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Conformational rigidity in mesitylene-based calix[4]arenes adopting a 1,3-alternate conformation

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Abstract

Two chiral derivatives of a mesitylene-based calix[4]arene known to exist in the 1,3-alternate conformation were prepared by the attachment of homochiral residues to the four *exo*-hydroxy groups. Thus, the enantiotopic protons of the central scaffold became diastereotopic, leading to a doubling of their ^{1}H NMR signals in one example. From the temperature independence of the NMR spectrum, a lower limit of 24.2 kcal/mol could be estimated for the barrier of ring inversion. MM3 calculations confirm the 1,3-alternate conformation as the energy minimum, and estimate a barrier of 25.7 kcal/mol for the 1,3-alternate-to-1,3-alternate* interconversion process. This high barrier is due to the repulsive steric interactions between *exo*-methyl groups at vicinal rings when these groups pass each other. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

Calix[4]arenes, macrocyclic phenol-formaldehyde tetramers, are easily synthesised and functionalised which makes them attractive starting materials for the preparation of specific hosts with tailor-made properties.[1,2] The number of possible and attainable structures and shapes is enlarged by the fact that calix[4]arenes may adopt four different conformations by appropriate functionalisation: cone, partial cone (*paco*), 1,2-alternate (*1,2-alt*) and 1,3-alternate (*1,3-alt*). Depending on the substituents, these conformations can be flexible or rigid on the laboratory timescale.[†]

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[†] A barrier equal or higher than 23 kcal/mol is usually sufficient to separate two interconverting species at 298 K (Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 219–235). Therefore, they may be regarded as ‘rigid’ on the laboratory timescale. When discussing rigidity and flexibility of conformers, a second timescale (the NMR timescale) is also usually applied. A molecule involved in a dynamic process which exchanges two groups is considered rigid on the NMR timescale if at the given temperature the exchange rate is smaller than the frequency difference (in s^{-1}) between the groups.

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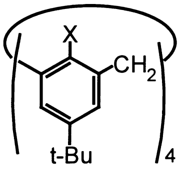

1a X = OH
1b X = SH
1c X = Me

The parent calix[4]arene tetrols (e.g. **1a**) adopt the *cone* conformation which is stabilised by a cyclic array of intramolecular hydrogen bonds. The *endo*-OH groups can pass through the centre of the macrocycle,‡ and this *cone*-to-*cone* interconversion (topomerisation) can be easily monitored by variable temperature ^{1}H NMR since it exchanges the methylene protons. At slow exchange conditions on the NMR timescale, a pair of doublets is observed for the methylene protons which upon raising the temperature broaden and coalesce into a singlet. Depending on the solvent, energy barriers in the range of 14.5–16 kcal/mol have been derived by the coalescence method.

Tetramercaptocalix[4]arene **1b** derived from **1a** by replacing the hydroxyls by SH groups, was found to exist in the *1,3-alt* conformation in the crystalline state.[3–5] The ^{1}H NMR spectrum displays a singlet for the protons of the methylene bridge in a broad temperature range, in agreement with a fixed *1,3-alt* conformation.[3–5] However, the same pattern would result if the conformation is flexible and rapid rotation of the aryl rings is taking place. Like **1b** the mesitylene-based calix[4]-arene **2** adopts a *1,3-alt* conformation (X-ray, NMR), and it has been conjectured that the substituent pattern renders the molecule conformationally rigid.[6,7] Molecular mechanics calculations[8] suggested, however, that *endo*-methyl as well as *endo*-thiol groups can pass the annulus of a calix[4]arene skeleton. This has been corroborated by NMR experiments for the *p*-*tert*-butyl-25,27-dihydroxy-26,28-dimethylcalix[4]arene.[9] Thus, one could conclude that systems possessing those groups should be flexible on the laboratory timescale.

The determination of the barrier of aryl rotation through the annulus of symmetric calix[4]arenes adopting the *1,3-alt* conformation is problematical. The coalescence method is not applicable since the protons within a methylene group are homotopic and their mutual exchange (as a result of ring inversion) is NMR silent. Thus, the general question arises, how to distinguish by NMR spectroscopy between the slow and fast exchange regimes of symmetric calix[4]arene systems adopting the *1,3-alt* conformation.

2. Results and discussion

2.1. Desymmetrisation of the calix skeleton

A possible approach to solve this problem is based on the desymmetrisation of the calixarene by the introduction of homochiral substituents which do not perturb the rotational process. We have chosen the mesitylene derived calix[4]arene **2** with four *endo*-methyl and eight *exo*-methyl

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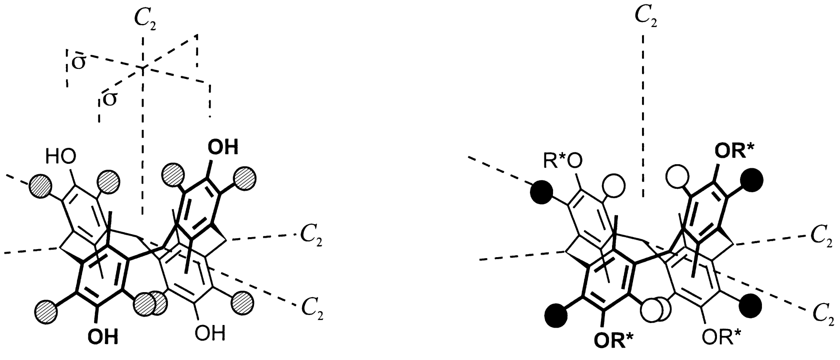
‡ The same is true for methoxy groups (and ethoxy groups at higher temperatures), while the propoxy group cannot pass the annulus at the laboratory timescale.

groups[10] as an appropriate model compound to test this idea since its four *exo*-hydroxyl groups can serve as anchoring points for the chiral residues.

The calix[4]arene scaffold of **2** possesses D_{2d} symmetry in the *1,3-alt* conformation. Attachment of four identical chiral residues to the OH-groups should not interfere with a conformational interconversion, but should reduce the symmetry to D_2 (cf. Fig. 1). Although pairs of protons within each methylene group are homotopic (they are symmetry related by the C_2 axis passing through opposite methylene groups), pairs of proximal methylene groups (as well as pairs of *exo*-methyls on the same ring) are symmetry unequivalent (diastereotopic) provided the rotation through the annulus of the calixarene is slow on the timescale of the observation. Under slow exchange conditions the methylene bridges as well as the *exo*-methyl groups should display two singlets each in the ^{1}H NMR spectrum.[§] A rapid conformational inversion of the macrocycle involving rotation of *all* rings through the annulus and fast rotation of the chiral side chains (under the timescale of observation) would result in an averaged D_4 symmetry.[11] In this averaged symmetry, pairs of proximal methylene groups as well as pairs of *exo*-methyls on the same ring are homotopic and would each display a singlet. The attachment of the chiral residues therefore enables the detection of the process (*1,3-alt*→*1,3-alt**) involving the passage of the four rings through the annulus.



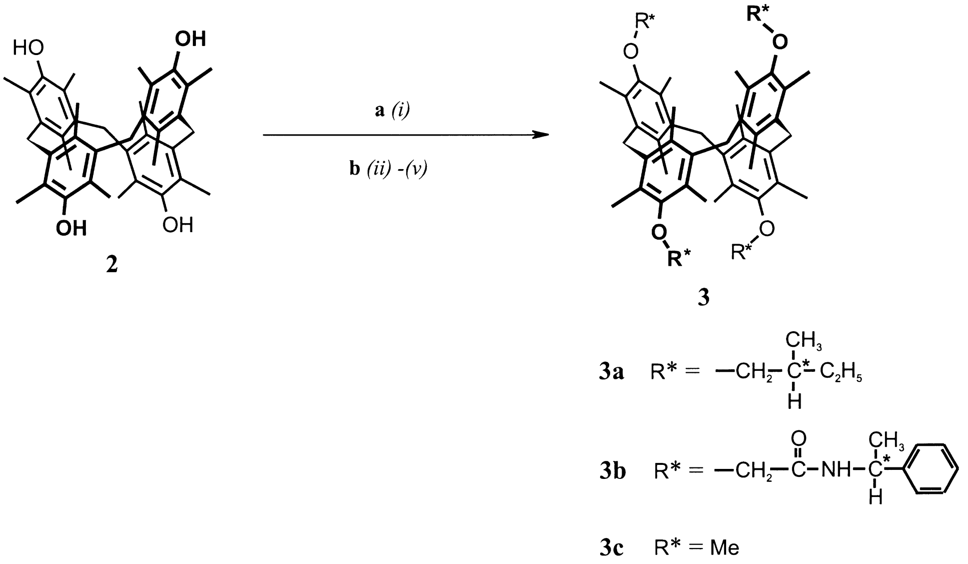
2 **3**

Figure 1. Desymmetrisation of the D_{2d}-symmetrical calix[4]arene **2** to a D_2-symmetrical derivative **3** by the introduction of four homochiral residues R*

2.2. Syntheses

Calix[4]arene **2** was first time synthesised by Pappalardo et al. by condensation of 2,4,6-trimethylphenol with 3,5-dichloromethyl-2,4,6-trimethyl phenol.[6] Later the condensation of 3-bromomethyl-2,4,6-trimethylphenol was found to be more convenient.[12] Two chiral derivatives of **2** were prepared, see Scheme 1. The tetraether **3a** was obtained by *O*-alkylation with (*S*)-1-bromo-2-methylbutane in DMF using NaH as base. The tetraamide **3b** required four synthetic steps. Alkylation of calix[4]arene **2** with an excess of ethyl bromoacetate in acetone catalysed by K_2CO_3

[§] Since the diastereotopic methylene protons are located at different carbon atoms, there is no mutual coupling and their corresponding signals should appear as singlets.



Scheme 1. Reagents and conditions: (i) RBr, DMF, NaH, rt; (ii) $BrCH_2C(O)OEt$, acetone, K_2CO_3, reflux; (iii) NaOH, $EtOH/H_2O$, reflux; (iv) $SOCl_2$, benzene, reflux; (v) phenylethylamine, THF, NEt_3, rt

gave the tetraethylester which was hydrolysed under alkaline conditions in ethanol/water. The resulting tetraacid[12] was then converted into the acid chloride by reaction with thionyl chloride which finally was reacted with (*S*)-1-phenylethylamine to give the chiral tetraamide **3b**. ^1H NMR spectra of **3a** and **3b** (400 MHz, $CDCl_3$, rt) are in agreement with the proposed structures, and precluding accidental isochrony, suggest that no racemisation of the chiral groups took place under the reaction conditions.

2.3. ^1H NMR measurements

Compound **3a** did not display any splitting of the singlets of the *exo*-methyl or the methylene protons in the 400 MHz ^1H NMR spectrum ($CDCl_3$, rt). The spectrum of compound **3b**, however, showed two singlets each for the protons of the *exo*-methyl groups and the methylene bridges. This is in agreement with a *1,3-alt* conformation of D_2 symmetry (Fig. 2) in which the *1,3-alt→1,3-alt** process is slow on the NMR timescale. Since the rotational barriers of **3a** and **3b** are expected to be similar, it can be concluded that the lack of signal splitting observed for **3a** is due to accidental isochrony of the diastereotopic signals and not the result of fast rotation of the rings through the cavity. Most likely this is due to the nature of the groups attached to the stereocenters (H, CH_3 and C_2H_5 for **3a** and H, CH_3 and C_6H_5 for **3b**) which are sufficiently different only in **3b**.

In order to determine the barrier of the *1,3-alt→1,3-alt** process, the spectrum of **3b** was recorded in nitrobenzene-d_5 at various temperatures. The two methylene signals, which resonate at about 3.6 ppm at 296 K, shift downfield upon raising the temperature and it is not clear whether they coalesce or merge. However, even at the highest temperature examined (451.5 K)¶ the two

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¶ This highest temperature was determined accurately with an 'NMR thermometer', a sample of ethylene glycol (Van Geet, A. L. *Anal. Chem.* **1968**, 40, 2227–2229).

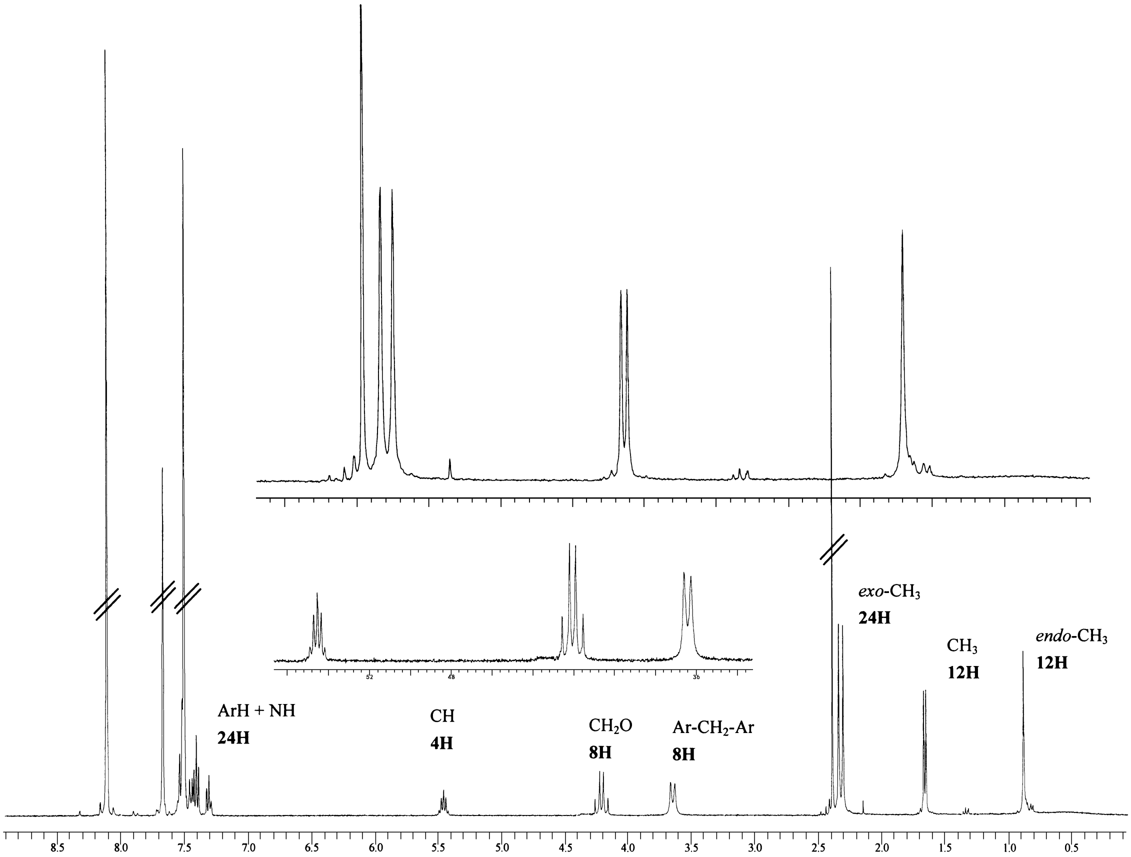


Figure 2. ^{1}H NMR spectrum of **3b** (400 MHz, nitrobenzene-d_5, rt) and expansions of the methyl (top), methylene and methine regions. Two singlets each are observed for the bridging methylene and extraannular methyl protons

exo-methyl groups remained anisochronous. On the basis of the chemical shift difference at 298 K ($\Delta\nu = 8.1$ Hz) a rate of exchange of 18 s^{-1} at the coalescence temperature was estimated using the Gutowsky–Holm equation.[13] Since the coalescence temperature must be higher than 452 K, a lower limit of 24.2 kcal/mol can be estimated for the topomerisation barrier.

2.4. Molecular mechanics calculations

Molecular mechanics calculations using the MM3(96) force field[14–17] were carried out in order to provide insight into the energetic stability of the basic conformations and into the threshold pathways of conformational interconversion. Compound **3c**, the tetramethyl ether of **2** was chosen as model for **3a** and **3b** in order to facilitate the calculations by reduction of the number of rotable bonds.

2.4.1. Preferred conformation

Table 1 lists the calculated energy differences of the low energy conformers of **3c** and, for means of comparison, the corresponding values for the parent *p-tert*-butylcalix[4]arene **1a** and its tetramethyl analogue **1c**.

Table 1
Calculated energy differences (MM3(96), in kcal/mol) for the low-energy conformers **1a**, **1c** and **3c**

	1,3-alt	*paco*	*cone*	*1,2-alt*
1a	11.0	5.8	0.0	7.4
1c	0.0	3.4	8.1	5.4
3c	0.0	6.2	8.2	13.4

In agreement with the available experimental data the calculations indicate that the replacement of the *intra*-annular OH groups in the parent **1a** by methyl groups (**1c** and **3c**) results in the complete energetical destabilisation of the *cone* in favour of the *1,3-alt* conformation. The calculations predict that **3c** should exist exclusively in the *1,3-alt* conformation under experimental conditions. The high energy differences between the basic conformations are mainly due to the torsional term while the nonbonding energies hardly differ. The steric strain exerted by the close proximity of the methyl substituents (*endo–endo*, *exo–exo* as well as *endo–exo*) not only leads to a distortion of the metacyclophane skeleton but also to a considerable deviation of the aromatic rings from planarity thus resulting in very unfavourable torsional contributions. The repulsive interactions between the *endo*-methyl substituents are best compensated in the *1,3-alt* conformer. As shown in Fig. 3 the aromatic rings are tilted with respect to the mean macrocyclic plane by 114° which diminishes the repulsive contacts between the *endo*- and *exo*-methyl groups of adjacent rings, the distance between the carbon atoms being 3.93 Å.[||] In contrast, the shortest distances between two methyl groups are 3.18 Å in the *cone*, 3.44 Å in the *paco* and 3.29 Å in the *1,2-alt*

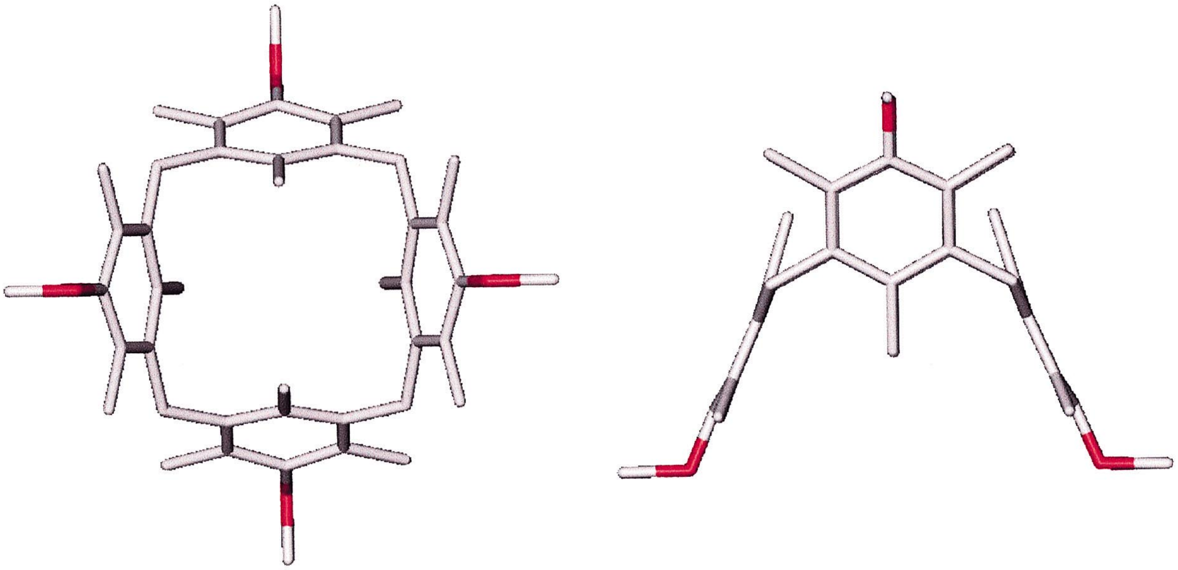


Figure 3. Top and side view of the calculated *1,3-alt* conformer of **3c**

[||] The comparison of the calculated global minimum of **3c** with the X-ray structure of **2** (Ref. 6) yielded an RMS value of 0.19 Å for all heavy atoms.

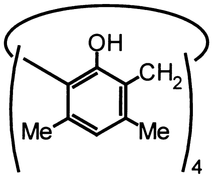
conformer. Due to the repulsions between the methyl groups both the calculated *cone* and *1,2-alt* conformers of **3c** deviate from their ideal symmetry (C_{4v} and C_{2h}, respectively) and adopt a lower symmetry (C_s and approximate C_2, respectively).

2.4.2. Topomerisation of *3b*

In the C_2-symmetrical *1,2-alt* form of **3c** pairs of distal rings are symmetry unequivalent. An *1,3-alt→paco→1,2-alt* process together with its reverse path (which possesses the same energy due to microscopic reversibility) will not result in topomerisation of **3b** since the rings which pass through the annulus in the forward process are *the same rings* which pass in the reverse pathway. To achieve topomerisation an additional step must be included which exchanges pairs of the symmetry unequivalent rings in the *1,2-alt* conformation. In this step severe methyl–methyl interactions between vicinal *syn* rings are introduced.

2.4.3. Rotational barriers

The rotational barriers for the ring inversion processes of **3c** were calculated by means of the coordinate driver procedure.[8] The lowest energy pathway which involves the stepwise rotation of the four aromatic rings through the macrocyclic annulus proceeds via the *paco* ($\Delta E^{\ddagger}_{1,3\text{-}alt \rightarrow paco} = 14.8$ kcal/mol) and *1,2-alt* conformations ($\Delta E^{\ddagger}_{paco \rightarrow 1,2\text{-}alt} = 25.7$ kcal/mol) while the pathway passing a *cone* intermediate ($\Delta E^{\ddagger}_{paco \rightarrow cone} = 33.3$ kcal/mol)[**] is higher in energy. The lower barrier for the *1,3-alt→paco* interconversion in comparison to *paco→1,2-alt* (or *paco→cone* inversion) is in agreement with the fact that the *exo*-methyl groups have not passed each other in the former step. The overall barrier calculated for the *1,3-alt→1,3-alt** interconversion of **3c** is higher than for **1c** ($\Delta E^{\ddagger} = 14.6$ kcal/mol) thus indicating the influence of the *exo*-methyl groups.



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The rotational barrier calculated for the *1,3-alt→1,3-alt** interconversion of **3c** (25.7 kcal/mol) is substantially higher than the experimental barrier determined for the *cone→cone** inversion of the octamethyl calix[4]arene **4** (10.7 kcal/mol).[10a] At first sight this is surprising, since both compounds are structurally related, both possessing eight *exo*-methyl groups. However, those barriers refer to two different processes. Calixarene **4** adopts a *flattened cone* conformation in which the two pairs of rings are symmetry unequivalent and the protons within each methylene group are diastereotopic. A *flattened cone→1,3-alt→flattened cone** pathway is sufficient to topomerise the rings and the methylene protons since, once the *1,3-alt* conformation is reached, all the rings (as well as all the methylene protons) become symmetry equivalent. Since, in this pathway the methyl groups on vicinal rings do not pass each other, the barrier is relatively low. The analogous process *1,3-alt→flattened cone→1,3-alt* will not result in topomerisation of the *1,3-alt* conformation of **3b**, and the process is NMR silent. Only a higher energy rotational pathway which involves rotation

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[**] All energy differences for the barriers are given with respect to the global energy minimum.

of all four rings through the annulus can be detected by NMR. Since this process requires that the methyl groups on vicinal rings pass each other, the overall barrier is higher

3. Conclusions

Calix[4]arenes with *endo*-methyl groups are conformationally flexible on the laboratory timescale.[9] The calculations suggest that in **3b** the NMR silent *1,3-alt→paco→1,3-alt* process should possess a relatively low barrier and therefore the compound cannot be viewed as completely rigid at the laboratory timescale. The high barrier found in **3b** for the *1,3-alt→1,3 alt** process is not due to its *endo*-methyl groups but most likely originates from the repulsive steric interactions involved with the rotational step in which the *exo*-methyl groups pass each other.

The strategy described here, to make enantiotopic protons or groups diastereotopic by the attachment of chiral groups may also be used in other cases to elucidate conformational problems in calixarene chemistry.

4. Experimental

^{1}H NMR spectra were recorded on Bruker AC200 (200 MHz) and Bruker Avance DRX 400 MHz spectrometers. Chemical shifts are reported as δ values in ppm relative to $(CH_3)_4Si$ as internal standard. FD-mass spectra were recorded on a Finnigan MAT 8230. $[\alpha]_D^{20}$ values were determined on JASCO DIP 360 Digital polarimeter in dichloromethane. Melting points are uncorrected. All compounds were structurally characterised by their ^{1}H NMR and mass spectra, their purity was additionally confirmed by TLC. The procedure for the preparation of intermediate products was published before.[12]

4.1. Molecular mechanics calculations

A conformational search was performed for **3c** with the stochastic search routine of the standard MM3(96) force field using the default parameters except for the number of pushes which was set to 10 000. The low-energy conformers of **1a** and **1c** obtained from previous calculations[8] were reoptimised with the MM3(96) force field. All possible rotational pathways for the *1,3-alt→1,3-alt** interconversion of **3c** were calculated forward and backward by means of the coordinate driver method. The stationary points along the reaction co-ordinates and the minima obtained from the stochastic search were refined using the full matrix Newton–Raphson minimisation algorithm and identified as energy minima or transition states by means of the eigenvalues of the Hessian matrix. The analysis and visualisation of the calculated structures was carried out using the SYBYL software.

4.2. Tetraether *3a*

The cyclophane **2** (0.2 g, 0.34 mmol) was dissolved under argon in dry DMF (6 mL), NaH (0.065 g, 2.7 mmol) was added, and the slurry was stirred for 30 min. Then (*S*)-(+)-1-bromo-2-methylbutane (0.334 mL, 2.7 mmol) was added dropwise and the stirring was continued for 7 days at room temperature. The excess of NaH was destroyed by the addition of methanol and the mixture evaporated to dryness. The resulting residue was dissolved in dichloromethane. The solution was washed three times with water, dried over sodium sulphate and evaporated. Crystallisation from chloroform/methanol afforded 0.155 g (52%) of pure **3a**; m.p. = 283–284°C; $[\alpha]_D^{20}$ = +8.7 (CH_2Cl_2); ^1H NMR 200 MHz ($CDCl_3$) δ (ppm) 3.89 (s, 8H, $ArCH_2Ar$), 3.52–3.33 (m, 8H, OCH_2), 2.30 (s, 24 H, $ArCH_3$), 1.98–1.76 (m, 4H, CH), 1.75–1.18 (m, 8H, CH_2), 1.09 (d, 12H, CH_3, J = 6.5 Hz), 1.07 (s, 12H, $ArCH_3$), 0.96 (t, 12H, CH_3, J = 7.3 Hz); MS (FD) m/z 873.7 (M^+).

4.3. Tetraamide 3b

A solution of the cyclophane tetraacid chloride (0.218 g, 0.243 mmol) in 15 mL dry THF was added dropwise under an argon atmosphere to a stirred solution of (*S*)-(–)-1-phenylethylamine (0.155 mL, 1.21 mmol) and triethylamine (0.150 mL, 1.07 mmol) in 35 mL of dry THF. After 12 h stirring the white precipitate was removed by filtration and the filtrate evaporated to dryness. The residue was dissolved in dichloromethane and washed with water (2×20 mL). After evaporation of solvent the crude product was crystallised first from cold methanol. Recrystallisation from chloroform/methanol finally afforded 0.23 g (77%) of pure **2b**; m.p. = 184–185°C; $[\alpha]_D^{20}$ = –4.7 (CH_2Cl_2); ^1H NMR 200 MHz ($CDCl_3$) δ (ppm) 7.47–7.13 (m, 24H, ArH and NH), 5.37–5.15 (m, 4H, CH), 4.15 (d, 4H, OCH_2, J = 15.4 Hz), 4.07 (d, 4H, OCH_2, J = 15.4 Hz), 3.87 (s, 8H, $ArCH_2Ar$), 2.26 (d, 24 H, $ArCH_3$, J = 6 Hz), 1.58 (d, 12H, CH_3, J = 6.9 Hz), 1.05 (s, 12H, $ArCH_3$); MS (FD) m/z 1238.1 (M^+).

Acknowledgements

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References

1. Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 713–745.
2. Gutsche, C. D. In *Monographs in Supramolecular Chemistry*; Stoddart, F., Ed. Calixarenes revisited. The Royal Society of Chemistry: Cambridge, 1998.
3. Gibbs, C. G.; Gutsche, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 5338–5339.
4. Delaigue, X.; Harrowfield, J. M.; Hosseini, M. W.; De Cian, A.; Fischer, J.; Kyritsakas, J. *J. Chem. Soc., Chem. Commun.* **1994**, 1579–1580.
5. Gibbs, C. G.; Sujeeth, P. K.; Rogers, J. S.; Stanley, J. S.; Krawiec, M.; Watson, W. H.; Gutsche, C. D. *J. Org. Chem.* **1995**, *60*, 8394–8402.
6. Pappalardo, S.; Ferguson, G.; Gallagher, J. F. *J. Org. Chem.* **1992**, *57*, 7102–7109.
7. For additional examples of calix[4]arenes bearing *endo*-methyl groups, see: (a) Wu, T. T.; Speas, J. R. *J. Org. Chem.* **1987**, *52*, 2330–2332. (b) Schätz, R.; Weber, C.; Schilling, G.; Öser, T.; Huber-Patz, U.; Irngartinger, H.; von der Lieth, C.-W.; Pipkorn, R. *Liebigs Ann.* **1995**, 1401–1408.
8. Thondorf, I.; Brenn, J. *J. Mol. Struct. (Theochem)* **1997**, *398/399*, 307–314.
9. Van Gelder, J. M.; Brenn, J.; Thondorf, I.; Biali, S. E. *J. Org. Chem.* **1997**, *62*, 3511–3519.
10. For additional examples of calixarene derivatives substituted in all *meta*-positions, see: (a) Dahan, E.; Biali, S. E. *J. Org. Chem.* **1991**, *56*, 7269–7274. (b) Mascal, M.; Naven, R. T.; Warmuth, R. *Tetrahedron Lett.* **1995**, *36*, 9361–9364.

11. For a discussion on averaged symmetry, see: Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; p. 91.
12. Mogck, O.; Parzuchowski, P.; Nissinen, M.; Böhmer, V.; Rokicki, G.; Rissanen, K. *Tetrahedron* **1998**, *54*, 10053–10068.
13. Gutowsky, H. S.; Holm, C. H. *J. Chem. Phys.* **1956**, *25*, 1228–1234.
14. Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551–8566.
15. Lii, J.-H.; Allinger, N. L. *J. Am. Chem. Soc.* **1989**, *111*, 8566–8575.
16. Lii, J.-H.; Allinger, N. L. *J. Am. Chem. Soc.* **1989**, *111*, 8576–8582.
17. MM3(96) is included in the SYBYL 6.5 program package (Tripos Ass., Inc., St. Louis, MO 63144).