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Stereoselective alkylation of thiacalix[4]arenes

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Abstract—A direct tetraalkylation of thiacalix[4]arenes using procedures well established in 'classical' calixarene chemistry usually gives the *1,3-alternate* conformers as the main product (*n*-PrI/K_2CO_3/acetone) while the *cone* conformers are obtained only in very poor yields (*n*-PrI/NaH/DMF). Surprisingly, the so far almost inaccessible *cone* conformers can be prepared in high yields using the two-step procedure: dialkylation–dialkylation, opening the way for their further utilisation in supramolecular chemistry.

Thiacalix[4]arenes **1a**,**b** have emerged recently as novel members of the calix[*n*]arene[1] family. Despite the fact that they are easily accessible on multi-gram scale,[2] the utilisation of thiacalixarenes in supramolecular chemistry is still rather restricted because of the lack of general derivatisation methods allowing regio- and/or stereoselective transformations of the molecule.

There are numerous examples[3] in the recent literature demonstrating that the presence of four sulfur atoms imparts the system with many novel features when compared with 'classical' calixarenes. Thus, it was shown that the tetraalkylation of **1a** and **1b** with ethyl bromoacetate using the acetone/M_2CO_3 reaction system (M = Na, K and Cs) exhibits a pronounced template effect.[4] This reaction smoothly leads to high yields (>60%) of the corresponding tetraacetates in three different conformations (*cone*, *partial cone*, *1,3-alternate*) depending on the cation used. On the other hand, alkylations with simple alkyl halides under conditions well established in calix[4]arene chemistry did not give the same conformational outcomes.[5] The conformer distribution of the products clearly reflects significantly different behaviour and conformational preferences[6] of thiacalixarenes **1a** and **1b** compared to 'classical' calix[4]arenes.

One of the main drawbacks of thiacalixarene chemistry so far is the fact that the *cone* conformers, which are potentially the most interesting for many applications in supramolecular chemistry, are generally inaccessible by direct alkylation procedures.[7] Unfortunately, the above mentioned tetraester derivative excludes the use of common organometallic reagents, which partly hinders its utilisation in subsequent chemical transformations. Consequently, we have carried out a systematic study on the tetraalkylation of thiacalix[4]arenes using alkyl halides, which are bulky enough to immobilise the product in a specific conformation. In this paper we report a surprisingly simple synthetic method leading stereoselectively to the *cone* conformation, opening the door for its further utilisation.

In our previous study[8] we have shown that the direct alkylation of **1b** using the *n*-PrI/NaH/DMF system (conditions known to yield almost exclusively the *cone* conformation in calix[4]arenes) gives only a mixture of *cone* and *1,3-alternate* conformers (53:47) in low overall yield (31%). Similarly, the use of KH as a base led to an even more complex mixture *cone*/*partial cone*/*1,3-alternate* = 6/67/27 in 36% yield. During our ongoing research in thiacalixarene derivatisation we found a surprising phenomenon, which is unprecedented in classical calixarene chemistry. When distally dipropoxylated thiacalixarene **2b** is used as a starting point for a subsequent alkylation the stereochemical outcomes of alkylation are completely different when compared with direct tetraalkylation of **1b**. In other words, direct alkylation gave much lower yields than the corresponding repeated dialkylation/dialkylation process (Scheme 1).

Hence, the alkylation[9] of **2b**, carried out using the *n*-PrI/NaH/DMF system, leads to the corresponding *cone* **3b** (72% yield) accompanied by a smaller amount of *partial*

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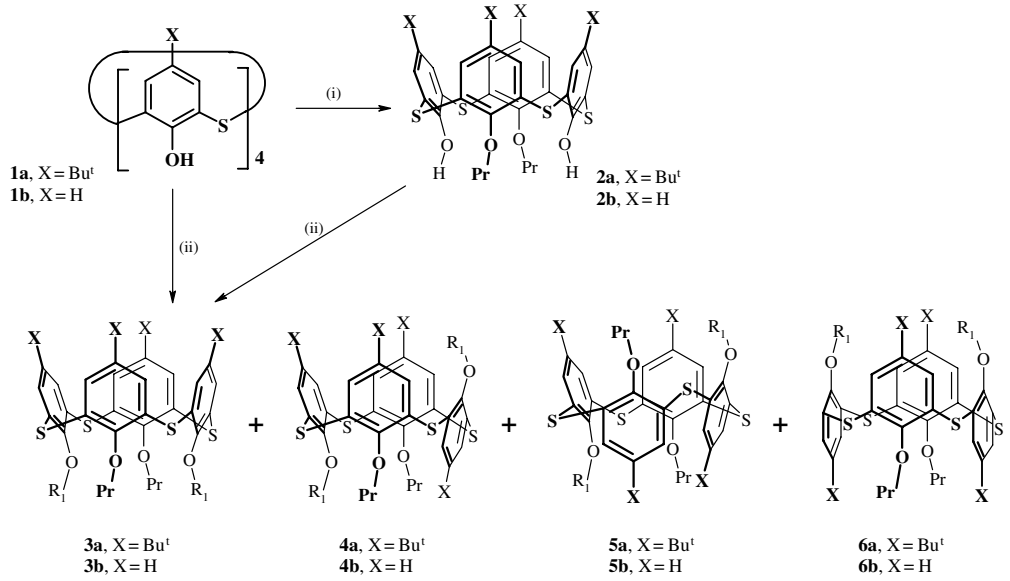

Scheme 1. Reagents and conditions: (i) *n*-PrI, K_2CO_3/acetone, or *n*-PrI/TBAB/NaOH, toluene/water (50–55%); (ii) for the alkylation conditions see Table 1.

cone **4b** (21%). Similar results were also obtained with other alkylating agents (Table 1). Thus, the alkylation of **2b** with *n*-butyl bromide under identical reaction conditions (room temp, 2 days) gave the corresponding tetraalkylated derivatives $\mathbf{3b_{Bu}}$ and $\mathbf{4b_{Bu}}$ in 70/30 ratio (*cone*/*partial cone*). The highest selectivity towards the *cone* conformation was achieved using benzyl bromide with 87/13 ratio of $\mathbf{3b_{Bn}}$ and $\mathbf{4b_{Bn}}$. On the other hand, the reaction mixture obtained with potassium hydride as a base did not show the presence of the *cone* conformation and the *partial cone* **4b** and *1,3-alternate* **6b** were formed as the main products in 41/59 ratio.

Interestingly, the presence of *tert*-butyl groups on the upper rim had dramatic consequences on the conformational outcome. As follows from Table 1, the two-step alkylation procedure does not operate for **2a** and in this case only a mixture of the *partial cone* **4a** and the *1,3-alternate* **6a** were obtained. To the best of our knowledge, such a profound influence of the upper rim substitution on the alkylation of the lower rim has never been observed.

Starting dialkylated thiacalixarenes **2a** and **2b** were obtained in approximately 50% yields either by alkylation of **1a**,**b** with *n*-propyl iodide in the presence of K_2CO_3 as a base (Method A)[10] or preferentially, by the alkylation under phase transfer catalysis (Method B).[11] While the former method uses column chromatography or crystallization to obtain pure products, the latter one is very simple and scalable for multi-gram scale preparation. It is noteworthy that thiacalixarenes **1a**,**b** again possess different reactivity compared to the 'classical' calix[4]arenes, which gave tetraalkylated compounds as the main products under otherwise identical conditions.[12]

The structures of the products were confirmed by ^{1}H NMR spectroscopy and in the case of the tetrapropoxy derivatives **3b**–**6b** also by direct comparison with original samples prepared previously.[13] Interesting conformational behaviour was found in case of the *cone* conformers **3b**, $\mathbf{3b_{Bu}}$ and $\mathbf{3b_{Bn}}$. The ^{1}H NMR spectra at 293 K ($CDCl_3$) are heavily diffused and some signals had even almost disappeared at 273 K. On the other hand, these signals appeared again at lower temperatures (243 K) with doubled multiplicity. This indicated an additional dynamic process ascribed to the *pinched cone–pinched cone* interconversion between two identical conformers possessing lower C_{2v} symmetry. Such behaviour has been already described as an intrinsic and characteristic feature[14] of all known thiacalix[4]arene derivatives possessing the *cone* conformation.

Moreover, the final proof of structures **3b**, **4b** and **6b** was by X-ray crystallography.[15] Suitable single crystals were grown by slow evaporation of an ethyl acetate/

Table 1. Alkylation of thiacalix[4]arenes using the *n*-PrI/NaH/DMF system

Starting compd	Overall yield	Relative ratio of conformers (%)			
		3	**4**	**5**	**6**
1a[b]	27	—	24	32	44
1a[a,b]	70	—	—	30	70
1b[b]	35	53	47	—	—
1b[a,b]	37	6	67	—	27
2a	85	—	30	—	70
2a[a]	30	—	45	—	55
2b	94	77	23	—	—
2b[a]	61	—	41	—	59
2b[c]	85	70[e]	30[e]	—	—
2b[d]	87	87[f]	13[f]	—	—

[a] KH used as base instead of NaH.
[b] From Ref. 13.
[c] *n*-Butyl bromide used for the second alkylation.
[d] Benzyl bromide used for the second alkylation.
[e] 25,27-Dipropoxy-26,28-dibutyloxy derivatives $\mathbf{3b'_{Bu}}$, $\mathbf{4b'_{Bu}}$.
[f] 25,27-Dipropoxy-26,28-dibenzyloxy derivatives $\mathbf{3b''_{Bn}}$, $\mathbf{4b''_{Bn}}$.

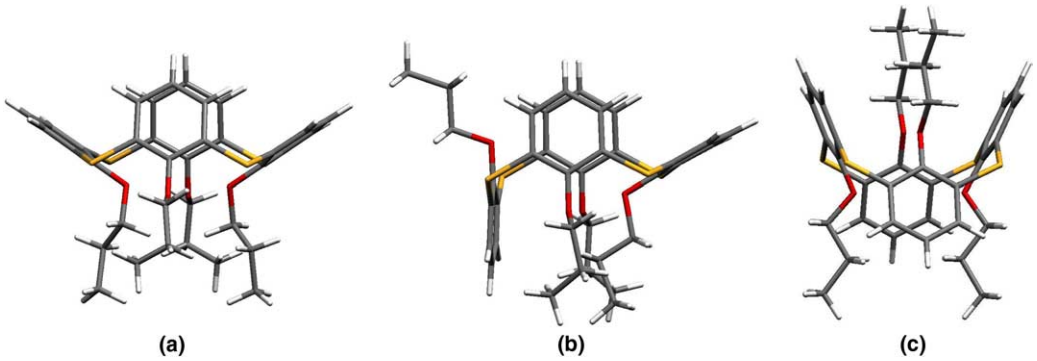

Figure 1. (a) Crystal structures of **3b** (*cone*); (b) crystal structure of **4b** (partial cone); (c) crystal structure of **6b** (*1,3-alternate*).

$CHCl_3$ solution and the corresponding crystal structures are shown in Figure 1.

In conclusion, we have shown that thiacalix[4]arenes provide surprisingly different conformational outcomes from alkylation reactions when compared with classical calix[4]arenes. While the *cone* conformers bearing four simple alkyl groups on the lower rim are almost inaccessible by direct alkylation of the thiacalixarenes **1a**,**b**, the two-step dialkylation/dialkylation procedure leads smoothly to the *cone* conformers in high yields. Synthetic procedures leading selectively to other conformers are currently under investigation.

Acknowledgements

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9. Alkylation—general procedure: A mixture of **1** or **2** (0.15 mmol), NaH or KH (0.9 mmol) and propyl iodide (2 mmol) was stirred at rt in 6 mL of anhydrous DMF for 24 h. The reaction mixture was than carefully neutralised with diluted hydrochloric acid and extracted with chloroform. The organic layer was washed with water, dried over $MgSO_4$ and evaporated to dryness. The semi-solid residue was purified by column chromatography on silica gel using petroleum ether/chloroform (gradient from 10:1 to 5:1) as eluent or using preparative TLC on silica gel. Isolated yields of the corresponding conformers are collected in Table 1.
Compounds **3b**, **4b**, **5b** and **6b** were identical with samples previously prepared.[13]
5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrapropoxy-thiacalix[4]arene (*1,3-alternate*) **6a**. Mp: >350 °C ($CHCl_3$/ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.6 (t, 12H, –CH_2–CH_3, J = 7.7 Hz), 1.00 (m, 8H, –CH_2–CH_3), 1.25 (s, 36H, Bu^t), 3.79 (t, 8H, O–CH_2–, J = 7.7 Hz), 7.3 (s, 8H, H-arom). EA calcd for $C_{52}H_{72}O_4S_4$: C, 70.22; H, 8.16; S, 14.42. Found C, 70.76; H, 8.37; S, 14.96.
5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrapropoxy-thiacalix[4]arene (*partial cone*) **4a**. Mp: 227–230 °C (acetone). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.6 (t, 3H, –CH_2–CH_3, J = 7.4 Hz), 0.7 (t, 3H, –CH_2–CH_3, J = 7.5 Hz), 1.02–1.12 (m, 24H, Bu^t + CH_3), 1.32 (s, 9H, Bu^t), 1.38 (s, 9H, Bu^t), 1.42–1.56 (m, 2H, –CH_2–CH_3), 1.7–1.96 (m, 6H, –CH_2–CH_3), 3.64–3.86 (m, 4H, –O–CH_2–), 3.86–4.1 (m, 4H, –O–CH_2–), 7.08 (d, 2H, H-arom, J = 2.6 Hz), 7.41 (d, 2H, H-arom, J = 2.6 Hz), 7.61 (s, 2H, H-arom), 7.68 (s, 2H, H-arom). EA calcd for $C_{52}H_{72}O_4S_4$: C, 70.22; H, 8.16; S, 14.42. Found C, 70.52; H, 8.29; S, 14.76.
25,27-Dibutoxy-26,28-dipropoxythiacalix[4]arene (*cone*) **3b$_{Bu}$**. Mp: 188–190 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$,

300 MHz) δ (ppm): 0.97 (m, 12H), 1.48 (br s, 4H), 1.85 (m, 8H), 4.08 (br s, 8H), 6.2–7.6 (very br s, 12H, H-arom). EA calcd for $C_{38}H_{44}O_4S_4$: C, 65.86; H, 6.40. Found C, 65.51; H, 6.33.

25,27-Dibutoxy-26,28-dipropoxythiacalix[4]arene (*partial cone*) **4b$_{Bu}$**. Mp: 232–224 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.8–2.2 (m, 24H), 3.62 (m, 4H), 4.15 (m, 4H), 6.53 (t, 2H, H-arom, J = 7.6 Hz), 6.73 (d, 2H, H-arom, J = 7.6 Hz), 6.91 (t, 2H, H-arom, J = 7.6 Hz), 7.53 (d, 4H, H-arom, J = 7.6 Hz), 7.68 (d, 2H, H-arom, J = 7.6 Hz). EA calcd for $C_{38}H_{44}O_4S_4$: C, 65.86; H, 6.40. Found C, 65.71; H, 6.65.

25,27-Dibenzyloxy-26,28-dipropoxythiacalix[4]arene (*cone*) **3b$_{Bn}$**. Mp: 197–199 °C (acetone). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.96 (br s, 6H, –CH_3), 1.87 (br s, 4H, –CH_2–CH_3), 4.06 (br s, 4H, –O–CH_2–), 5.28 (br s, 4H, –CH_2–Ph), 6.4–7.6 (br s, d, 22H, H-arom). EA calcd for $C_{44}H_{40}O_4S_4$: C, 69.44; H, 5.30. Found C, 69.11; H, 5.05.

25,27-Dibenzyloxy-26,28-dipropoxythiacalix[4]arene (*partial cone*) **4b$_{Bn}$**. Mp: 220–222 °C (acetone). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.6–2.2 (m, 10H), 3.79 (m, 2H), 4.01 (m, 2H), 4.64 (s, 2H, –CH_2–Ph), 5.26 (s, 2H, –CH_2–Ph), 6.3–8.0 (m, 22H, H-arom). EA calcd for $C_{44}H_{40}O_4S_4$: C, 69.44; H, 5.30. Found C, 69.19; H, 5.21.

10. Dialkylation of thiacalixarene, Method A: To a suspension of thiacalix[4]arene **1b** (2 g, 4.026 mmol) and K_2CO_3 (0.612 g, 4.429 mmol) in dry acetone (50 mL) was added propyl iodide (7.2 mL, 0.024 mol). The reaction mixture was refluxed for 72 h and then allowed to cool to room temperature. After evaporation of the solvent with a rotary evaporator, the mixture was taken up in $CHCl_3$ (50 mL) and washed with 1 M HCl solution (50 mL) and with brine (50 mL). The organic layer was dried over $MgSO_4$, and the solvent was evaporated. Column chromatography on silica gel using petrol ether/$CHCl_3$ 3:1 mixture gave pure 25,27-dipropoxythiacalix[4]arene **2b** (1.24 g, 53%) as white crystals. Mp: 259–241 °C (acetone). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.15 (t, 6H, –CH_2–CH_2–CH_3, J = 7.4 Hz), 2.0–2.2 (m, 4H, –CH_2–CH_2–CH_3), 4.32 (t, 4H, –CH_2–CH_2–CH_3, J = 6.6 Hz), 6.5 (t, 2H, H-arom, J = 7.7 Hz), 6.81 (t, 2H, H-arom, J = 7.7 Hz), 6.86 (d, 4H, H-arom, J = 7.7 Hz), 7.44 (s, 2H, –OH), 7.62 (d, 4H, H-arom, J = 7.7 Hz). EA calcd for $C_{30}H_{28}O_4S_4$: C, 62.04; H, 4.86; S, 22.08. Found C, 61.98; H, 5.11; S, 21.54. IR ($CHCl_3$): 3391.6 cm^{-1} ν(OH).
11. Method B: A mixture of the starting thiacalix[4]arene **1b** (1 mmol), aqueous NaOH 50% w/w (1 mL), propyl iodide (10 mmol) and tetrabutylammonium bromide (0.03 g, 0.1 mmol) in toluene (25 mL) were stirred at 90–100 °C for 15 h. After cooling, water (10 mL) was added and the phases were separated. The organic layer was washed with dilute aqueous HCl (20 mL) and water (2 × 20 mL). The organic layer was dried over $MgSO_4$. The solvent was removed under a reduced pressure and the residue was reprecipitated from $CHCl_3$–MeOH mixture to yield **2b** as a white powder (48% yield). Product was identical with compound obtained by method A.
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15. X-ray crystallography: Data were collected at 293 K on an Enraf-Nonius CAD4 diffractometer with graphite monochromated Cu Kα radiation. The structures were solved by direct methods.[16]

X-ray data for **3b**: $C_{36}H_{40}O_4S_4$, M = 664.95 g/mol, monoclinic system, space group $C2/c$, a = 21.740(2), b = 9.423(2), c = 19.057(2) Å, β = 112.39(1)°, Z = 4, V = 3610(1) Å^3, D_c = 1.22 g cm^{-3}, μ(Cu Kα) = 27.0 mm^{-1}, crystal dimensions of 0.2 × 0.3 × 0.3 mm. The whole structure was refined anisotropically by full matrix least-squares on F values[17] to final R = 0.1112 and R_w = 0.1042 using 2186 independent reflections (θ_{max} = 68°). Hydrogen atoms were located from expected geometry and were not refined. ψ-Scan was used for absorption correction. Crystallographic data were deposited in CSD under CCDC registration number 216679.

X-ray data for **4b**: $C_{36}H_{40}O_4S_4$, M = 664.95 g/mol, orthorhombic system, space group $Pcab$, a = 15.714(2), b = 17.046(2), c = 25.986(2) Å, Z = 8, V = 6961(1) Å^3, D_c = 1.27 g cm^{-3}, μ(Cu Kα) = 28.0 mm^{-1}, crystal dimensions of 0.3 × 0.4 × 0.4 mm. The whole structure was refined anisotropically by full matrix least-squares on F values[17] to final R = 0.0756 and R_w = 0.0699 using 3943 independent reflections (θ_{max} = 68°). Hydrogen atoms were located from expected geometry and were not refined. Crystallographic data were deposited in CSD under CCDC registration number 245374.

X-ray data for **6b**: $C_{36}H_{40}O_4S_4$, M = 664.95 g/mol, orthorhombic system, space group $Pcnb$, a = 10.961 (1), b = 17.723(1), c = 18.229(1) Å, Z = 4, V = 3541.2(4) Å^3, D_c = 1.25 g cm^{-3},μ(Cu Kα) = 27.5 mm^{-1}, crystal dimensions of 0.4 × 0.6 × 0.6 mm. The whole structure was refined anisotropically by full matrix least-squares on F values[17] to final R = 0.0651 and R_w = 0.0498 using 2184 independent reflections (θ_{max} = 68°). Hydrogen atoms were located from expected geometry and were not refined. ψ-Scan was used for absorption correction. Crystallographic data were deposited in CSD under CCDC registration number 216680.
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