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An Easy Access to Tetra-O-Alkylated Calix[4]arenes of Cone Conformation

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Abstract: Fully O-alkylated calix[4]arenes have been synthesized by the alkylation of p-tert-butylcalix[4]arene and its 1,3-dialkylated derivatives in liquid-liquid phase-transfer catalytic process. **$1H_4$** and **$1H_2R_2$** could effeciently be deprotonated by aqueous NaOH (50% w/w)-toluene system and alkylated with alkyl (aralkyl, allyl) halogens in good yields affording calix[4]arene tetraethers of cone conformation.

INTRODUCTION

Calix[4]arenes are cyclic tetramers made up of phenols and formaldehyde. This versatile class of compounds[1,2] has extensively been studied in the last decade mainly in order to obtain new complexing agents by appropriate functionalizations of the parent molecule. A number of ligands based on calix[4]arenes capable of selective complexation of cations, anions and neutral molecules have been synthesized[3].It is known that p–tert–butylcalix[4]arene (**$1H_4$**) adopts a cone conformation due to strong hydrogen-bonding interactions among the OH groups. Introduction of alkyl substituents into the OH groups, however, suppresses the conformational freedom by inhibiting the oxygen-through-the-annulus rotation and results in conformational isomers[3,4]. In calix[4]arenes there can exist four different conformers: cone, partial cone, 1,2-alternate and 1,3-alternate. The structure of these conformers can be distinguished by the characteristic ^1H NMR patterns arising from the $ArCH_2Ar$ methylene protons[3,5].

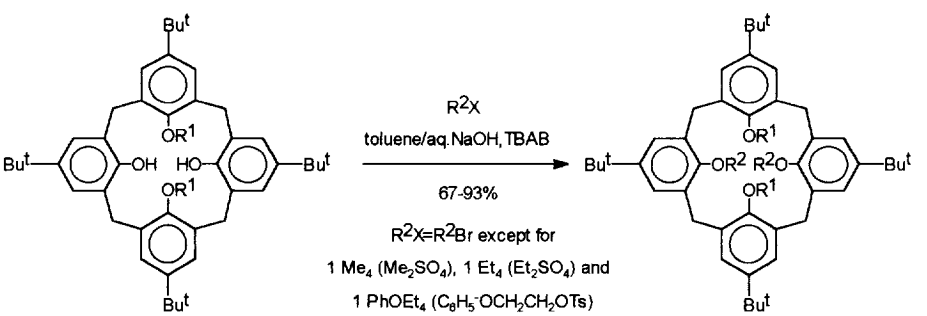
The tetra-O-alkylation of calix[4]arene (**$1H_4$**) has been investigated by Shinkai at. al.[4] The reactions were carried out in THF/DMF(10:1 v/v) mixed solvent at reflux temperature using excess of alkyl halogens and oily dispersed NaH as base. The conformer distribution of tetra-O-alkylation product was determined by HPLC. The authors claimed 100% yield of **$1R_4$** and different conformations of products depending on the bulkiness of the alkyl groups. According to their explanation the tetra-O-methylation and -ethylation are thermodynamically controlled affording the conformationally mobile **$1Me_4$** and **$1Et_4$** in partial cone, whereas the conformationally inmobile **$1Pr_4$** and **$1Bu_4$** are formed under kinetic controll approximately in 1:1 ratio of cone and partial cone isomers.The latter conformer mixtures could not be isomerized when heated in 1,1,2,2-tetrachloroethane (147° C) for 3 days. It means that the n-propyl and n-butyl groups are bulky enough to inhibit the oxygen-through-the-annulus rotation[4]. On the contrary to Shinkai's observation Reinhoudt at. al.[6] have published the

preparation of **1Pr$_4$** exclusively in the cone conformation by reaction of **1H$_4$** with 1-iodopropane in NaH/DMF at 75°C for 18h. The possible intermediates and the stereochemical outcome of the tetraalkylation of calix[4]arenes were published in a separate paper[7]. The authors have shown that the tetraalkylation of calix[4]arenes can proceed via at least two different dialkylated intermediates and the conformer distribution of the tetraalkylated product were strongly influenced by the solvent and base used. Ethylation with EtI in DMF or MeCN/NaH system resulted in only cone **1Et$_4$** whereas in the presence of KH or KOtBu in different solvents (DMF, MeCN, THF) an isomer mixture was obtained with the predominance of partial cone **1Et$_4$**. It means that a strong template effect of one or more Na^+ ions can keep the negatively charged oxygen atoms close together in the cone conformation. It is interesting to note that the THF/NaH system was found quite ineffective for tetraethylation since only a little amount of monosubstituted product had been formed after 24h[7].

RESULTS AND DISCUSSION

These findings and the disadvantages of the published procedures (expensive dry solvents, hazardous NaH in large scale, long reaction, etc.) prompted us to try the exhaustive alkylation of **1H$_4$** and several diametricelly disubstituted calix[4]arenes (**1H$_2$Pr$_2$, 1H$_2$Bu$_2$, 1H$_2$Bn$_2$**) as well, in PTC system. Of liquid-liquid and solid-liquid systems the former was found to be superior because of the cheap solvent, easy handling of base, relatively short reaction time and good yields. The alkylation was carried out in toluene solvent at 90-100°C with exess of aqueous NaOH (50% w/w), alkylating agent and 10mol% (in relation to **1H$_4$**) of tetrabutylammonium bromide (TBAB). Other PT catalyst e.g. TEBAC, $Oct_3MeN^+Cl^-$, etc. should also be effective but not tried. Generally alkyl bromides were used (except for **1Me$_4$**, **1Et$_4$** and **1PhOEt$_4$** as indicated on the scheme). Alkyl iodides are not suitable agents in PTC alkylations since I^- anion formed in the reaction decreases the rate of phase-transfer process by "poisoning" the PT catalyst.

It is interesting to note that tetra-alkylation of the parent calix[4]arene were found to be unsuccessful when using this PTC method. The sodium phenolate precipitated from the reaction mixture as a thick mass and could not effectively be transferred into the organic phase. By decreasing the aqueous NaOH concentration to 20% w/w, a fairly stirrable mixture was found but the alkylation, however, hardly procceded after 10h. Attempts to try more polar solvents than toluene are in progress.



1 H$_2$R$^1_2$ **1 R$^1_2$R$^2_2$**

Table 1. Starting materials

1 $H_2R^1{}_2$	1 H_4	1 H_2Pr_2	1 H_2Bu_2	1 H_2Bn_2
R^1	H	C_3H_7	C_4H_9	$C_6H_5CH_2$

Table 2. Tetra-alkyl calix[4]arenes prepared by PTC alkylation

1 $R^1{}_2R^2{}_2$	1 Me_4 (a)	1 Et_4 (b)	1 Pr_4 (c)	1 Bu_4 (d)	1 A_4 (e)	1 Bn_4 (f)	1 $PhOEt_4$ (g)
R^1	CH_3	C_2H_5	C_3H_7	C_4H_9	CH_2=CH-CH_2	C_6H_5-CH_2	C_6H_5-OCH_2CH_2
R^2	CH_3	C_2H_5	C_3H_7	C_4H_9	CH_2=CH-CH_2	C_6H_5-CH_2	C_6H_5-OCH_2CH_2

1 Pr_2A_2 (h)	1 Bu_2A_2 (i)	1 Bn_2A_2 (j)	1 Pr_2Bn_2 (k)
C_3H_7	C_4H_9	C_6H_5-CH_2	C_3H_7
CH_2=CH-CH_2	CH_2=CH-CH_2	CH_2=CH-CH_2	C_6H_5-CH_2

In all cases, except for **1Me$_4$** and **1Et$_4$** exclusively cone products were obtained.

Calixarenes are reported ineffective cation carriers in neutral solution, they show, however, significant transport ability in strongly basic medium[2]. Although p-tert-butylcalix[4]arene is rather poor Na^+ ion extractant[8], we have checked the necessity of the PT catalyst during the alkylation. Tetrabutylation of **1H$_4$** was repeated under the same conditions but whitout TBAB and found that after 6h no **1Bu$_4$** but a little amount of **1H$_3$Bu** and **1H$_2$Bu$_2$** had been formed. Thus the PT catalyst should be regarded to be essential in the rapid progress of reaction. Taking into consideration the mechanism of the quaternary ammonium salt in the PTC process and the cone selectivity of alkylation as well, the reactive nucleophile in the organic phase is supposed to be a polyphenolate complex anion with one or more Na^+ and at least one N^+R_4 counter ions. The former is mainly responsible for the cone selectivity whereas the latter transfers the anionic species into the organic phase providing a strong nucleophilic phenolate of loose ion-pair character. The necessity of Na^+ template for the cone selectivity was proved by two alkylations when **1H$_4$** was reacted with PrBr and BuBr in the presence of aq.KOH (50% w/w) base under the same PT conditions. In both cases mixture of conformers (paco: 80%, 1,3alt: 15% calculated from ^{1}H NMR) was formed whereas the cone product could only be detected.

Tetra-alkylcalix[4]arenes with mixed functionalities (**1R$^1{}_2$R$^2{}_2$**, e.g. **1h-1k**) are also easily accessible by this procedure when starting from 1,3(distal)-dialkylated derivatives (**1H$_2$R$_2$**)[4,10]. Obviously no matter that **1H$_2$R$^1{}_2$** is alkylated with R^2X or **1H$_2$R$^2{}_2$** with R^1X the same products can be obtained (e.g. **1k**).

We have found PTC procedure for the cone selective O-alkylation of p-tert-butylcalix[4]arene and selected 1,3(distal)-dialkylated calix[4]arenes. Similar alkylation of calix[6]arene derivates is being investigated.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR spectra were recorded on JEOL FX-100 instrument in $CDCl_3$. TMS was used as an internal standard. Precoated silica gel plates (Merck 60 F_{254}) were used for analitical TLC. All chemicals were reagent grade and used without further purification. p–tert–Butylcalix[4]arene **1 H_4**[9], 1,3-dialkylated calix[4]arenes **1 H_2Pr_2**[4], **1 H_2Bu_2**[4], **1 H_2Bn_2**[10] were prepared as described in literature.

General procedure for the alkylation of p-tert butylcalix[4]arene derivatives

A mixture of the starting calix[4]arene derivative (1mmol) toluene (25ml), aq. NaOH 50% w/w (1ml), alkylating agent (10mmol for **1** H_4 and 5mmol for the others) and tetrabutylammonium bromide (0.03g 0.1mmol) were vigorously stirred at 90-100°C for 6h. After cooling, water (10ml) was added and the phases were separated. The organic phase was washed with dilute aq.HCl (20ml) and water (20ml) subsequently. The toluene solution was dried (Na_2SO_4) then evaporated to dryness. The residue was triturated with methanol to give a white solid which was recrystallized.

Compound **1Me_4(a), 1Et_4(b), 1Pr_4(c), 1Bu_4(d), 1A_4(e),** and **1Bn_4(f)** were earlier prepared by others. We have found different mps for **1a**, **1b** and **1c** as indicated in literature[4,11], but the ^{1}H NMR spectra were in accordance with the published data.

*5,11,17,23-Tetra-t-butyl-25,26,27,28-tetrametoxycalix[4]arene (***1a***)*

Yield: 80%, mp: 242-43°C (MeOH-$CHCl_3$) (lit.mp: 226,5-228°C[11] ^{1}HMR δ: 6.65 (br s, 8H, ArH), 4.25-2.90 (m, 20H, CH_2 and CH_2O), 1.25 (br s, 36H, t-bu) (partial cone in accordance with lit.[11])

*5,11,17,23-Tetra-t-butyl-25,26,27,28-tetraethoxycalix[4]arene (***1b***)*

Yield:72%, mp:242-244°C (BuOH) (lit.mp:261-262°C[11]), ^{1}H NMR δ: 7.20, 7.10, 6.85, 6.60 (s,s,d,d, 2H each, ArH), 4.05, 3.05 (d, J=12Hz, 4H, $ArCH_2Ar$), 3.65, 3.70 (d, 4H, $ArCH_2Ar$), 3.55-3.70 and 3.75-3.90 (m, 8H, OCH_2), 1.05, 1.35 and 1,38 (s, each 18H,9H,9H, t-Bu) 1.00, 1.32 and 1.42 (t, each 3H,3H,6H, CH_3)(partial cone in accordance with lit.[4,11])

*5,11,17,23-Tetra-t-butyl-25,26,27,28-tetrapropoxycalix[4]arene (***1c***)*

Yield:67%, mp:212-215°C (i-PrOH) (lit.mp:246-247°C[4]), ^{1}H NMR δ: 6.75 (s, 8H, ArH), 4.42 and 3.10 (d, J=12Hz, 8H, $ArCH_2Ar$, cone[4]), 3.80 (t, 8H, OCH_2), 2.03 (m, 8H, $CH_2(CH_3)$), 1.10 (s, 36H, t-Bu), 1.00 (t, 12H, CH_3)

*5,11,17,23-Tetra-t-butyl-25,26,27,28-tetrabutoxycalix[4]arene (***1d***)*

Yield:71% (85% from 1 H_2Bu_2) mp:172-3°C (i-PrOH) (lit.mp: 175-176°C[4]), ^{1}H NMR δ: 6.75 (s, 8H, ArH), 4.40 and 3.08 (d, J=12Hz, 8H, $ArCH_2Ar$, cone[4]), 3,85 (t, 8H, OCH_2), 2.00 (m, 8H, $CH_2(CH_2O)$), 1.42 (m, 8H, $CH_2(CH_3)$), 1.07 (s, 36H, t-Bu), 1.01 (t, 12H, CH_3)

5,11,17,23-Tetra-t-butyl-25,26,27,28-tetraallyloxycalix[4]arene (**1e**)

Yield:88% mp:182-184°C (i-PrOH) (lit.mp: 188-189°C[11]), ^{1}H NMR δ: 6.75 (s, 8H, ArH), 6.45 (m, 4H, =CH), 5.25 (d, 4H, CH_2=), 5.19 (d, 4H, CH_2=), 4.45 (d, J=7.5Hz, 8H,OCH_2), 4.37 and 3.15 (d, J=12Hz, 8H, $ArCH_2Ar$, cone[11]), 1.07 (s, 36H, t-Bu)

5,11,17,23-Tetra-t-butyl-25,26,27,28-tetrabenzyloxycalix[4]arene (**1f**)

Yield:89% mp:232-234°C (BuOH) (lit.mp: 230-231°C[11]), ^{1}H NMR δ: 7.22 (s, 20H, ArH), 6.67 (s, 8H, ArH), 4.85 (s, 8H, OCH_2), 4.18 and 2.85 (d, J=12Hz, 8H, $ArCH_2Ar$, cone[11]), 1.07 (s, 36H, t-Bu)

5,11,17,23-Tetra-t-butyl-25,26,27,28-tetra-2-phenoxyethoxycalix[4]arene (**1g**)

Yield:74% mp:143-145°C (BuOH), ^{1}H NMR δ: 7.25-6.80 (m, 20H, ArH), 6.75 (s, 8H, ArH), 4.42 and 3.10 (d, J=12Hz, 8H, $ArCH_2Ar$, cone),4.30 (s, 16H, OCH_2CH_2O), 1.10 (s, 36H, t-Bu), Anal. calcd. for $C_{76}H_{88}O_8$(1129.52): C 80.82, H 7.85, Found C 80.25, H 7.79

5,11,17,23-Tetra-t-butyl-25,27-diallyloxy-26,28-dipropoxycalix[4]arene (**1h**)

Yield:92% (from 1 H_2Pr_2) mp:216-217°C (i-PrOH), ^{1}H NMR δ: 6.85 (s, 4H, ArH), 6.55 (s, 4H, ArH, m, 2H, CH=), 5.25 (d, 2H, CH_2=), 5.15 (d, 2H, CH_2=), 4.55 (d, J=7.5Hz, 4H, OCH_2CH=), 4.40 and 3.12 (d, J=12Hz, 8H, $ArCH_2Ar$, cone), 3.70 (t, 4H, OCH_2CH_2), 1.90 (m, 4H, $CH_2(CH_3)$), 1.21 and 0.95 (s, 18H each, t-Bu), 1.02 (t, 6H, CH_3), Anal. calcd. for $C_{56}H_{76}O_4$ (813.21): C 82.71, H 9.42, Found: C 82.45, H 9.35

5,11,17,23-Tetra-t-butyl-25,27-diallyloxy-26,28-dibutoxycalix[4]arene (**1i**)

Yield:83% (from 1 H_2Bu_2) mp:199-201°C (i-PrOH), ^{1}H NMR δ: 6.92 (s, 4H, ArH), 6.58 (s, 4H, ArH, m, 2H, CH=), 5.28 (d, 2H, CH_2=), 5.18 (d, 2H, CH_2=), 4.60 (d, J=7.5Hz, 4H, OCH_2CH=), 4.41 and 3.15 (d, J=12Hz, 8H, $ArCH_2Ar$, cone), 3.80 (t, 4H, OCH_2CH_2), 1.90 (m, 4H, $CH_2(CH_2O)$), 1.45 (m, 4H,$CH_2(CH_3)$), 1.20 and 0.96 (s, 18H each, t-Bu), 1.05 (t, 6H, CH_3), Anal. calcd. for $C_{58}H_{80}O_4$ (841.27): C 82.81, H 9.58, Found: C 82.45, H 9.52

5,11,17,23-Tetra-t-butyl-25,27-diallyloxy-26,28-dibenzyloxycalix[4]arene (**1j**)

Yield:88% (from 1 H_2Bn_2) mp:202-204°C (i-PrOH), ^{1}H NMR δ: 7.25 (s, 10H, ArH), 7.00 (s, 4H, ArH), 6.45 (s, 4H, ArH), 6.25 (m, 2H, CH=), 4.90 (d, 2H, CH_2=), 4.80 (d, 2H, CH_2=), 4,72 (s, 4H, OCH_2Ph), 4.52 (d, J=7.5Hz, 4H, OCH_2CH=), 4.38 and 3.02 (d, J=12Hz, 8H, $ArCH_2Ar$, cone), 1.90 (m, 4H, $CH_2(CH_2O)$), 1.32 and 0.95 (s, 18H each, t-Bu), Anal. calcd. for $C_{64}H_{76}O_4$ (909.30): C 84.54, H 8.42, Found: C 84.25 H 8.35

5,11,17,23-Tetra-t-butyl-25,27-dibenzyloxy-26,28-dipropoxycalix[4]arene (**1k**)

Yield:93% (from 1 H_2Pr_2) mp:219-220°C (BuOH), ^{1}H NMR δ: 7.30 (br s, 10H, ArH), 7.03 (s, 4H, ArH), 6.48 (s, 4H, ArH), 4,72 (s, 4H, OCH_2Ph), 4.42 and 3.14 (d, J=12Hz, 8H, $ArCH_2Ar$, cone), 3.78 (t, 4H, $OCH_2(CH_2)$), 1.76 (m, 4H, $CH_2(CH_3)$), 1.30 and 0.95 (s, 18H each, t-Bu), 0.90 (t, 6H, CH_3), Anal. calcd. for $C_{64}H_{80}O_4$ (913.33): C 84.16, H 8.83, Found: C 84.38, H 8.90

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