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## Metal Ion Control of Stereochemistry in the Acetylation of Calix[4]arene 1,3-diethers

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1,3-Dialkoxycalix[4]arenes **1–3** in Et<sub>2</sub>O give diacetylated derivatives in the fixed cone conformation with AcCl/NaH, whereas the stereoisomeric compounds in the partial cone structure are produced in high yield using AcCl/EtOTf.

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The recently reported observation of Shinkai *et al.*<sup>1</sup> of a remarkable metal template effect in the alkylation of calix[4]arenes prompts us to communicate our result on the acetylation of 1,3-dialkoxycalix[4]arenes where similar effects have been observed. Calix[4]arenes functionalized at the phenolic OH groups with bulky alkyl or acyl groups are conformationally immobile and can exist as one of four different stereoisomers, namely the cone, partial cone, 1,3-alternate and 1,2-alternate.<sup>2</sup>

We have recently reported on the synthesis of several conformationally rigid, stereoisomeric crown ethers and on their complexation behaviour toward alkali metal cations, which has shown a strong dependence of the cation binding efficiency on the stereochemistry of the ligands.<sup>3</sup>

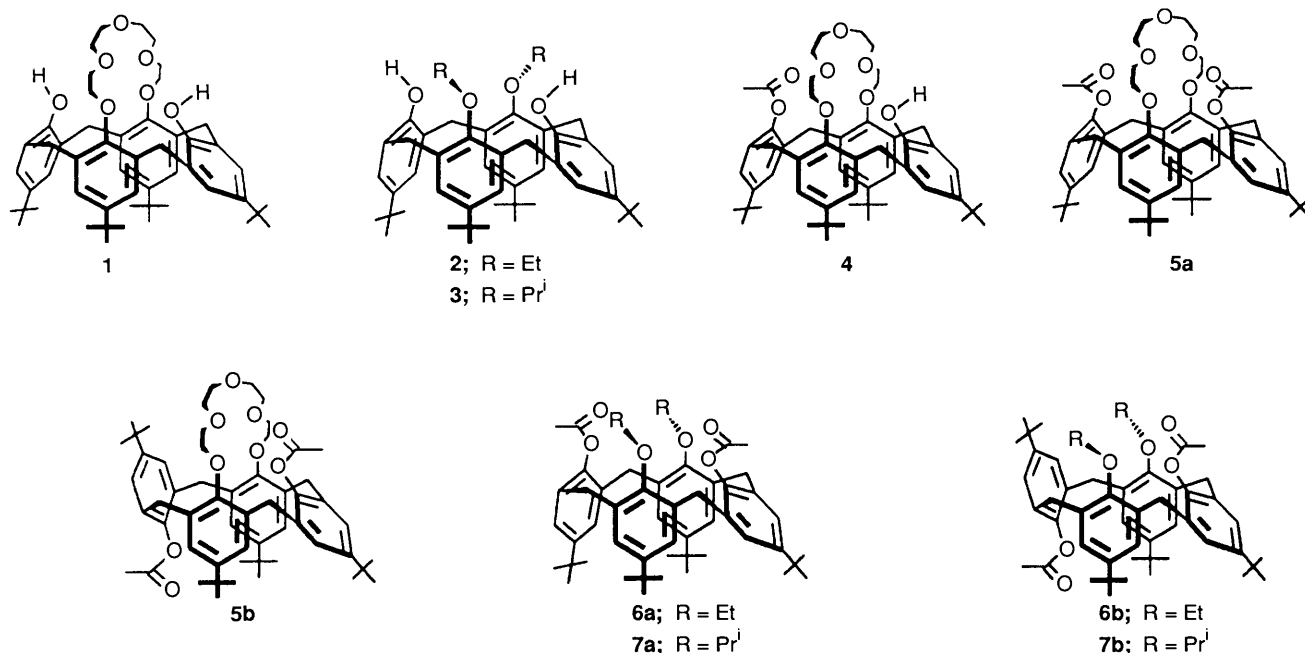
For our studies on catalysis in supramolecular complexes<sup>4</sup>

we needed a series of acetyl derivatives of calix[4]arene crown ethers fixed in different conformations. Therefore, a number of acetylation procedures were carefully scrutinized. Whereas reaction of **1** with refluxing Ac<sub>2</sub>O (Ac = CH<sub>3</sub>CO) and AcONa gave a mixture of diacetylated stereoisomers in the cone **5a** and partial cone **5b** conformations, remarkable selectivity was found with less conventional acetylation procedures. Thus, treatment of **1** with EtOTf<sup>5</sup> in Et<sub>2</sub>O, followed by 2 mol equiv. of AcCl at room temperature, gave a quantitative yield of the partial cone compound **5b**. On the other hand, reaction of **1** and AcCl in the presence of powdered NaOH or KOH run in CH<sub>2</sub>Cl<sub>2</sub>, either with or without a phase transfer catalyst,<sup>6</sup> at room temperature, afforded exclusively the cone conformer **5a**. When only 1 mol equiv. of AcCl was used, monoacetyl calix[4]arene-crown-5 **4**, which has also a cone structure was selectively produced. A

**Table 1** Acetylation of *p-tert*-butylcalix[4]arene diethers 1–3

Substrates	Reaction conditions	Products			
			Yield % <sup>a</sup>	Conformation <sup>b</sup>	
<b>1</b>	NaOH, CH <sub>2</sub> Cl <sub>2</sub>	<b>5a</b>	95	Cone	
<b>1</b>	NaOH, CH <sub>2</sub> Cl <sub>2</sub> , TBAHS <sup>c</sup>	<b>5a</b>	75	Cone	
<b>1</b>	NaH, Et <sub>2</sub> O	<b>5a</b>	80	Cone	
<b>1</b>	EtOTf, Et <sub>2</sub> O	<b>5b</b>	70	Partial cone	
<b>2</b>	NaH, Et <sub>2</sub> O	<b>6a</b>	85	Cone	
<b>2</b>	EtOTf, Et <sub>2</sub> O	<b>6b</b>	88	Partial cone	
<b>3</b>	NaH, Et <sub>2</sub> O	<b>7a</b>	85	Cone	
<b>3</b>	EtOTf, Et <sub>2</sub> O	<b>7b</b>	80	Partial cone	

<sup>a</sup> Isolated yield after crystallization. <sup>b</sup> The sole conformation observed in the <sup>1</sup>H NMR spectrum of crude reaction mixture. <sup>c</sup> TBAHS = Tetrabutylammonium hydrogen sulphate.



nearly quantitative yield of the diacetyl derivative **5a** was also obtained when acetylation of **1** with AcCl was carried out in diethyl ether using NaH as a base. The behaviour shown by the calixcrown **1** seems to be quite general for 1,3-dialkoxycalix[4]arenes since also the 1,3-diethoxy and the 1,3-diisopropoxy derivatives **2** and **3** give similar results (Table 1).\*

The structure of the compounds synthesized have been assigned on the basis of MS, <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic evidence. Particularly significant is the position of the methylene triplets (ArCH<sub>2</sub>Ar) in the <sup>13</sup>C NMR spectra which are always around 31 ppm for compounds **5a**, **6a** and **7a** in the cone structure, whereas the stereoisomers in the partial cone **5b**, **6b** and **7b** also give a signal around 38–39 ppm, in agreement

with the recently introduced single rule for the determination of calix[4]arene conformations.<sup>7,†</sup>

The results obtained in this work point to a strong metal ion (or ion pair) control of stereoselectivity in acetylation reactions on calix[4]arenes, sodium giving exclusively derivatives in the cone structure and thallium exclusively partial cone compounds.

We are currently extending these reactions to other acylating agents in order to find new synthetic methodologies for the stereoselective acylation of calix[4]arenes at the lower rim.

## Experimental

**General Procedure for obtaining Acetylated Products in the Cone Structure.**—To a stirred suspension of NaH (2.5 mmol) and compounds **1–3** (1 mmol) in dry Et<sub>2</sub>O (30 ml), acetyl chloride (1.2 or 2.4 mmol) dissolved in Et<sub>2</sub>O (30 ml) was added dropwise at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for additional 2 h and then diluted with water and extracted with Et<sub>2</sub>O. The combined ethereal extracts were dried (MgSO<sub>4</sub>) and evaporated to give the pure compounds. For analytical purposes the compounds were further purified by crystallization.

**Compound 4.** Crystallized from MeOH (90% yield), m.p. 240–241 °C;  $\nu_{\max}$ (KBr)/cm<sup>-1</sup> 3470, 2980, 1750, 1610 and 1490;  $\delta_{\text{H}}$ (100 MHz, CDCl<sub>3</sub>) 7.18 and 7.06 (4 H, s, ArH), 6.77 (1 H, s, ArOH), 6.61 (2 H, d, *J* 2.3, ‡ ArH), 6.56 (2 H, d, ArH), 4.55 (2 H,

\* All new compounds gave spectral data (IR, NMR) in accord with the assigned structure and satisfactory combustion analyses. Mass spectra (DCI) show in all cases the correct molecular ion: **6a**, m.p. 216–217 °C (crystallized from CHCl<sub>3</sub>–MeOH); **6b**, m.p. 306–307 °C (from CHCl<sub>3</sub>–MeOH); **7a**, m.p. 334–335 °C (from hexane); **7b**, m.p. 328–329 °C (from MeOH).

† In the light of this general rule those methylene signals present around 38–39 ppm in the previously reported <sup>13</sup>C NMR spectra of calixcrown ethers (ref. 3) should be assigned to the ArCH<sub>2</sub>Ar methylene bridges having the two aromatic rings in the *trans* orientation, which is present in the partial cone structure of calix[4]arenes.

‡ *J* Values in Hz.

d,  $J$  12.9, ArCH<sub>2</sub>Ar), 4.14 (2 H, d,  $J$  13.0, ArCH<sub>2</sub>Ar), 4.10–3.45 (16 H, m, OCH<sub>2</sub>CH<sub>2</sub>O), 3.20 (4 H, d, ArCH<sub>2</sub>Ar), 2.89 (3 H, s, Ac), 1.32 and 1.31 (9 H, s, Bu<sup>t</sup>) and 0.80 (18 H, s, Bu<sup>t</sup>);  $\delta_{\text{C}}$ (25 MHz, CDCl<sub>3</sub>) 173.7, 151.3, 150.6, 147.7, 145.5, 145.1, 140.2, 135.0, 132.4, 131.3, 127.7 (s), 125.6, 125.2, 124.6 (d), 74.3, 71.7, 70.8, 69.7 (t), 34.3, 33.8, 33.7 (s), 31.8, 31.7, 31.6 (q), 31.0 (t) and 22.8 (q);  $m/z$  (DCI, +) 849 (M<sup>+</sup>) and 807 (Found: C, 75.95; H, 8.75. C<sub>54</sub>H<sub>72</sub>O<sub>8</sub> requires C, 76.31; H, 8.54).

**Compound 5a.** Crystallized from hexane, m.p. 244–245 °C;  $\nu_{\text{max}}$ (KBr)/cm<sup>-1</sup> 2980, 1765, 1610 and 1490;  $\delta_{\text{H}}$ (200 MHz, CDCl<sub>3</sub>) 7.10 (4 H, s, ArH), 6.51 (4 H, s, ArH), 4.4–4.1 (8 H, m, OCH<sub>2</sub>CH<sub>2</sub>O), 3.95 (4 H, d,  $J$  13.0, ArCH<sub>2</sub>Ar), 3.85–3.65 (8 H, m, OCH<sub>2</sub>CH<sub>2</sub>O), 3.17 (4 H, d, ArCH<sub>2</sub>Ar), 2.61 (6 H, s, Ac), 1.3 (18 H, s, Bu<sup>t</sup>) and 0.81 (18 H, s, Bu<sup>t</sup>);  $\delta_{\text{C}}$ (25 MHz, CDCl<sub>3</sub>) 170.6, 154.2, 146.5, 142.6, 134.8, 131.3 (s), 125.9, 124.7 (d), 73.4, 72.8, 71.1, 70.8 (t), 34.1, 33.8 (s), 31.6, 31.0 (q), 31.3 (t) and 21.5 (q);  $m/z$  (DCI, +) 891 (M<sup>+</sup>) and 849 (Found: C, 74.8; H, 8.6. C<sub>56</sub>H<sub>74</sub>O<sub>9</sub> requires C, 75.47; H, 8.37).

**General Procedure for obtaining Acetylated Products in the Partial Cone Structure.**—1,3-Dialkoxy-*p*-*tert*-butylcalix[4]-arenes **1–3** (1 mmol) and EtOTf (2.2 mmol) in dry Et<sub>2</sub>O (60 ml) were stirred at room temperature for 30 min. Acetyl chloride (2.5 mmol) in Et<sub>2</sub>O (40 ml) was then added dropwise and the reaction mixture stirred at room temperature for 2 h. It was then diluted with water and extracted with Et<sub>2</sub>O. The combined ethereal extracts were dried (MgSO<sub>4</sub>) and evaporated to give the pure compounds.

**Compound 5b.** Crystallized from chloroform–hexane, m.p. 265–266 °C;  $\nu_{\text{max}}$ (KBr)/cm<sup>-1</sup> 2980, 1765, 1610 and 1490;  $\delta_{\text{H}}$ (100 MHz, CDCl<sub>3</sub>) 7.15–7.10 (6 H, m, ArH), 6.79 (2 H, d,  $J$  2.3, ArH), 4.1–3.25 (24 H, m, ArCH<sub>2</sub>Ar and OCH<sub>2</sub>CH<sub>2</sub>O), 2.43 (3 H, s, Ac), 1.41 (9 H, s, Bu<sup>t</sup>), 1.18 (18 H, s, Bu<sup>t</sup>), 1.17 (9 H, s,

Bu<sup>t</sup>) and –0.15 (3 H, s, Ac);  $\delta_{\text{C}}$ (25 MHz, CDCl<sub>3</sub>) 171.9, 169.0, 154.0, 147.5, 147.0, 146.2, 145.6, 143.4, 134.2, 133.7, 131.4, 131.0 (s), 126.0, 125.9, 125.6, 124.8 (d), 72.4, 71.9, 71.1, 70.7 (t), 38.8 (t), 34.3, 34.2, 34.1 (s), 31.8, 31.5, 31.4 (q), 31.1 (t), 21.9 and 18.1 (q);  $m/z$  (DCI, +) 891 (M<sup>+</sup>) and 849 (Found: C, 75.1; H, 8.5. C<sub>56</sub>H<sub>74</sub>O<sub>9</sub> requires C, 75.47; H, 8.37).

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