Cavity effect of calix[4]arenes in electrophilic aromatic substitution reactions

Oliver Struck,[a] John P. M. van Duynhoven,[b] Willem Verboom,[a] Sybolt Harkema[c] and David N. Reinhoudt*[a]

[a] *Laboratories of Organic Chemistry, University of Twente, 7500 AE Enschede, The Netherlands*
[b] *Chemical Analysis, University of Twente, 7500 AE Enschede, The Netherlands*
[c] *Chemical Physics, University of Twente, 7500 AE Enschede, The Netherlands*

Electrophilic aromatic substitutions of hydroxymethylcalix[4]arenes with monosubstituted benzene derivatives give rise to very unusual *ortho*-selectivities caused by a cavity effect of the calix[4]arenes.

Cyclodextrins play an important role in supramolecular chemistry as molecular host systems capable of binding various organic guest molecules by non-covalent interactions in their hydrophobic cavity in polar solvents.[1] High selectivities have been reported in electrophilic aromatic substitution reactions of monosubstituted benzene derivatives,[2] in which the orientation of the substrate in the cyclodextrin dictates the regioselectivity.[3] Calix[4]arenes[4] also represent a very important class of compounds which upon functionalization of the lower and/or the upper rim have found widespread use as selective receptors for anions,[5] cations[4] and small neutral molecules.[4] Therefore we studied the acid-catalysed electrophilic aromatic substitution reaction between upper rim functionalized calix[4]arenes **2** and **3** and aromatic compounds of varying reactivity. Here we describe the first examples that, like in cyclodextrins, the hydrophobic cavity actively participates in a chemical reaction by directing the product distribution.

1-Hydroxymethyl-2,4-dinitrocalix[4]arene **2** was obtained in 84% yield *via* Gross formylation[6] at the upper rim of the 1,3-dinitro derivative **1**[7] and subsequent reduction of the aldehyde moiety by $NaBH_4$ in quantitative yield. Heating hydroxymethylcalix[4]arene **2** under reflux in toluene in the presence of a catalytic amount of toluene-*p*-sulfonic acid gave the benzylcalix[4]arene **4** in 90% yield in an unexpected ratio of 78% *ortho*-, 9% *para*- and 13% *meta*-isomers.† When the reaction of **2** was performed in anisole, calix[4]arene **5** (*ortho*/*para* ratio: 65/35) was isolated in 89% yield. In benzene or *p*-xylene, **2** gave **6** and **7**, in 80 and 78% yields, respectively.

^{1}H DQCOSY, TOCSY, ROESY and HMQC experiments were performed for the ^{1}H and ^{13}C NMR spectral assignments of the different products. The *ortho*- *para*- and *meta*-substitution patterns were identified by scrutiny of through-bond and through-space connectivity patterns and by matching of the ^{13}C NMR resonances with calculated/literature values.‡

The very unusual *ortho*/*para*/(*meta*)-ratios, especially in the benzylcalix[4]arene **4**, can be explained by the intermediate formation of a binary complex of toluene in the enlarged cavity of **2** by the two rigid and polar nitro groups. The orientation of the methyl group of the toluene molecule pointing into the calix[4]arene cavity should lead to a favoured *ortho*-attack of the *in situ* generated benzylic carbocation of **2** (Fig. 1). Probably the benzylic cation interacts with the neighbouring nitro groups preventing the conformational interconversion process and consequently gives rise to the formation of a real cavity. Only in the solid state are several examples known of inclusion complexes of *p-tert*-butylcalix[4]arene with monosubstituted benzene derivatives, *e.g.* with toluene and anisole.[8] In the *p-tert*-butylcalix[4]arene-toluene (1 : 1) complex the methyl group of the toluene points into the cavity.[8a]

Recrystallization of the isomer mixture of **4** from a mixture of acetone and water afforded light yellow crystals of the *ortho*-isomer. The X-ray crystal structure§ (Fig. 2) shows that *ortho*-**4** adopts a distorted flattened cone conformation,[9] in which, surprisingly, the two aromatic units bearing the polar NO_2-groups are folded into the cavity.[9,10] The interplanar angle between these two aromatic units was determined to be 24.5°.

In all experiments performed no indications were obtained that the present *o*/*p*(*m*)-ratios are the result of isomerizations

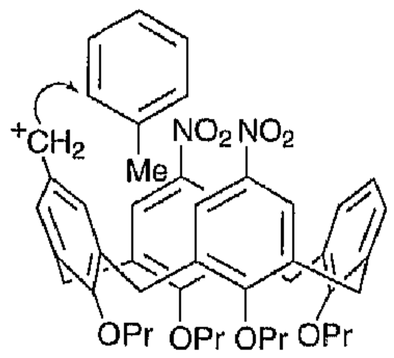
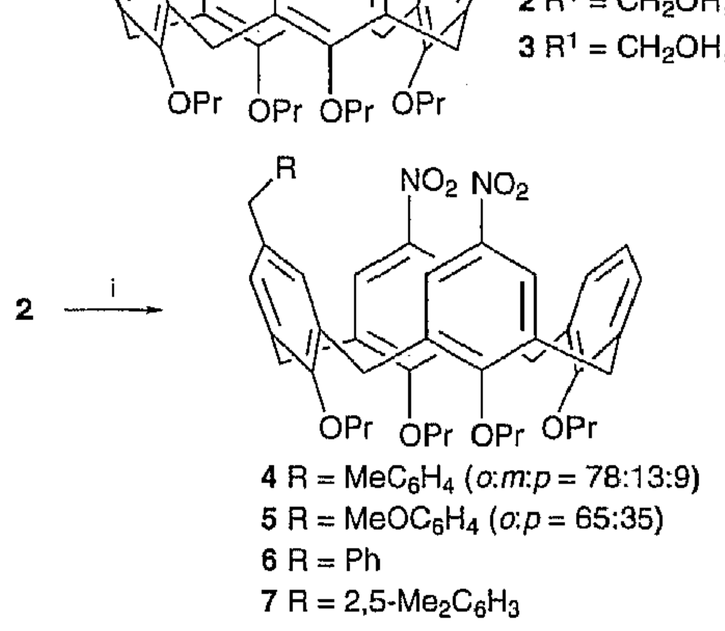


Fig. 1 Proposed complexation orientation of the intermediate benzylic carbocation of **2** with toluene



Scheme 1 *Reagents and conditions*: i, 2 mmol dm^{-3} of **2** in the respective aromatic solvent, *p*-TosOH (cat. amount), reflux, 19 h

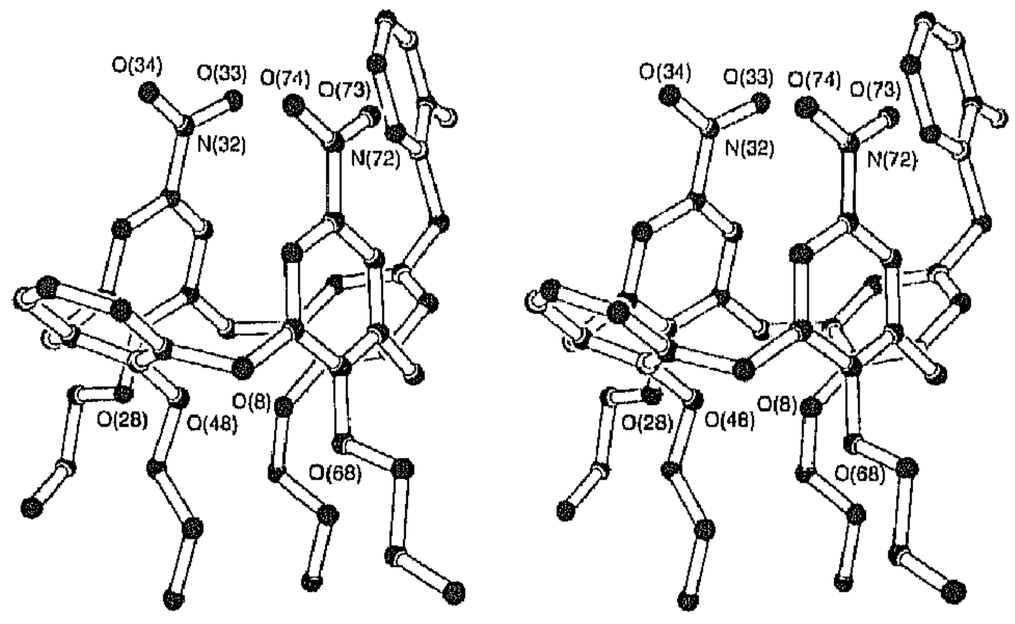


Fig. 2 Stereoscopic view of the crystal structure of the *ortho*-isomer of **4** (hydrogen atoms are omitted for clarity)

during the reactions: the determined *o/p/(m)*-ratio of **4** (19 h reaction time) did not change even after heating under reflux for 94 h in toluene in the presence of toluene-*p*-sulfonic acid. To exclude that, in the case of the electrophilic aromatic substitution products obtained, an intermolecular isomerization process with the respective aromatic solvent takes place, benzylcalix[4]arene **6** was heated under reflux in toluene in acidic conditions for 69 h. However, no exchange products could be detected by NMR or FAB MS spectroscopy.

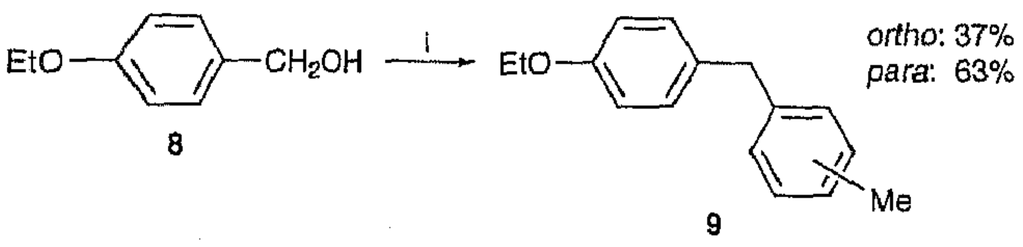
To support the existence of a calix[4]arene cavity effect a control experiment was performed under exactly the same conditions as described above[11] by reaction of *p*-ethoxybenzyl alcohol **8** with toluene which led to a conventional ratio of 37% *ortho*- and 63% *para*-product **9**.†,‡

When hydroxymethylcalix[4]arene **2** was heated under reflux in the less reactive chlorobenzene, two different products were isolated. The chlorobenzenecalix[4]arene **10** (38% yield) was exclusively formed as the *ortho*-isomer; no other isomers could be detected by ^{1}H NMR spectroscopy.‡ The second product (isolated in 10% yield) could be identified as the intramolecularly bridged calix[4]arene **11**. The structure of this very unexpected, diametrically methylene bridged cyclophane **11**¶ was determined by FAB MS and NOE spectroscopy.‖

The calix[4]arene skeleton is completely immobilized due to the shortest possible bridge.[12] A prerequisite for the formation of **11** is that calix[4]arene **2** adopts a 'collapsed' cone conformation during the reaction. This structural behaviour is also illustrated by the characteristic, high-field shifted ^{1}H NMR signal at δ 5.6 for the aromatic protons of the bridged nuclei in **11** due to shielding effects of the neighbouring aromatics.

In case of the monofunctionalized calixarene **3**, prepared by reduction of the corresponding monoaldehyde,[6] the calixarene cavity is much less pronounced than in **2**. The reaction of **3** in toluene led to an inseparable mixture of the *ortho/para*-toluene isomers **12** and the methylene bridged calix[4]arene **13** in 90% overall yield (**12**:**13** = 85:15). **12** was determined to be 58% *ortho* and 42% *para*.†,‡ In chlorobenzene the intramolecularly bridged cyclophane **13** was exclusively formed in 56% yield.

Either an intra- and/or an inter-molecular (cavity effect supported) Friedel–Crafts reaction takes place upon heating under reflux hydroxymethylcalix[4]arenes **2** and **3** in aromatic solvents under acidic conditions. This depends on the substitution pattern at the upper rim and on the reactivity of the aromatic solvents. The preferred formation of the respective *ortho*-isomers can be explained by a favourable orientation of the



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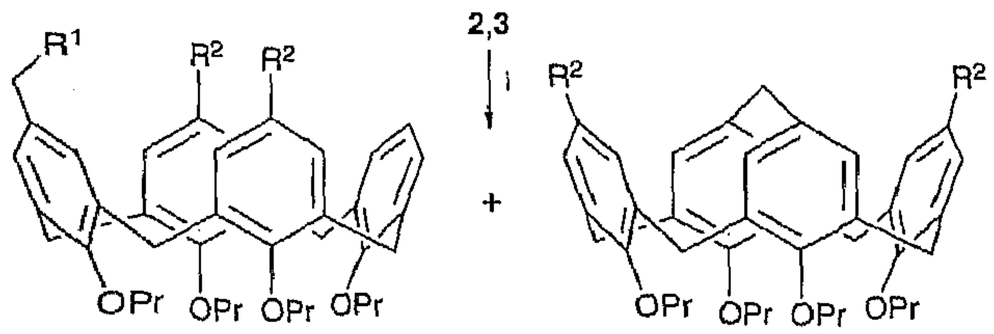
Scheme 2 *Reagents and conditions*: i, 2 mmol dm^{-3} of **8** in toluene, *p*-TosOH (cat. amount), reflux, 19 h



10 R^1 = *o*-ClC_6H_4, R^2 = NO_2 **11** R^2 = NO_2
12 R^1 = MeC_6H_4 (*o*:*p* = 58:42), R^2 = H **13** R^2 = H

Scheme 3 *Reagents and conditions*: i, 2 mmol dm^{-3} of **2**, **3** in the respective aromatic solvent (toluene or chlorobenzene), *p*-TosOH (cat. amount), reflux, 24 h

guest molecules in the calix[4]arene cavities during the reaction. To the best of our knowledge these results represent the first example of a cavity effect of calix[4]arenes in a chemical reaction.

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Footnotes

† The *ortho/para/(meta)*-ratio determination of **4**, **5**, **9** and **12** was carried out by ^{1}H NMR (400 MHz) spectroscopy by means of spectral deconvolution in Lorentzian lineshapes using standard Varian (VNMR) software.

‡ For compounds **4**, **5**, **9**, **10**, **12/13**.

§ *Crystal data* for *ortho*-**4**; $C_{48}H_{54}N_2O_8$, M = 786.97, monoclinic, space group $P2_1/c$, a = 13.409(6), b = 15.287(7), c = 21.021(7) Å, β = 101.44(6)°, U = 4224 Å^3, Z = 4, D_c = 1.238 g cm^{-3}, T = 165 K. Reflections were measured in the ω/2θ scan mode, graphite monochromated Mo-Kα (λ = 0.71073 Å) radiation [scan width (ω) (1.0 + 0.35 tan θ)°; 3 < θ < 20°] on a Enraf Nonius CAD4 diffractometer. A total of 2101 reflections with $F_o^2 > 3\sigma(F_o^2)$ was used in the refinement. The number of parameters refined was 524 (scale factor, extinction parameter, positional and anisotropic thermal parameters of the non-H atoms, H atoms put at calculated positions and treated as riding atoms). The final R-factors were R = 0.074, R_w = 0.076. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/95.

¶ Building of the corresponding CPK molecular model of **11** (or **13**) is not possible.

‖ For instance the distance between the aromatic proton *ortho* to the diametrically bridged nuclei and the outer methylene proton was determined to be 3.3(2) Å by quantitative NOE analysis, which is in good agreement with the respective, calculated distance of 3.0 Å of the energy-minimized structure of **11** (Quanta/CHARMM Version 3.3).

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