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Formation of upper rim acylated calix[4]arenes using a sacrificial zinc anode

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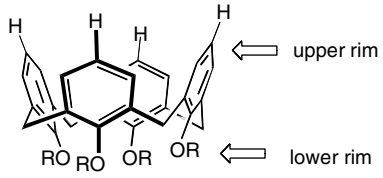
Abstract—A straightforward electrosynthetic method is described, which allows upper rim acylation of non-*p*-halogenated calix[4]-arenes. For example, a solution of tetrapropoxycalix[4]arene **4** was electrolysed in the presence of $ZnBr_2$ in an undivided cell fitted with a sacrificial zinc anode using pure acetonitrile as solvent, yielding an organozinc species, which was then treated with acetyl chloride in the presence of a palladium catalyst to afford 5,11-diacetyl-25,26,27,28-tetrapropoxycalix[4]arene **5** in ca. 35% yield after workup.

Through the pioneering studies of Gutsche in the late 1970's, calixarenes have rapidly become the most employed macrocyclic compounds in supramolecular chemistry.[1–6] Although many methods are now available that allow their straightforward functionalisation, electrochemistry has only scarcely been employed for their chemical modification, the only derivatives obtained electrochemically being calixquinones.[7–9] In the present work, we report an electrochemical method suitable for the upper rim acylation of calix[4]arenes (**A**), which relies on the use of a zinc electrode. It is noteworthy that chemical acylations of the upper rim have already been reported and may be achieved either by Friedel–Crafts acylations,[10] or through the Fries rearrangement route starting from calixarenes with acetate groups at the lower rim.[11]



A

When we started our investigations aiming at the synthesis of upper rim acylated calix[4]arenes, we first decided to employ a methodology, which had previously been developed by Périchon and co-workers[12–14] for the acetylation of aromatic halides (Scheme 1). This method is based on the cobalt-catalysed, electrochemical formation of an arylzinc species starting from an *halogenated arene*, followed by a palladium-catalysed, chemical coupling of an arylzinc intermediate with acyl moieties. For these experiments, a zinc anode is used that furnishes the Zn^{2+} cations. An organocobalt species serves as a transmetallation catalyst for the formation of the organozinc species.

Applying Périchon's method to the brominated calixarene **1** unexpectedly afforded a mixture of two diacetylated compounds, **2** and **3**, the latter still containing a Br substituent. Both calixarenes were formed in ca. 30% yield. They were characterised by ^1H and ^{13}C NMR, mass spectroscopy and elemental analysis.[15,16] The ES-MS spectrum of **2** displays a main peak at *m*/*z* 699 corresponding to the $[\mathbf{2}+Na]^+$ cation and that of **3** shows a peak at *m*/*z* 779 due to the $[\mathbf{3}+Na]^+$ cation. The NMR spectrum of **2** is consistent with a C_{2v}-symmetrical structure. In keeping with a C_s-symmetrical compound, the spectrum of **3** displays two AB patterns

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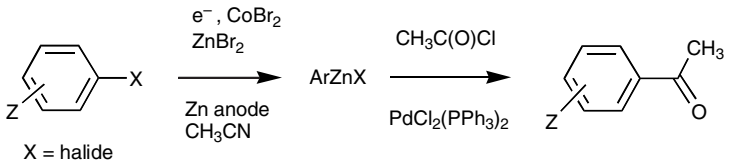
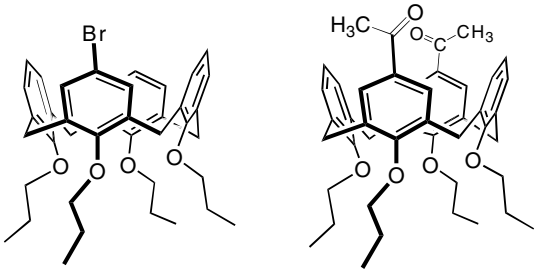
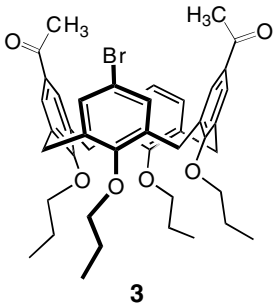


Scheme 1.

for the ArCH_2Ar bridging groups. As expected for cone conformers, in both ^{1}H NMR spectra the ArCH_2Ar protons appear as AB patterns with AB separations larger than the critical value of 0.7 ppm.[1a] The acetyl protons appear as singlets, respectively, at 2.39 and 2.40 ppm. The presence of carbonyl functions was also evidenced by the signals at 197.49 ppm (**2**) and 197.52 ppm (**3**) in the corresponding ^{13}C NMR spectra.



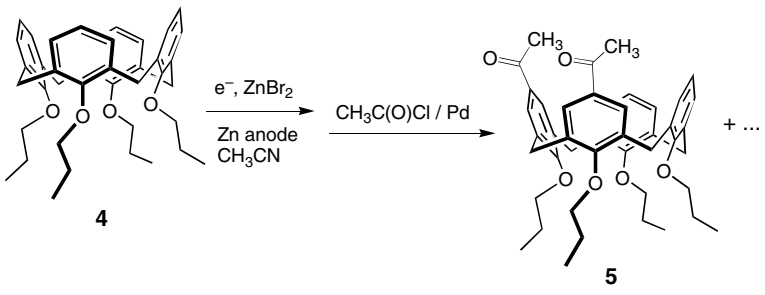


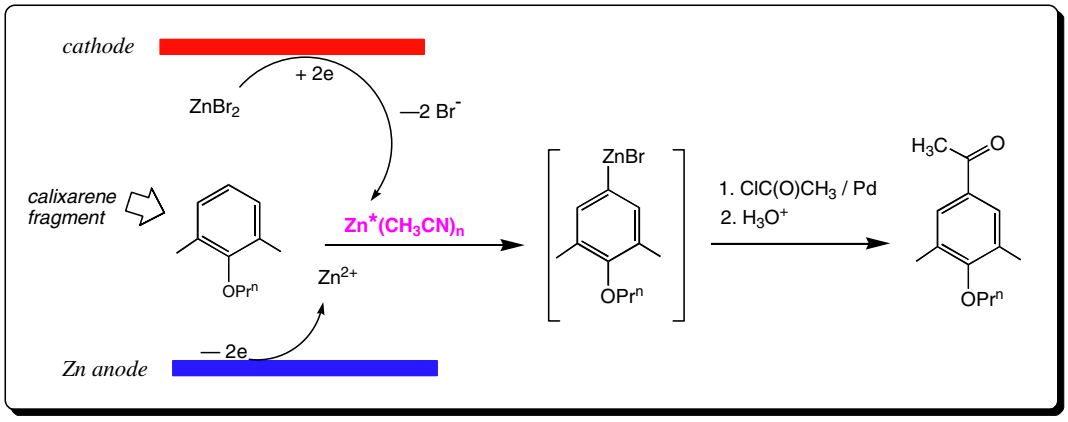
These results unambiguously demonstrate that applying Périchon's method to the bromo derivative **1** leads to multiply acylated compounds, hence excluding the occurrence of a unique acylation mechanism. Logically, we repeated the acylation experiment under similar experimental conditions with a non-brominated calixarene, namely **4**. This experiment resulted in the formation of the diacetylated compound **5** in ca. 25 % yield, besides other products that could not be separated chromatographically. In keeping with a proximally functionalised calixarene, the ^{1}H NMR spectrum of **5** shows three AB systems for the ArCH_2Ar protons (2H:4H:2H) and a single peak (6H) for the two acetyl groups. The ^{13}C{^{1}H} NMR spectrum confirmed the presence of equivalent acetyl groups (peaks at 197.44 ppm (CO) and 26.36 ppm (Me of acetyl)). Finally, contrary to our expectations, we found that acetylation of **4** does not require the presence of cobalt dibromide, compound **5** being formed in 35% yield in the absence of this salt. Note, that other acylated compounds were formed under these conditions, for example, the monoacetylated calixarene, but their chromatographic separation turned out to be difficult.

In view of the results presented above, we propose that acylation of non-substituted rings of calix[4]arenes occur according to a mechanism involving the formation of an arylzinc intermediate resulting from direct CH activation by a highly active zinc species '$Zn^*(CH_3CN)_n$' (Scheme 2). It noteworthy that at the precise moment where $ClC(O)CH_3$ is added to the solution, no $ZnBr_2$ is present longer in the solution, hence excluding a Friedel–Crafts acetylation of **4**.

We found that when the same procedure was applied to anisole, 4′-methoxyacetophenone was formed selectively, its formation occurring however 2–3 times quicker than by a $ZnBr_2$-catalysed Friedel–Crafts acylation.

Overall, this study shows, for the first time, that calixarenes can be acylated at the upper rim using an electrochemical method that does not require halogenated starting products. It turned out that this method allows for multiple functionalisation, resulting notably in an unreported di-acylation product. Further work is aimed at optimising the functionalisation reactions described in this work and applying the 'activated Zn' methodology to the synthesis of other functionalised calixarenes.





Scheme 2.

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15. The reactions were run as follows: in an undivided cell fitted with zinc rod (0.8 cm diameter) as anode and a stainless steel cathode were introduced freshly distilled acetonitrile (~50 mL) containing TEAP (0.1 mol L^{-1}) as supporting electrolyte, 0.250 g of **1** (0.37 mmol), 0.022 g (0.10 mmol) of $CoBr_2$ and ca. 0.158 g (0.7 mmol) of $ZnBr_2$ (formed by electroreduction of 1,2-dibromoethane in the presence of zinc anode). A constant current intensity of 0.2 A was applied. The reaction carried out at room temperature was stopped after consumption of 2 F/mol of **1**. To the solution resulting from the electrolysis of **1**, $[PdCl_2(PPh_3)_2]$ (0.025 g, 3.56×10^{-2} mmol) and an excess of acetyl chloride (1 mL) were added and allowed to react. The solution was stirred for 2–3 h and quenched with 2 mol L^{-1} HCl (30 mL). After evaporation of acetonitrile under reduced pressure, dichloromethane (50 mL) was added to the residue. The resulting suspension was washed with water (3×250 mL) to ensure complete removal of water-soluble salts. The extracts were dried over $MgSO_4$ upon which the solvent was removed under reduced pressure. The products were purified by flash column chromatography on silica gel using hexane/ethyl acetate 80:20 (v/v) as eluent.
16. Physical data for synthesised compounds: 5,17-diacetyl-25,26,27,28-tetrapropoxycalix[4]arene **2**. This compound was separated chromatographically (silica gel 60, $R_f = 0.3$, hexane/ethyl acetate 80:20 v/v). Yield: 0.070 g (28%). ^{1}H NMR ($CDCl_3$, 400 MHz): 7.12 (s, 4H, arom H), 6.59 (m, 6H, ArH), 4.41 and 3.14 (AB system, 8H, $^2J = 13.6$ Hz), 3.81 and 3.79 (2t, 8H, OCH_2), 2.39 (s, 6H, $C(O)CH_3$), 1.83 (m, 8H, OCH_2CH_2), 0.94 and 0.92 (2t, 8H, CH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): 197.49 (C=O), 161.01, 156.47 (2s, OC(aryl)), 135.27, 134.73, 131.21, 128.73, 128.62, 122.47 (8s, arom. C), 76.92 (s, OCH_2), 76.82 (s, OCH_2), 31.02 (s, $ArCH_2$), 26.24 ($C(O)CH_3$), 23.37 and 23.23 (2s, CH_2CH_3), 10.35, 10.37 and 10.27 (2s, CH_3CH_2). MS (ESI): m/z 699 $[M+Na]^+$. Anal. Calcd for $C_{44}H_{52}O_6 \cdot 0.25CH_3CO_2Et$: C, 77.33; H, 7.79. Found: C, 77.21; H, 8.00.
5-Bromo-11,23-diacetyl-25,26,27,28-tetrapropoxycalix[4]arene **3**. This compound was separated chromatographically (silica gel 60, $R_f = 0.4$, hexane/ethyl acetate 80:20 v/v). Yield: 0.084 g (30%). ^{1}H NMR ($CDCl_3$, 400 MHz): 7.40 (s, 2H, ArH), 7.37 (br s, 2H, ArH), 6.54 (t, 1H, ArH, $^3J = 7.2$ Hz), 6.41 (s, 2H, H of ArBr), 6.32 (d, 2H, ArH, $^3J = 7.2$ Hz), 4.40 (d, 2H, $ArCH_{ax}Ar$, $^2J = 13.6$ Hz), 4.34 (d, 2H, $ArCH_{ax}Ar$, $^2J = 13.6$ Hz), 3.87 (m, 4H, OCH_2), 3.70 (m, 4H, OCH_2), 3.18 (d, 2H, $ArCH_{eq}Ar$, $^2J = 13.6$ Hz), 3.11 (d, 2H, $ArCH_{eq}Ar$, $^2J = 13.6$ Hz), 2.40 (s, 6H, MeC(O)), 0.96 (2 overlapping t, 6H, CH_2CH_3), 0.85 (t, 6H, CH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): 197.52 (C=O), 161.78, 155.83 and 155.12 (3s, OC(aryl)), 136.29–115.11 (arom. C), ~76.9 (3s overlapping with $CHCl_3$, OCH_2), 76.82 (s, OCH_2), 31.07 (s, $ArCH_2$), 30.92 (s, $ArCH_2$), 26.45 ($C(O)CH_3$), 23.37, 23.25 and 23.17 (3s, CH_2CH_3), 10.54, 10.47 and 10.09 (3s, CH_3CH_2). MS (ESI): m/z 779 $[M+Na]^+$. Anal. Calcd for $C_{44}H_{51}O_6Br \cdot 0.5CH_3CO_2Et$: C, 69.08; H, 6.93. Found: C, 69.14; H, 6.93.

5,11-Diacetyl-25,26,27,28-tetrapropoxycalix[4]arene **5**. The synthesis of this compound was carried without addition of $CoBr_2$. The compound was separated chromatographically (silica gel 60, $R_f = 0.4$, hexane/ethyl acetate 80:20 v/v). Yield: 0.095 g (35%) (note, beside the starting compound other acylated products were detected, but these could not be isolated as pure compounds). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.14 (s, 4H, *m*-ArH of OArC(O)Me), 6.52–6.50 (m, 4H, *m*-ArH of OAr), 6.43 (t, 2H, *p*-ArH, $^2J = 7.4$ Hz), 4.41, 4.38, 4.36 (3d, 1H:2H:1H, A part of ArCH_2Ar groups, $^2J = 13.2$, 13.6 and 14.0 Hz), 3.18, 3.14 and 3.08 (3d, 1H:2H:1H, B part of ArCH_2Ar groups, $^2J = 14.0$, 13.6 and 13.2 Hz), 3.88–3.72 (m, 8H, OCH_2), 2.28 (s, 6H, C(O)Me), 1.86–1.77 (m, 8H, OCH_2CH_2), 1.18–0.90 (2 overlapping t, 6H, CH_2CH_3). $^{13}C\{^1H\}$ ($CDCl_3$, 100.63 MHz): δ 197.44 (s, *C*(O)Me), 161.11 and 156.52 (2s, arom. C_q–O), 135.65–122.01 (arom. C's), 76.80 and 76.71 (2s, OCH_2), 31.09, 31.03 and 30.93 (3s, ArCH_2Ar), 26.36 (s, C(O)CH_3), 23.30 and 23.24 (2s, CH_2CH_3), 10.31 and 10.27 (2s, CH_2CH_3). MS (ESI): *m*/*z* 699.5 $[M+Na]^+$. Anal. Calcd for $C_{44}H_{52}O_6 \cdot 0.25CHCl_3$: C, 75.20; H, 7.45. Found: C, 75.21; H, 7.40.