Simple synthesis of calix[4]arenes in a 1,2-alternate conformation†

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The least accessible calix[4]arene conformers—1,2-alternates—can be very easily prepared using a proximal dialkylation and subsequent peralkylation reaction sequence.

Calixarenes[1] and their close relatives thiacalixarenes[2] represent extremely versatile host frameworks, as demonstrated by their mass applications in supramolecular chemistry. Probably, the most attractive feature of these macrocyclic compounds lies in the tuneable shape of their molecules—a property that is systematically used in the design and synthesis of novel receptors, and more sophisticated supramolecular systems. Thus, calix[4]arene can be immobilised in four basic conformations (atropoisomers) provided that R is equal to *n*-propyl or higher alkyl groups (Fig. 1).

Three of these four conformers are easily accessible on a multigram scale using stereoselective alkylation of the parent calix[4]arene. Hence, the chemistry of the cone, partial cone and 1,3-alternate conformers is now well established. On the other hand, 1,2-alternates have so far only been isolated in higher (albeit non-impressive) yields under special conditions, *e.g.* when using oligoethylene glycol ditosylates[3] for alkylation. Consequently, the chemistry of this conformation remains virtually unknown because of the lack of a suitable preparation methods.[4] In this Communication, we report on a surprisingly simple and general synthetic procedure leading stereoselectively to the 1,2-alternate conformation (Scheme 1), which opens the door for the application of this last ''missing'' calixarene conformer in supramolecular chemistry.

As direct alkylation of the parent calix[4]arenes didn't give the 1,2-alternate conformation in acceptable yields,[5] we chose the corresponding 25,26-dipropoxy derivative, **2**, as a suitable candidate for an alkylation study. The preparation of proximal dipropoxy derivative **2**, based on the alkylation of starting calixarene **1** with propyl bromide/NaOH in a DMSO–H_2O mixture, was recently published by Kalchenko *et al.*[6] Nevertheless, the original procedure did not work appropriately in our hands. After some improvements (extended reaction time from 4–6 h to 14–16 h and a higher amount of NaOH base), we finally succeeded in isolating **2** in 90% yield. Using our modification, product **2** is now available on a multigram scale (10 g) without the necessity for chromatographic purification.

Dipropoxy derivative **2** was then subjected to a subsequent alkylation procedure with propyl iodide/base/solvent (see Table 1) to achieve the synthesis of 1,2-alternate tetrapropoxy calixarene **3**. Theoretically, the alkylation of **2** can lead to the formation of three different conformers: cone, 1,2-alternate and partial cone. As the signals of all of these conformations are nicely separated in the aromatic part of ^{1}H NMR spectra (Fig. 2), ^{1}H NMR analysis of the crude reaction mixtures was used throughout our study as very simple analytical tool. A preliminary screening (small scale reaction—50 mg) using various alkylation conditions commonly applied in calixarene chemistry showed that neither hydride (NaH) nor carbonates (Cs_2CO_3, K_2CO_3) gave the corresponding conformer. Hence, using potassium carbonate as a weak base (Table 1, runs 4–6) led to complicated reaction mixtures, variously containing unreacted **2**, and partly and fully alkylated products, where 25,26,27-tripropoxycalix[4]arene (cone) was identified as the main product.

Similar results were obtained with caesium carbonate in DMF or acetone (Table 1, runs 1 and 2), while the alkylation in acetonitrile gave the unwanted partial cone conformer (Table 1, run 3) in a highly stereoselective manner (86% partial cone, 13% cone, 1% 1,2-alternate).

The alkylation of **2**, carried out using the *n*-PrI/NaH/DMF system, led exclusively to the corresponding cone conformation (Table 1, run 7). On the other hand, identical reaction conditions using KH (Table 1, run 8) instead of NaH gave quite a promising conformational outcome, with a significant content of the desired conformation (22 : 44 : 34 = cone/partial cone/1,2-alternate), indicating the importance of the potassium cation. A similar trend in the conformer

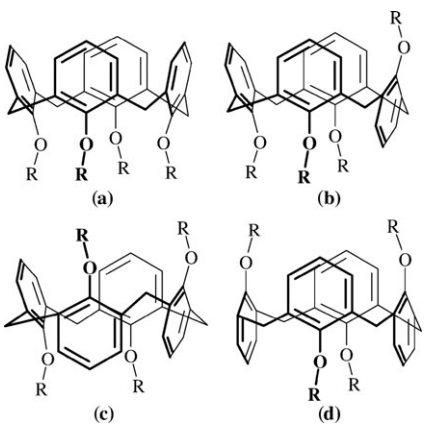

Fig. 1 The four basic conformations of calix[4]arene: (a) cone, (b) partial cone, (c) 1,2-alternate and (d) 1,3-alternate.

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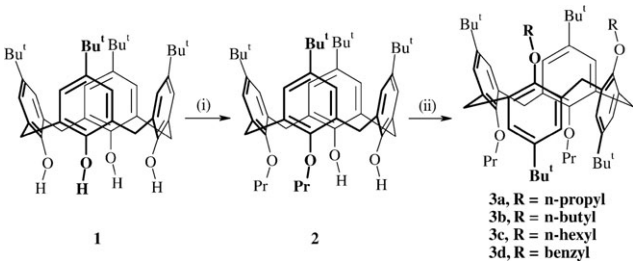

Scheme 1 Synthesis of calix[4]arene in the 1,2-alternate conformation: (i) PrBr/NaOH, DMSO–H_2O, 75 °C, overnight (90%); (ii) for reaction conditions, see Table 1.

distribution was found using the *t*-BuOK/toluene system (Table 1, run 9). Finally, the application of bulky potassium salts Me_3SiOK or KHMDS led to very high contents of 1,2-alternates in the reaction mixtures. The best results were achieved using PrI/KHMDS in THF at room temperature (Table 1, run 12), where the desired conformer **3a** formed in a surprisingly high ratio—cone/partial cone/1,2-alternate = 1 : 17 : 82.

To check the general applicability of these reaction conditions, we have carried out similar alkylations using other alkylation agents, such as butyl iodide (Table 1, run 13), hexyl iodide (Table 1, run 14) and benzyl bromide (Table 1, run 15). In all cases, very high conformational outcomes of the corresponding 1,2-alternates **3b–3d** were obtained (around 80%).

Based on these preliminary results, we have attempted to scale-up the procedure to synthetically interesting values. Hence, starting from 200–500 mg of **2**, the corresponding 1,2-alternates **3b–3d** were obtained in 55, 68 and 54% yields (after column chromatography), respectively. As KHMDS is a relatively expensive agent, we attempted a bigger-scale reaction‡ (5.0 g of **2**) using cheaper Me_3SiOK as the base. The resulting tetrapropoxy derivative, **3a**, was smoothly isolated in 65% yield after column chromatography, providing multigram scale accessibility to the 1,2-alternates using our method.§

Table 1 Alkylation of derivative **2** with propyl iodide

	Reaction conditions[a]				Conformer distribution		
Run	Base	Solvent	Temp./°C	Time/h	Cone	Paco	1,2-
1	Cs_2CO_3	DMF	90	140		[b,f]	
2	Cs_2CO_3	Acetone	Reflux	160		[b,f]	
3	Cs_2CO_3	MeCN	Reflux	16	13	86	1
4	K_2CO_3	DMF	90	160		[b,f]	
5	K_2CO_3	Acetone	Reflux	160		[b,f]	
6	K_2CO_3	MeCN	Reflux	16		[b]	
7	NaH	DMF	90	160	100	0	0
8	KH	DMF	90	140	22	44	34
9	*t*-BuOK	Toluene	110	16	11	62	27
10	Me_3SiOK	THF	r.t.	140	3	29	68
11	Me_3SiOK	THF	Reflux	160	4	25	71
12	KHMDS	THF	r.t.	160	1	17	82
13	KHMDS	THF	r.t.	160	7	15	78[c]
14	KHMDS	THF	r.t.	160	2	18	80[d]
15	KHMDS	THF	r.t.	160	4	18	78[e]

[a] Five equivalents of base and alkylation agent were used. [b] Complex reaction mixture of starting compounds, and partly and fully alkylated derivatives. [c] Butyl iodide used for alkylation. [d] Hexyl iodide used for alkylation. [e] Benzyl bromide used for alkylation. [f] 25,26,27-Tripropoxycalix[4]arene (cone) isolated as the main product.

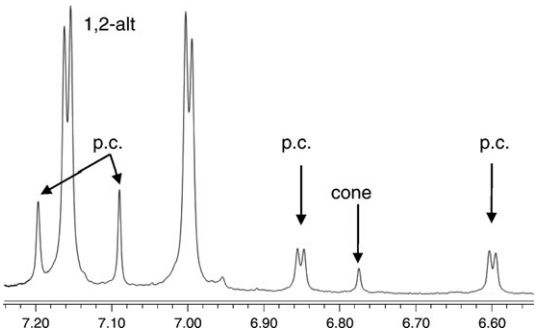

Fig. 2 ^1H NMR spectrum (aromatic part) of the crude reaction mixture showing three conformations of tetrapropoxycalixarene (1,2-alt = 1,2-alternate, p.c. = partial cone and cone = cone).

The structures of compounds **3a–3d** were confirmed by $^1H/^{13}C$ NMR spectroscopy. Thus, tetrapropoxy derivative **3a** exhibits for its methylene bridges two doublets (δ 3.10 and 4.18), with a typical geminal coupling constant J = 12 Hz, and one singlet at δ 3.86, exactly in accordance with the proposed 1,2-alternate structure. On the other hand, compounds **3b–3d** show much more complex splitting patterns in the methylene bridge region, reflecting the lower symmetry of the system. Thus, derivative **3c** exhibits 2 × 2 doublets (J = 12 Hz) for equatorial (δ 3.09 and 3.11) and axial (δ 4.14 and 4.18)

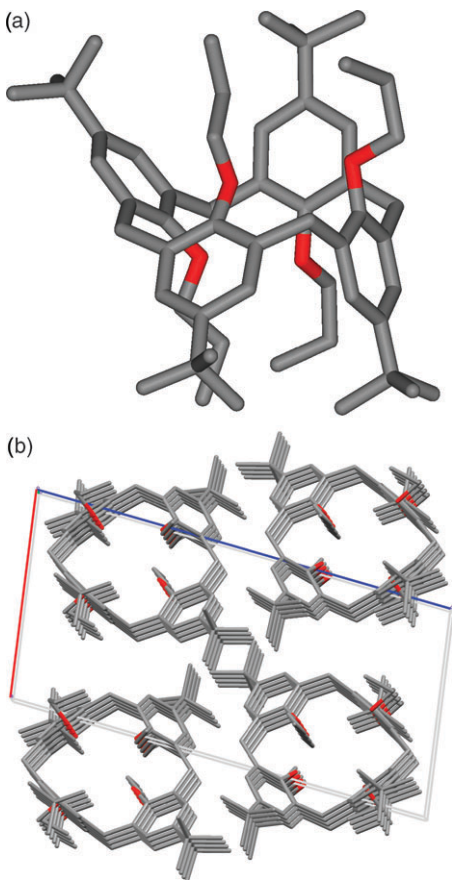

Fig. 3 (a) Solid-state structure of **3a**, as determined by single-crystal X-ray diffraction. Hydrogen atoms are omitted for clarity. (b) Molecular packing of **3a**, as determined by single-crystal X-ray diffraction. Hydrogen atoms and propyl groups are omitted for clarity.

protons of the $-CH_2-$ bridges in the "conical" part of structure, and one broad singlet (δ 3.86) for the remaining methylene bridges in the "alternate" fragment of the molecule.

Final proof of the structures of **3a** and **3d** were obtained by X-ray crystallography.¶ Suitable single crystals were grown by the slow evaporation of a methanol/$CHCl_3$ solution. The asymmetric unit contains one molecule of **3a** in the 1,2-alternate conformation (Fig. 3). All of the propoxy chains are disordered over two or even three positions—a typical phenomenon well known in the chemistry of alkyl-substituted calixarenes. One of the propoxy chains on each side of the molecule is oriented slightly into the cavity of the calixarene (with distances of 4.4 and 4.7 Å between the central CH_2 group and the opposite phenyl ring), while the other propyl group remains outside. Crystal packing of **3a** leads to the infinite channels along the b-axis, with the shortest distance between neighbouring channels being 3.8 Å (Fig. 3b).

In conclusion, calix[4]arenes immobilised in the 1,2-alternate conformation can be easily prepared on a multigram scale using a sequential dialkylation/dialkylation procedure. This opens the door to further development of the chemistry of this last "missing" calix[4]arene conformation, and finally, for its possible applications in supramolecular chemistry.

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Notes and references

‡ *Synthesis and characterization of* **3a**: Potassium trimethylsilanolate (4.36 g, 34.0 mmol, 5 equiv.) was added to a stirred solution of **2** (5.0 g, 6.8 mmol) in 300 ml of dry THF and the reaction mixture stirred at room temperature. After 30 min, 3.32 ml (5.78 g, 34.0 mmol, 5 equiv.) of propyl iodide was added and the reaction mixture stirred at room temperature for 6 d. The reaction mixture was then poured into 250 ml of 10% aqueous HCl and solution was extracted with 4 × 40 ml of DCM. The organic layers were combined, washed subsequently with 50 ml of a saturated solution of Na_2SO_3 and 50 ml of water, and dried over $MgSO_4$. The solvents were evaporated to dryness and the crude product was purified by column chromatography on silica gel using a DCM : petroleum ether 1 : 10 (v/v) mixture as the eluent to give **3a** (3.60 g, 65 %) as a white powder. mp 280–284 °C (lit.[5a] 279–280 °C). ^{1}H NMR (300 MHz, $CDCl_3$, 296 K) δ 0.59 (t, 12H, J = 7.4 Hz, $-CH_3$), 0.86–0.91 (m, 8H, $-CH_2-$), 1.30 (s, 36H, Bu), 3.10 (d, 2H, $-CH_2-$, J = 12.4 Hz), 3.24–3.40 (m, 8H, $-OCH_2$), 3.86 (s, 4H, $-CH_2-$), 4.18 (d, 2H, J = 12.1 Hz, $-CH_2-$), 7.01 (d, 4H, J = 2.2 Hz, Ar-H) and 7.14 (d, 4 H, J = 2.2 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, 296 K) δ 10.02, 22.32, 29.19, 31.65, 33.94, 39.20, 74.33, 125.28, 125.66, 132.00, 133.79, 143.72 and 154.14; IR (KBr) ν_{max} (cm^{-1}): 2960 (vs), 2873 (m), 1472 (m), 1210 (m); TOF-MS ESI$^+$ required 816.6 for $C_{56}H_{80}O_4$, found 839.7 $[M + Na]^+$ (100%).

§ Our attempts at reaction time optimisation revealed that in small scale experiments (50 mg), the reaction using Me_3SiOK completed in 2 d, while KHMDS needed 4 d stirring at room temperature. At synthetic multigram scales, we recommend a longer reaction time of 5 d.

¶ *X-Ray data for* **3a**: $C_{56}H_{80}O_4$, M = 817.20 g mol^{-1}, triclinic, space group P-1, a = 9.771(4), b = 13.056(5), c = 20.194(10) Å, α = 79.31(4), β = 80.22(5), γ = 84.12(5)°, Z = 2, V = 2488.0(19) Å^3, D_c = 1.091 g cm^{-3}, μ(Cu-K$_\alpha$) = 0.506 mm^{-1}, crystal dimensions 0.06 × 0.18 × 0.32 mm. Data were collected at 150(2) K on an Xcalibur PX diffractometer with graphite monochromated Cu-K$_\alpha$ radiation. The structure was solved by direct methods[7] using the SHELX suite of programs[8] and anisotropically refined by full-matrix least-squares on F^2 values to give final R = 0.1125 and wR = 0.3084 using 9889 independent reflections (θ_{max} = 77.92°) and 615 parameters. The positions of disordered groups were found from the electron density maps. Disordered fragments were then placed in appropriate positions, and all distances between neighbouring atoms and angles were fixed. Site occupancies were refined for the different parts, with the same thermal parameters being used for atoms within each of the various fragments. At the end of the refinement, site occupancies were fixed and the hydrogen atoms were placed in calculated positions.

X-ray data for **3d**: $C_{64}H_{77}O_4$, M = 910.26 g mol^{-1}, monoclinic system, space group $P21/c$, a = 14.957(2), b = 20.196(2), c = 19.100(2) Å, β = 106.679(9)°, Z = 4, V = 5526.6(9) Å^3, D_c = 1.097 g cm^{-3}, μ(Cu-K$_\alpha$) = 0.509 mm^{-1}, crystal dimensions of 0.06 × 0.15 × 0.28 mm. Data were collected at 150(2) K on a Xcalibur PX diffractometer with graphite monochromated Cu-K$_\alpha$ radiation. The structure was solved by direct methods[7] using the SHELX suite of programs[8] and anisotropically refined by full-matrix least-squares on F^2 values to final R = 0.0807 and wR = 0.2212 using 11474 independent reflections (θ_{max} = 76.66°) and 603 parameters. The positions of disordered groups were found from the electron density maps. Disordered fragments were then placed in appropriate positions, and all distances between neighbouring atoms and angles were fixed. Site occupancies were refined for the different parts with the same thermal parameters for the same atoms in the various fragments. At the end of refinement, site occupancies were fixed and hydrogen atoms were placed in calculated positions.

CCDC 666975 and 666976. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b718278c

1 For books on calixarenes, see: (*a*) *Calixarenes 2001*, ed. Z. Asfari, V. Böhmer, J. Harrowfield and J. Vicens, Kluwer Academic Publishers, Dordrecht, 2001; (*b*) *Calixarenes in Action*, ed. L. Mandolini and R. Ungaro, Imperial College Press, London, 2000; (*c*) C. D. Gutsche, Calixarenes Revisited, , in *Monographs in Supramolecular Chemistry*, ed. J. F. Stoddart, Royal Society of Chemistry, Cambridge, 1998, vol. **6**.

2 For recent reviews on thiacalixarenes, see: (*a*) N. Iki and S. Miyano, *J. Inclusion Phenom. Macrocyclic Chem.*, 2001, **41**, 99; (*b*) P. Lhoták, *Eur. J. Org. Chem.*, 2004, 1675.

3 (*a*) G. Ferguson, A. J. Lough, A. Notti, S. Pappalardo, M. F. Parisi and A. Petringa, *J. Org. Chem.*, 1998, **63**, 9703; (*b*) A. Arduini, L. Domiano, A. Secchi, R. Ungaro, F. Ugozzoli, O. Struck, W. Verboom and D. N. Reinhoudt, *Tetrahedron*, **53**, 3767; (*c*) S. Pappalardo, A. Petringa, M. F. Parisi and G. Ferguson, *Tetrahedron Lett.*, **37**, 3907.

4 A multi-step synthesis leading to tetrapropoxycalix[4]arene (1,2-alternate in low overall yield) consisting of (i) distal dibenzylation, (ii) distal dipropylation, (iii) deprotection of benzyl groups and (iv) distal dipropylation has been described. See: P. J. Kenis, O. F. Noordman, S. Houbrechts, G. J. van Hummel, S. Harkema, F. C. J. M. van Veggel, K. Clays, J. F. J. Engbersen, A. Persoons, N. F. van Hulst and D. N. Reinhoudt, *J. Am. Chem. Soc.*, 1998, **120**, 7875–7883.

5 (*a*) K. Iwamoto, K. Fujimoto, T. Matsuda and S. Shinkai, *Tetrahedron Lett.*, 1990, **31**, 7169; (*b*) K. Iwamoto, K. Araki and S. Shinkai, *J. Org. Chem.*, 1991, **56**, 4955; (*c*) K. Iwamoto, K. Araki and S. Shinkai, *Tetrahedron*, 1991, **47**, 4325.

6 V. I. Boyko, A. A. Podoprigorina, A. V. Yakovenko, V. V. Pirozhenko and V. I. Kalchenko, *J. Inclusion Phenom. Macrocyclic Chem.*, 2004, **50**, 193.

7 A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori and R. Spagna, *J. Appl. Crystallogr.*, 1999, **32**, 115.

8 (*a*) G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Crystallogr.*, 1990, **46**, 467; (*b*) G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Crystallogr.*, 1993, **49**, C53.