**$_4$: m.p. 133–135 °C, yield 29%; IR (Nujol), no ν_{OH}; ^{1}H NMR ($CDCl_3$, room temperature), δ_H = 1·01 and 1·14 (CH_3, t and d, 3H each), 1·27–1·38 and 1·58–1·70 (CH_2C, m, 1H each), 1·97–2·10 (CH, m, 1H), 3·4–3·6 (OCH_2 and $ArCH_2Ar$, m, 4H), 6·6–7·0 (Arh, m, 3H). Analysis: found, C 81·52, H 9·11; calculated for $C_{48}H_{64}O_4$, C 81·77, H 9·15%. The $ArCH_2Ar$ methylene protons in 1,3-alternate conformers usually appear as a singlet resonance.[5,6] In **1**$_4$, on the other hand, they appeared as a multiple resonance probably because of distortion of the calix[4]arene ring induced by bulky *O*-substituents. Partial-cone-**1**$_4$: m.p. 159–161 °C, yield 28%; ^{1}H NMR ($CDCl_3$, room temperature), δ_H = 0·75 (CH_3, d, 3H), 0·83–0·93 (CH_3 and one of CCH_2C protons, m, 4H), 0·95–1·07 (CH_3, m, 9H), 1·09–1·15 and 1·20 (CH_3, m and d, 6H and 3H), 1·23–1·44 (CCH_2C, m, 4H), 1·59–1·76 (CCH_2C and CH, m, 4H), 2·02 and 2·05–2·17 (CH, m, 2H and 1H), 3·03–3·12 and 4·16–4·23 ($ArCH_2Ar$, m, 2H each), 3·16–3·23, 3·36–3·42 and 3·46–3·54 (OCH_2, m, 1H, 1H and 3H), 3·56–3·72 (OCH_2 and $ArCH_2Ar$, m, 7H), 6·01–6·08, 6·97–7·06 and 7·23–7·28 (ArH, m, 2H, 4H and 2H) 6·38 and 6·78–6·87 (ArH, t and n, 2H each). Analysis: found, C 81·67, H 9·22; calculated for $C_{48}H_{64}O_4$, C 81·77, H 9·15%. The assignment of the ^{1}H NMR spectrum for partial-cone-**1**$_4$ was achieved with the aid of 2D ^{1}H–^{1}H COSY. We confirmed on the basis of NOE that (*S*)-2-methylbutyl protons in phenyl unit C (see Figure 2) appears at the highest magnetic field (Figure 8).

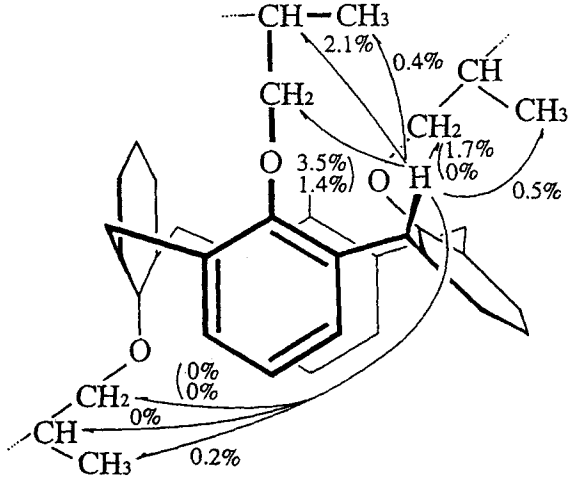


Figure 8. NOE peak intensities with respect to H_{endo} in Ar(phenyl unit B)—CH_2—Ar(phenyl unit C) of partial-cone-**1**$_4$ ($CDCl_3$, room temperature)

37,38,39,40,41,42-Hexakis[(S)-2-methylbutoxy]calix[6]arene (**1**$_6$). Calix[6]arene–37,38,39,40,41,42-hexols (1·17 g, 1·84 mmol), (*S*)-2-methylbutyl bromide (10·0 g, 66·2 mmol) and K_2CO_3 (22·9 g, 166 mmol) were allowed to react in a manner similar to that described for partial-cone-**1**$_4$ and 1,3-alternate-**1**$_4$: m.p. 256–259 °C, yield 64%; ^{1}H NMR ($CDCl_2CDCl_2$, 130 °C), δ_H = 0·74 and 0·84 (CH_2C, m, 1H each), (CH_3, d and t 3H each, 1·11–1·25 and 1·43–1·56 (CCH_2C, m, 1H each), 1·65–1·76 (CH, m, 1H), 3·33–3·41 and 3·44–3·52 (OCH_2, m, 1H each), 3·91 ($ArCH_2Ar$, s, 2H), 6·65 and 6·84 (ArH, t and d, 1H and 2H). Analysis: found, C 81·66, H 9·04; calculated for $C_{72}H_{96}O_6$, C 81·77, H 9·15%.

25,27-Bis[(S)-2-methylbutoxy]calix[4]arene–26,28-diol (**6**). Calix[4]arene-25,26,27,28-tetrol (0·70 g, 1·65 mmol) and (*S*)-2-methylbutyl bromide (5·0 g, 33·1 mmol) were allowed to react in THF (30 ml)–DMF (3 ml) in a manner similar to that described for cone-**1**$_4$. In this mixed solvent the reaction stopped at the disubstituted stage: m.p. 242–243 °C, yield 54%; ^{1}H NMR ($CDCl_3$, room temperature), δ_H = 1·04 and 1·31 (CH_3, t and d, 6H each), 1·46–1·58 and 1·75–1·89 (CCH_2C, m, 2H each) 2·03–2·16 (CH, m, 2H), 3·74–3·89 (OCH_2, m, 4H), 3·32–3·41 and 4·25–4·38 ($ArCH_2Ar$, m, 4H each), 6·65, 6·72, 6·89–6·93 and 7·03–7·08 (ArH, t, t, m and m, 2H, 2H, 4H and 4H), 8·01 (OH, s, 2H). Analysis: found, C 80·86, H 7·89; calculates for $C_{38}H_{44}O_4$, C 80·82, H 7·85%. The ^{1}H NMR data indicate that the product is 1,3-disubstituted **6**. The difficulty with tetra-*O*-substitution is ascribed to high steric crowding on the narrow lower rim.

25,26-Bis[(S)-2-methylbutoxy]-26,28-dimethoxycalix[4]arene (**2**). Compound **6** (0·40 g, 0·71 mmol) in THF (20 ml)–DMF (2 ml) was treated with oil-dispersed NaH (net 60%; 0·23 g, 5·67 mmol) and reacted with methyl iodide (4·02 g, 28·3 mmol) at reflux temperature for 20 h. The work-up is similar to that described for partial-cone-**1**$_4$ and 1,3-alternate-**1**$_4$: m.p. 177–179 °C, yield 55%; ^{1}H NMR ($CDCl_3$,

$-10\,^{\circ}C$), $\delta_H = 0{\cdot}94$–$1{\cdot}03$ [CH_3 (cone) and CH_3 (partial-cone p.c.), m, 9H], 1·07 and 1·11 [CH_3 (p.c.), dd, 3H], 1·20 [CH_3 (cone), d, 6H], 1·23–1·46 [CH_2C (cone) and CCH_2C (p.c.), m, 3H], 1·47–1.56 [CH_2C (p.c.), m, 0·5H], 1·67–1·77 [CH_2C (cone) and CH_2C (p.c.), m, 2·5H], 1·90–2·05 [CH (cone) and CH (p.c.), m, 3H], 3.00 [OCH_3 (p.c.), s, 1·5H], 3·12 and 3·20 [$ArCH_2Ar$ (p.c.) and $ArCH_2Ar$ (cone), d, 1H and 2H], 3·26–3·33 and 3·39–3·45 [OCH_2 (p.c.), m, 0·5H each], 3·48–3·55 [OCH_2 (cone), m, 2H], 3·55–3·78 [OCH_2 (cone), OCH_2 (p.c.), OMe (p.c.) and $ArCH_2Ar$ (p.c.), m, 6·5H], 3·93 [OCH_3 (cone), s, 6H], 4·07 and 4·11 [$ArCH_2Ar$ (p.c.), dd, 1H], 4.36 and 4.39 [$ArCH_2Ar$ (cone), dd, 4H], 6·22–6·35, 6·50, 6·88–7·02, 7·10, 7·18 and 7·27–7·33 (ArH, m, t, m, d, d and m, 7H, 1H, 4H, 1H, 4H and 1H). Analysis: found,
C 80·96, H 8·15; calculated for $C_{40}H_{48}O_4$, C 81·04, H 8.16%.

2,6-Dimethyl[(S)-2-methylbutoxy]benzene (**3**). This compound was synthesized from 2,6-dimethylphenol (3·36 g, 27·5 mmol) and (*S*)-2-methylbutyl chloride (8·6 g, 0·83 mol) in DMF at 55 °C in the presence of K_2CO_3 (57·1 g, 0·418 mol): b.p. 123–124 °C/7·2 Torr, yield 74%; IR (neat), no ν_{OH}; ^1H NMR ($CDCl_3$, room temperature), $\delta_H = 0{\cdot}97$ and 1·08 (CH_3, t and d, 3H each), 1·22–1·37 and 1·56–1·69 (CCH_2C, m, 1H each), 1·81–1·93 (CH, m, 1H), 2·27 ($ArCH_3$, s, 6H), 3·51–3·56 and 3·59–3·65 (OCH_2, m, 1H each), 6·86–6·92 and 6·99 (ArH, m and d, 1H and 2H). Analysis: found, C 81·29, H 10·40; calculated for $C_{13}H_{20}O$, C 81·20, H 10·48%.

5,11,17,23-Tetrakis[(S)-2-methylbutanoyl]calix[4]arene-25,26,27,28-tetrol (**7**). (*S*)–2-Methylbutanoyl chloride (2·84 g, 23·6 mmol) and $AlCl_3$ (3·14 g, 2·35 mmol) were stirred in nitrobenzene for 30 min at room temperature under a stream of nitrogen. Calix[4]arene-25,26,27,28-tetrol (2·00 g, 4·71 mmol) was added and the mixture was heated at 70 °C for 2 h. After cooling, the mixture was diluted with ice–water (300 ml) and extracted with chloroform. The organic layer was washed twice with water. Evaporation of the solvent resulted in viscous brown oil, which was crystallized from chloroform–methanol. Finally, the solid product was recrystallized from chloroform–methanol: m.p. 264–265 °C, yield 65%; IR (Nujol) ν_{OH} 3160 cm^{-1}, $\nu_{C=O}$ 1670 cm^{-1}; ^1H NMR ($CDCl_3$, room temperature), $\delta_H = 0{\cdot}85$ and 1·10 (CH_3, t and d, 3H each), 1·35–1·48 and 1·67–1·79 (CCH_2C, m, 1H each), 3·22–3·33 (CH, m, 1H), 3·60–3·86 and 4·17–4·44 ($ArCH_2Ar$, m, 1H each), 7·77 (ArH, s, 2H), 10·13–10·27 (OH, bs, 1H). Analysis: found, C 75·66, H 7·35; calculated for $C_{48}H_{56}O_8$, C 75·76, H 7·42%.

5,11,17,23-Tetrakis[(S)-2-methylbutanoyl]-25,26,27,28-tetramethoxycalix[4]arene (**4₄**). This compound was synthesized from **7** (0·50 g, 0·66 mmol) and methyl iodide (3·73 g, 26·3 mmol) in DMF (30 ml) at 60 °C for 5 h in the presence of Cs_2CO_3 (8·56 g, 26·3 mmol). The work-up is similar to that described above. Finally, the product was recrystallized from chloroform–methanol: m.p. 191–192 °C, yield 88%; IR (Nujol), no ν_{OH}, $\nu_{C=O}$ 1670 cm^{-1}; ^1H NMR ($CDCl_3$ room temperature), $\delta_H = 0{\cdot}62$–$2{\cdot}02$ (CH_3 and CCH_2C, m, 32H), 2·92–3·14 [OCH_3 (p.c.) and CH, m, 4·7H], 3·27 [$ArCH_2Ar$ (p.c.), d, 1·8H], 3·36 [$ArCH_2Ar$ (cone), d, 0·4H], 3·40–3·55 (CH, m, 2H), 3·71–3·86 [OCH_3 (p.c.) and $ArCH_2Ar$ (p.c.), m, 11·7H], 3·91 [OCH_3 (cone), s, 1·2H], 4·07 [$ArCH_2Ar$ (p.c.), d, 1·8H], 4·40 [$ArCH_2Ar$ (cone), d, 0·4H], 7·26 [ArH (p.c.), d, 1·8H], 7·43 [ArH (cone), s, 0·8H], 7·55 [ArH (p.c.), d, 1·8H], 7·79 [ArH (p.c.), s, 1·8H], 7·98 [ArH (p.c.), s, 1·8H]. Analysis: found, C 76·44, H 7·86; calculated for $C_{52}H_{64}O_8$, C 76·44, H 7·90%.

5,11,17,23,29,35-Hexakis[(S)-2-methylbutanoyl]calix[6]arene-37,38,39,40,41,42-hexols (**8**). Calix[6]arene-37,38,39,40,41,42-hexols (1·00 g, 1·57 mmol), (*S*)-2-methylbutanoyl chloride (1·23 g, 10·2 mmol) and $AlCl_3$ (1·36 g, 10·2 mmol) were allowed to react in a manner similar to that described for **7**: m.p. >305 °C, yield 31%; ^1H NMR ($CDCl_3$, room temperature), $\delta_H = 0{\cdot}88$ and 1·16 (CH_3, t and d, 3H each), 1·42–1·54 and 1·71–1·84 (CH_2C, m, 1H each), 3·29–3·40 (CH, m, 2H), 7·87 (ArH, s, 2H), 10·47 (OH, bs, 1H). Analysis: found, C, 75·38, H, 7·33; calculated for $C_{72}H_{84}O_{12} \cdot 0{\cdot}4\ CH_3OH$, C 75·34, H 7·47%.

5,11,17,23,29,35-Hexakis[(S)-2-methylbutanoyl]-37,38,39,40,41,42-hexamethoxycalix[6]arene (**4₆**). *Compound* **8** (0·50 g, 0·438 mmol), methyl iodide (3·73 g, 26·3 mmol) and Cs_2CO_3 (2·57 g) were allowed to react in a manner similar to that described for **4₄**: m.p. 240–241 °C, yield 84%; IR (Nujol), no ν_{OH}, $\nu_{C=O}$ 1680 cm^{-1}; ^1H NMR ($CDCl_3$, room temperature), $\delta_H = 0{\cdot}83$ and 1·90 (CH_3, t and d, 3H each), 1·32–1·45 and 1·64–1·76 (CH_2C, m, 1H each), 3·12–3·23 (CH, m, 1H), 3·29 (OMe, s, 3H), 4·00 ($ArCH_2Ar$, s, 3H), 7·61 (ArH, s, 2H). Analysis: found, C 76·29, H 8·01; calculated for $C_{78}H_{96}O_{12}$, C 76·44, H 7·90%.

2,6-Dimethyl-4-[(S)-2-methylbutanoyl]phenol (**9**). This compound was synthesized from 2,6-dimethylphenol (1·00 g, 8·19 mmol), (*S*)-2-methylbutanoyl chloride (1·18 g, 9·82 mmol) and $AlCl_3$ (1·31 g, 9·82 mmol) in CS_2 at reflux temperature for 2 h. The work-up is similar to that described for **7**. Finally, the product was purified by column chromatography (SiO_2, eluent chloroform): m.p. 71–73 °C, yield 13%; IR (Nujol), ν_{OH} 3370, $\nu_{C=O}$ 1650 cm^{-1}; ^1H NMR

($CDCl_3$, room temperature), $\delta_H = 0{\cdot}89$ and $0{\cdot}16$ (CH_3, t and d, 3H each), $1{\cdot}30$–$2{\cdot}02$ (CH_2C, m, 2H), $2{\cdot}30$ ($ArCH_3$, s, 6H), $3{\cdot}00$–$3{\cdot}64$ (CH, m, 1H), $5{\cdot}19$ (OH, s, 1H), $7{\cdot}65$ (ArH, s, 2H). Analysis: found, C $75{\cdot}32$, H $8{\cdot}66$; calculated for $C_{13}H_{17}O_2$, C $76{\cdot}06$, H $8{\cdot}35\%$.

2,6-Dimethyl-4-[(S)-2-methylbutanoyl] anisole (5). *Compound* **9** ($0{\cdot}21$ g, $1{\cdot}02$ mmol), methyl iodide ($1{\cdot}45$ g, $10{\cdot}2$ mmol) and K_2CO_3 ($11{\cdot}41$ g, $10{\cdot}4$ mmol) were allowed to react in a manner similar to that described for $\mathbf{4}_4$: b.p. $150\,^{\circ}C/5$ mmHg; IR (Nujol), no ν_{OH}, $\nu_{C=O}$ $1675\ cm^{-1}$; ^1H NMR ($CDCl_3$, room temperature), $\delta H = 0{\cdot}89$ and $1{\cdot}16$ (CH_3, t and d, 3H each), $1{\cdot}36$–$1{\cdot}55$ and $1{\cdot}68$–$1{\cdot}89$ (CCH_2C, m, 1H each), $2{\cdot}32$ ($ArCH_3$, s, 6H), $3{\cdot}25$–$3{\cdot}42$ (CH, m, 1H), $3{\cdot}75$ (OMe, s, 3H), $7{\cdot}62$ (ArH, s, 2H). Analysis: found, C $75{\cdot}62$, H $9{\cdot}00$; calculated for $C_{14}H_{20}O_2 \cdot 0{\cdot}02CHCl_3$, C $75{\cdot}62$, H $9{\cdot}06\%$.

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