Casting heteracalixarenes from calixarene templates: A unique synthetic strategy

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SUPPLEMENTARY INFORMATION

CONTENTS

1. Experimental

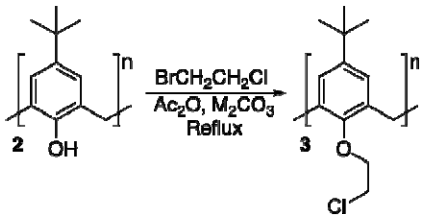
All the reagents used were of AR grade, procured from Sigma-Aldrich. The reagents were used without further purification. The solvents were dried appropriately wherever required. Melting points were taken in a single capillary tube using Toshniwal melting point apparatus and are uncorrected. Elemental analysis was carried out on Heraeus CarloEbra 1108 elemental analyzer. ^{1}H NMR spectra were recorded on Bruker DPX-400 AVANCE in DMSO-d6 with tetramethylsilane as internal standard. Liquid chromatography was conducted on Waters Acquity UPLC system (Milford, MA, USA) with Waters analytical column, type UPLC BEH C18 reversed phase (1.75µm particle size, 100 mm long and 2.1 mm internal diameter) maintained at 40 °C, mobile phase composition was methanol: 0.01% acetic acid (90:10 v/v). Mass measurements were done on Waters, Quattro Premier XE (Milford, MA, USA), equipped with electrospray ionization and operating in positive ionization mode.

2. Synthesis and Characterization

2.1. *Calix[n]arenes (CnAs; n=4-8)* $\mathbf{2}_n$

Calix[*n*]arenes were prepared by established procedures (monographs by C.D.Gutsche).[1]

2.2. *2-chloroalkyl-ethers of calix[n]arenes* $\mathbf{3}_n$



General procedure: $\mathbf{2}_n$ (25 mmol) was suspended in dry acetone (500 ml) containing anhydrous alkali carbonate (1.5× *n* ×25 mmol) and 1,2-chlorobromoethane (2× *n* ×25 mmol). The mixture was heated under reflux for 6-14 h. After cooling, the solid residue was filtered and washed thrice

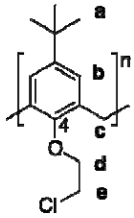
with dichloromethane (50 ml). The combined filtrates were evaporated in vacuo to remove solvents. From the solid residue containing the mixture of conformational isomers, the *cone* isomer **3**$_n$ was separated by fractional crystallization from ethanol-chloroform (4:1) solution.

Table S1. Characterization Data for **3**$_n$ (%Yield, MS, M.P. and Elemental Analysis)

Product (3$_n$)	**3$_4$**[a]	**3$_5$**[a]	**3$_6$**[b]	**3$_7$**[b]	**3$_8$**[b]
Base (Alkali)	NaOH	NaOH/KOH	KOH/RbOH	RbOH	CsOH
Yield (%)	86	35/42	33/19	26	41
ESI-MS (*m/z*, *M+1*)	900	1125	1349	1574	1798
M.P. (^{o}C)	>300	>300	-	-	-
Elemental Analysis (Calcd. C: 69.48, H: 7.62)	C: 69.40 H: 7.59	C: 69.35 H: 7.56	C: 69.39 H: 7.63	C: 69.36 H: 7.64	C: 69.41 H: 7.56

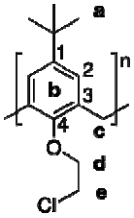
[a]Isolated yields of *cone* conformer, [b]Total yield of mixture of conformers

Table S2. ^{1}H NMR Data for **3**$_n$



n	**a**	**b**	**c**	**d**	**e**	**J_c**
4	1.19	6.41	3.24 & 4.66(d)	4.35(d)	4.18(d)	12.6
5	1.18	6.49	3.66 & 5.58(d)	4.37(d)	4.14(d)	12.5
6	-	-	-	-	-	-
7	-	-	-	-	-	-
8	-	-	-	-	-	-

Table S3. ^{13}C NMR Data for **3**$_n$

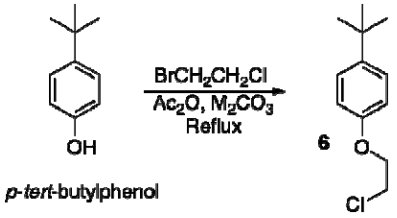


n	**a**	**b$_{1,3,4}$**	**b$_2$**	**c**	**d**	**e**
4	31.6	143.1-160.7 (3)	135.9	32.6	75.0	43.1
5	31.1	143.3-159.9 (3)	135.9	32.7	74.8	43.1
6	-	-	-	-	-	-
7	-	-	-	-	-	-
8	-	-	-	-	-	-

Note: values separated by '&' depict two signals from structurally equivalent but conformationally different atoms.
values separated by hyphen (-) depict a range with multiple peaks where individual peaks can not be assigned.

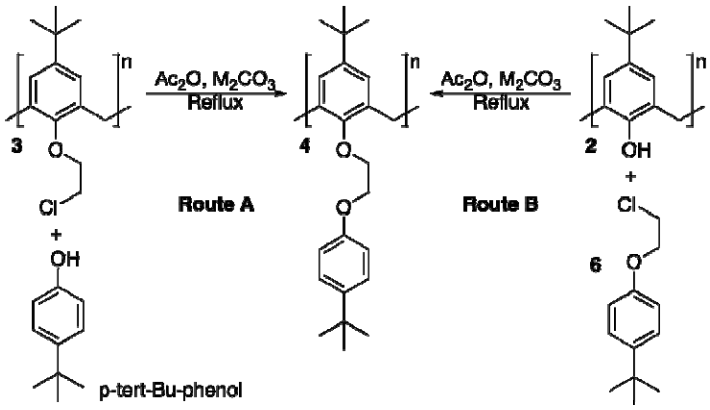
It would be appropriate to note here that, the 2-chloroethyl ethers of calixarenes **2**$_{6\text{-}8}$, when in solution, exist as an equilibrated mixture of continually inter-converting conformers. Thus, no matter in which conformation are they found in their crystal structure, they are impossible to completely stabilize in any specific conformation in a reaction mixture.

2.3. *2-Chloroalkyl-(p-tert-butyl)phenyl ether* ***6***



General procedure: *p-tert*-butylphenol (100 mmol) was suspended in dry acetone (500 ml) containing a 1.5 fold excess of anhydrous alkali carbonate (150 mmol) and 2 fold excess of 1,2-chlorobromoethane (200 mmol). The mixture was heated under reflux for 4 h. After cooling, the solid residue was filtered and washed with dichloromethane (50 ml) three times. The combined filtrates were evaporated *in vacuo* to remove solvents. The solid residue was crystallized from ethanol. Yield 89%. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ 7.50 (s, 2H; Ar-H), 6.92 (s, 2H; Ar-H), 1.34 (s, 9H; *t*-Bu), 4.23 (s, 2H; OCH_2), 4.12 (s, 2H; CH_2Cl); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ31.3 (3), 34.2(1) (*t*-Bu), 125.4(2), 114.7(2), 142.9(1), 156.6(1) (Ar), 75.2(2) (OCH_2), 43.1(2) (CH_2Cl) ; ESI MS: Calcd. 213, Found: 214 (M+1); Elemental analysis for $C_{70}H_{84}O_7S_7$: Calcd: C 67.76, H 8.06; Found: C 67.69, H 8.09.

2.4. *Calix[n]arene-(p-tert-butyl)phenyl 1,2-diethers* $\boldsymbol{4_n}$



General procedure:

Route A: A mixture of $\mathbf{3}_n$ (25 mmol) and p-tert-butylphenol (2× *n* ×25 mmol) was suspended in dry acetone (500 ml) containing anhydrous alkali carbonate (1.5× *n* ×25 mmol). The mixture was

heated under reflux for 10-24 h. After cooling, the solid residue was filtered and washed with dichloromethane (50 ml) three times. The combined filtrates were evaporated in vacuo to remove solvents. The product was crystallized from chloroform.

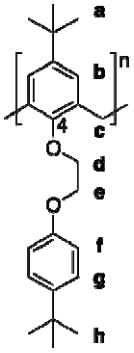
Route B: A mixture of $\mathbf{2}_n$ (25 mmol) and **6** (2× *n* ×25 mmol) was suspended in dry acetone (500 ml) containing anhydrous alkali carbonate (1.5× *n* ×25 mmol). The mixture was heated under reflux for 10-24 h. After cooling, the solid residue was filtered and washed with dichloromethane (50 ml) three times. The combined filtrates were evaporated in vacuo to remove solvents. From the solid residue containing the mixture of conformational isomers, the *cone* isomers $\mathbf{4}_n$ was separated by fractional crystallization from ethanol-chloroform (4:*n*) solution.

Table S4. Characterization Data for **4** (%Yield, MS, M.P. and Elemental Analysis)

Product (4*n*)	$\mathbf{4}_4$	$\mathbf{4}_5$	$\mathbf{4}_6$	$\mathbf{4}_7$	$\mathbf{4}_8$
Base (Alkali)	NaOH	NaOH	KOH	RbOH	CsOH
Route A (% Yield)	76	70	-	-	-
Route B (% Yield)[a]	82	78	70	59	37
ESI-MS (*m/z*, *M+1*)	1355	1693	2032	2370	2709
M.P. (°C)	>300	>300	>350	>350	>350
Elemental Analysis (Calcd. C: 81.61, H: 8.93)	C: 81.61 H: 8.80	C: 81.52 H: 8.79	C: 81.55 H: 8.95	C: 81.49 H: 8.81	C: 81.50 H: 8.87

[a]Isolated yields of *cone* conformer

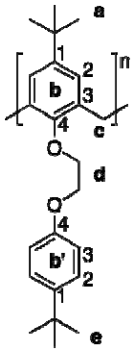
Table S5. ^{1}H NMR Data for $\mathbf{4}_n$



n	a	b,f	c	d,e	g	h	J_c
4	0.82 & 0.85	6.32,6.96	3.24 & 4.66(d)	4.35,5.43(d)	7.10 & 7.75	1.33	12.5
5	0.82 & 0.87	6.33,6.71	3.66 & 5.58(d)	4.37,5.33(d)	7.10 & 7.68	1.32	12.6
6	0.90 & 0.93	6.37,6.88	4.03 & 5.44(d)	4.25,5.41(d)	7.10 & 7.56	1.33	12.6
7	0.90 & 1.02	6.43,6.97	3.78 & 5.64(d)	4.25,5.53(d)	7.15 & 7.69	1.32	12.5
8	0.89 & 1.10	6.51,7.01	3.80 & 5.64(d)	4.25,5.55(d)	7.18 & 7.76	1.32	12.5

Note: values separated by '&' depict two signals from structurally equivalent but conformationally different atoms.

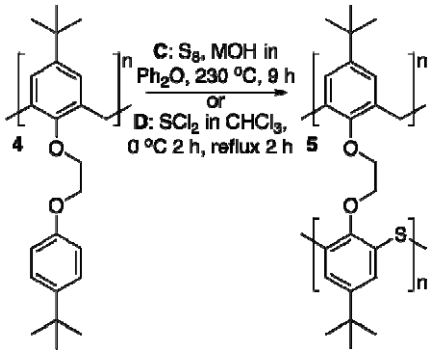
Table S6. ^{13}C NMR Data for $\mathbf{4}_n$



n	a	$b_{1,3,4}$, $b'_{1,4}$	b_2, $b'_{2,3}$	c	d	e
4	30.8 & 31.8	144.2-161.5 (5)	133.6-135.8 (3)	31.9	72.1 & 75.0	34.1 & 36.5
5	30.5 & 31.1	144.3-159.9 (5)	133.2-135.7 (3)	32.1	71.9 & 75.6	34.0 & 35.9
6	30.9 & 31.6	144.8-161.4 (5)	134.8-135.8 (3)	32.2	72.0 & 77.2	34.8 & 37.0
7	30.8 & 32.0	146.6-160.7 (5)	135.1-135.6 (3)	32.3	73.3 & 76.1	34.5 & 36.2
8	30.9 & 31.9	146.3-159.8 (5)	134.9-135.8 (3)	32.4	73.1 & 76.0	34.4 & 36.3

Note: values separated by '&' depict two signals from structurally equivalent but conformationally different atoms.
values separated by hyphen (-) depict a range with multiple peaks where individual peaks can not be assigned.

2.5. Calix[n]arene-thiacalix[n]arene pseudo dimers $\mathbf{5}_n$



General procedure: ***Method C:*** A mixture of **4** (25 mmol), elemental sulfur S_8 (50 mmol), and MOH (25 mmol) in super-dry diphenyl ether (100 ml) was stirred for 15 min, heated gradually to 160 °C over a period of 1 h and kept at this temperature for further 3 h. The temperature was again raised to 230 °C over a period of 3 h and maintained for further 3 h. The resulting reaction mixture was cooled to ambient temperature and analyzed by UPLC-MS. 1 ml of reaction mixture was sampled after every 30 min, loaded on solid phase extraction cartridge and washed with acetonitrile (1 ml x 2) to selectively remove decomposition residues. The products were then eluted with methanol (1 ml x 3) and 50 µl of the eluate was injected for analysis of product mixture. No isolable quantity of **5** was achieved in any case.

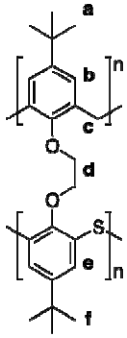
Method D: To a solution of **4** (10 mmol) in dry CH_2Cl_2 (100 ml) was added SCl_2 (40×*n* mmol in CH_2Cl_2) and stirred for 2 h at 0 °C. The reaction mixture was refluxed for 2 h and allowed to cool

to ambient temperature spontaneously. The excess of SCl_2 was destroyed with careful addition of iced water with continuous stirring. The organic layer was separated and evaporated to dryness with aid of vacuum. The residue obtained was washed with acetone, ethanol and chloroform:ethylacetate (1:1 v/v) mixture to obtain respective products **5**$_n$. The products were recrystallized in CH_2Cl_2.

Table S7. Characterization Data for **5**

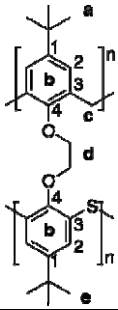
Product (5*n*)	**5$_4$**	**5$_5$**	**5$_6$**	**5$_7$**	**5$_8$**
Method D (% Yield)	62	58	57	54	32
ESI-MS (*m/z*, *M+1*)	1775	1844	2212	2581	2949
M.P. (^{o}C)	>350	>350	>350	>350	>350
Elemental Analysis (Calcd. C:74.96 H:7.66 S:8.70)	C: 75.01 H: 7.60 S: 8.66	C: 74.85 H: 7.63 S: 8.76	C: 74.91 H: 7.59 S: 8.68	C: 74.90 H: 7.61 S: 8.73	C: 74.89 H: 7.60 S: 8.67

Table S8. ^{1}H NMR Data for **5**



n	a	b	c	d	e	f	J_c
4	0.82 & 0.85	6.49 & 6.94	3.24 & 4.66(d)	4.35 - 5.43(4m)	7.12 & 7.66	1.33	12.7
5	0.82 & 0.87	6.49 & 6.69	3.66 & 5.58(d)	4.37 - 5.33(4m)	7.10 & 7.48	1.30	12.6
6	0.90 & 0.93	6.47 & 6.88	4.03 & 5.44(d)	4.25 - 5.41(4m)	7.10 & 7.56	1.31	12.6
7	0.90 & 1.02	6.51 & 6.97	3.78 & 5.64(d)	4.25 - 5.53(4m)	7.18 & 7.68	1.32	12.4
8	0.89 & 1.10	6.50 & 7.01	3.80 & 5.64(d)	4.25 - 5.55(4m)	7.15 & 7.77	1.32	12.5

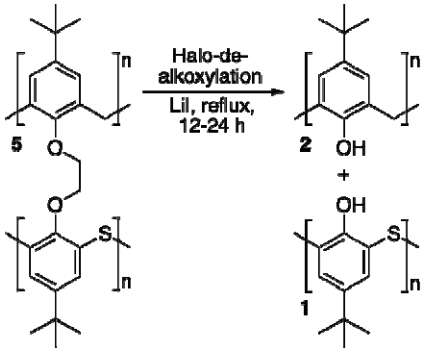
Table S9. ^{13}C NMR Data for **5**



n	a	$b_{1,3,4}$	b_2	c	d	e
4	30.9 & 31.8	144.3-160.9 (6)	134.2 & 135.4	31.9	72.6 & 74.0	33.5 & 34.3
5	29.8 & 31.1	144.1-158.7 (6)	133.6 & 135.0	31.7	70.1 & 73.6	35.0 & 35.9
6	30.5 & 31.6	143.6-161.1 (6)	134.4 & 135.9	31.9	73.0 & 78.2	33.7 & 35.0
7	30.9 & 32.0	147.5-160.8 (6)	135.0 & 135.9	33.0	74.4 & 76.1	35.2 & 36.6
8	30.8 & 31.9	147.4-158.9 (6)	134.8 & 135.7	33.0	74.6 & 77.0	35.2 & 36.5

Note: values separated by '&' depict two signals from structurally equivalent but conformationally different atoms.
values separated by hyphen (-) depict a range with multiple peaks where individual peaks can not be assigned.

2.6. Halo-de-alkoxylation of $\mathbf{5}_n$



General Procedure: A suspension of finely powdered $\mathbf{5}_n$ (20 mmol) in 50 ml 99% alcohol was stirred vigorously for 10 min and added with $50 \times n$ ml LiI solution (4 M in 50% aq. alcohol, v/v). The reaction mixture was brought to reflux with continuous vigorous stirring. The mixture was allowed to reflux for 12-24 h and allowed to cool. The reaction mixture was acidified with 100 ml 1 M hydrochloric acid and the products were recovered by filtration, followed by drying to yield solid residue. The residue was dissolved in 50 ml chloroform, filtered and chromatographed on silica gel (200 mesh, 100 mm, length × 15 mm, diameter column) using hexane:chloroform (1:1-2, v/v) mobile phase.

Table S10. Characterization Data for $\mathbf{1}_n$ (%Yield, MS, M.P. and Elemental Analysis)

Product (3_n)	$\mathbf{1}_4$	$\mathbf{1}_5$	$\mathbf{1}_6$	$\mathbf{1}_7$	$\mathbf{1}_8$
Yield (%)	85	84	79	73	64
ESI-MS (*m/z, M+1*)	722	902	1083	1264	1443
M.P. (^{o}C)	>300	>300	>300	>350	>350
Elemental Analysis (Calcd. C: 66.63, H: 6.71, S: 17.79)	C: 66.61 H: 6.69 S: 17.80	C: 66.57 H: 6.59 S: 17.82	C: 66.60 H: 6.71 S: 17.69	C: 66.45 H: 6.72 S: 17.73	C: 66.53 H: 6.68 S: 17.77

NMR spectra of all $\mathbf{1}_{4\text{-}8}$ derivatives have already been published,[2] and hence not repeated here.

2.7. Recovery of templating calix[n]arenes $\mathbf{2}_n$

It may be noticed here that some of the calix[*n*]arene templates (especially the odd numbered homologs) are themselves not very easy to prepare (and thus expensive), therefore it is highly desirable to recover the unreacted/partially reacted templates. In this regard, two strategies can be employed. That is, either to recover the unreacted fraction at the end of each step and hydrolyze

them appropriately, or collect unreacted fractions of all steps and proceed with the hydrolysis. Both the strategies were tested and give equally satisfactory results; however, from practical view point the latter strategy is beneficial. In practice, all the residual fractions (including solid residues, washings, mother liquor of crystallization etc.) are collected and evaporated to dryness under vacuum. The solid/semi-solid residue obtained is then washed/triturated with hexane and evaporated to dryness to give solid powder. The powder is washed with warm aq. ethanol (10% v/v) to remove inorganic salts. The final residue may then be subjected to alkaline hydrolysis with aq. NaOH/KOH (2 M) or halo-de-alkoxylation (as per section ***2.6*** above) under reflux conditions followed by usual work up. The purification may be carried out by crystallization (acetone vapor diffusion in chloroform solution of products at room temperature) or column chromatography. For the sake of obtaining a clear picture of quantitative recovery, the results of recovery (%) of calix[5]arene for all individual steps (in a complete reaction cycle) have been tabulated in table S11 as a representative example. Overall % recovery of $\mathbf{2}_5$ is ca. 70% in this case. Similarly, the % recovery ranges from ca. 60-75% for different homologs, which is very good for a four step reaction.

Table S11. % Recovery of calix[5]arene $\mathbf{2}_5$ for individual steps.

Reaction Step	$\mathbf{2}_5 \rightarrow \mathbf{3}_5$	$\mathbf{3}_5 \rightarrow \mathbf{4}_5$	$\mathbf{2}_5 \rightarrow \mathbf{4}_5$	$\mathbf{4}_5 \rightarrow \mathbf{5}_5$	$\mathbf{5}_5 \rightarrow \mathbf{2}_5$
Recovery (%)	39	21	14	32	86

% Recoveries are calculated on the basis of initial amount of $\mathbf{2}_5$ derivative reacted in each step.

3. A discussion on NMR Spectral data and conformational preferences of $\mathbf{5}_n$

The structure of pseudo dimers (calix-thiacalix tubes) $\mathbf{5}_n$ was confirmed by ^{1}H & ^{13}C NMR, and ESI-mass spectral data. The ^{1}H NMR spectra of all $\mathbf{5}_n$ homologs were well resolved. For instance, in case of $\mathbf{5}_6$, the ^{1}H NMR spectrum contains four singlets in the aromatic region (**b**:6.47 & 6.88 and **e**:7.10 & 7.56 in table **S8**), two pairs of multiplets of ethylene –OCH_2CH_2O– protons (4.25, 4.82, 5.05 & 5.41 total 4 signals, **d** in table **S8**), two doublets from bridging methylene group -

$ArCH_2Ar$- protons (**c**: 4.03 & 5.44), and also a set of singlets from *tert*-butyl groups (**a**: 0.90 & 0.93 and **f**: 1.31). ^{13}C NMR spectra contain eight sets of closely spaced aromatic signals (two in each set) in aromatic region (**b** in table **S9**), four signals of $-OCH_2CH_2O-$ carbons (**d** in table **S9**), and four signals from *p-tert*-butyl substituents of the upper rim (**a** from calix and **e** from thiacalix in table **S9**). The results of ^1H & ^{13}C NMR measurements are in very good agreement with existing literature, especially with the results of extensive study of structural preferences (of calix-, thiacalix-, and hybrid calix-thiacalix tubes, i.e. symmetric and asymmetric/pseudo dimers) carried out by Kovalev et al.[4] through NMR spectroscopy (tube $\mathbf{5_4}$ has already been reported by Kovalev et al.)

Now let us examine the NMR Spectra. The double set of all NMR signals, especially in the aromatic region, indicates that both calix frameworks (calix and thiacalix) of pseudo dimers $\mathbf{5_6}$ contain two type of aromatic rings, suggesting C_2v symmetry. Further, it is known that C*6*A and TC*6*A possess near C_2v symmetry in their crystal structure with a single conformation, but when solvated, they exhibit two different conformers (*flattened/pinched cone* – C_2v and *cone* C_6v) at lower temperature (as is evident from their NMR spectra). At higher temperature, in solution, they undergo rapid *pinched cone – cone – pinched cone* inter conversion, effectively giving averaged signals. A similar pattern of apparent asymmetry in present compounds (pseudo dimers) can be envisaged due to conformational properties of constituent calixarene fragments themselves, which form the tube (pseudo dimer). A more comprehensive discussion on the conformational preferences of calix[4]arene-thiacalix[4]arene tubes (and other symmetric tubes) can be availed by referring to the work of Kovalev et al.[4] where as the work of Beer et al.[5] may be of particular interest for study of conformational analysis of bis(calix[4]arene) tubes and their various derivatives (accomplished with the aid of NMR spectroscopy as well as X-ray diffraction analysis). The latter have also studied the metal complexation and accompanying structural changes for the bis-calix tubes.

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