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Unprecedented cyclisations of calix[4]arenes with glycols under the Mitsunobu protocol. Part 1: A new perspective for the synthesis of calixcrowns

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Abstract—Selective ring closures of *p-tert*-butylthiacalix[4]arene and *p-tert*-butylcalix[4]arene with oligoethylene glycols were performed under the Mitsunobu protocol using the DEAD/TPP system. The method opens a new perspective for the syntheses of 1,3-calixcrowns. © 2003 Elsevier Science Ltd. All rights reserved.

In the last decade a great number of supermolecules combining the unique properties of calixarenes and crown ethers have been described[1,2] and applied to analytical and separation chemistry.[3,4] These studies have been expanded to thiacalixcrowns: a series of distally and proximally bridged mono- and bis-crown-5 and -6 ethers have been described and their metal ion complexing abilities assessed.[5–9] A common feature of the synthesis of calixcrowns is the base promoted cyclisation of calixarenes or the thia analogues with oligoethylene glycol ditosylates.[1] The outcome of the reaction (bridging pattern, regio- and stereo-control) is strongly dependent on the cyclising agents and the template effect of the cations of the bases used. Alkali carbonate mediated ring closures lead to 1,3-bridged calixcrowns in cone or 1,3-alternate conformations and generally require 1–14 days heating of the reactants in MeCN. 1,2-Bridging can be attained with stronger bases (NaH, alkali alcoholates) under milder conditions and shorter times.[10,11] These protocols work with calix[4]arene tetrols where mono- and bis-crowns can be selectively obtained. The cyclisation of thiacalixarene counterparts, however, cannot be stopped effectively at the mono-stage, only biscrowns are available by this approach.[6,9]

In our previous paper[12] we demonstrated for the first time the selective *O*-alkylation of *p-tert*-butylthiacalix[4]arene with a series of alcohols under the Mitsunobu protocol[13,14] using triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD) in THF or toluene. In light of our results it is surprising that this extremely effective reaction has not been utilised fully in calixarene chemistry, apart from two literature examples.[15,16] It is also surprising but understandable, because of the dominance of templated cyclisations, that the Mitsunobu cyclisation of diphenols with glycols has remained unexplored (only a side reaction between 1,1′-bi-2-naphthol and a 1,3-diol derivative refers to cyclic products).[17] These preliminaries prompted us to explore the possibility of intramolecular reactions between calix[4]arenes and oligoethylene glycols under standard Mitsunobu conditions. The success of a selective 1:1 versus 2:2 coupling could not be predicted, especially if the lack of the metal ion template which plays an important role in the formation of crown ethers is considered.

The reactions were performed in toluene with *p-tert*-butylcalix[4]arene (CA) and *p-tert*-butylthiacalix[4]-arene (TCA) using commercial di-, tri- and tetraethylene glycols, aza and benzo analogues thereof, respectively, under two different conditions: (1) with the molar ratio of the CA or TCA: (glycol/TPP/DEAD)= 1: (1.5/3/3) at room temperature, (2) with the molar ratio of the CA or TCA: (glycol/TPP/DEAD)=1: (4/7/7) at 110°C. The outcome of the reactions is outlined in Scheme 1.

Keywords: calix[4]crowns; cyclisation; glycols; Mitsunobu reaction.
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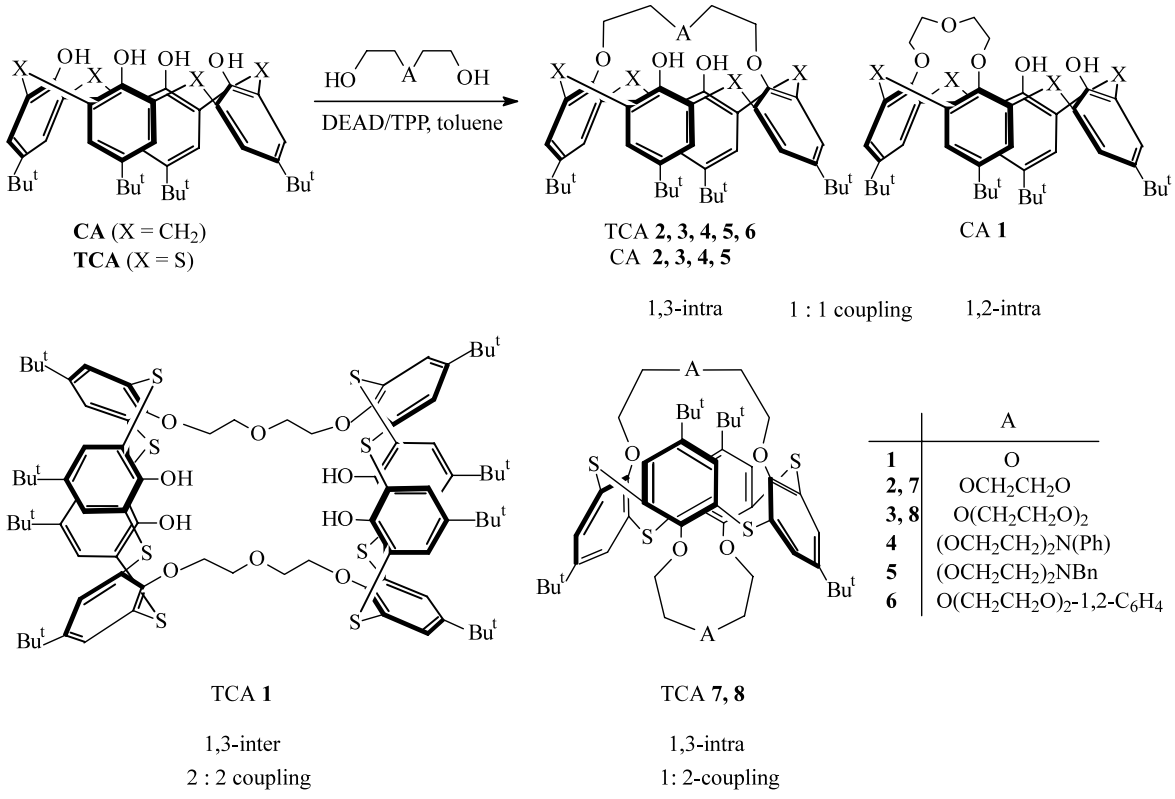

Scheme 1. Survey of reactions of calix[4]arenes with oligoethylene glycols under the Mitsunobu conditions.

The reactions of CA and TCA were completed within 10–30 min at room temperature affording 1,3-calix-monocrowns CA**2**–**5** and TCA**2**–**6** with unexpectedly high selectivity and in yields of 30–50% referring to the 1 mmol reaction scale. However, the yields were increased by scaling up, e.g. in 5 mmol experiments TCA**3** and TCA**4** were obtained in 60–70% yields. The short chained diethylene glycol **1** gave different results in respect of CA and TCA. In the former case it was not capable of bridging the distal 1,3-OH groups yielding, therefore, the proximal 1,2-calixcrown-3 derivative CA**1**. The 15% larger cavity of TCA prevented **1** by intermolecular coupling from any intramolecular ring closure, here the formation of the dimer TCA**1** was preferred. This compound is the first representative of a koiland-type multicavity receptor in the thiacalixarene series where two thiacalix units are connected by glycol chains. The highly symmetric structure of TCA**1** is reflected by the extremely simple ^{1}H NMR spectrum characteristic of the conic 1,3-calixcrowns. The dimer structure was unambiguously proved by positive FAB-MS (m/z: 1619 $[M+K]^+$).

During the high temperature reactions of TCA using an excess of glycols **2**, **3** and the TPP/DEAD reagents, 1,3-biscrowns TCA**7**, TCA**8** could be isolated as well as the dominant monocrowns TCA**2**, TCA**3**, but only in low yields (15%). Biscrowns cannot be prepared effectively by this one-pot procedure but a higher yield was achieved in a two-step method: when thiacalixcrown-5 TCA**3** was treated with tetraethylene glycol (110°C, 12 h) using a molar ratio of TCA**3**/**3**/TPP/DEAD = 1/2/4/4, the biscrown-5 TCA**8** was obtained in a 50% yield. With the aid of this ring closure, ditopic TCA receptors comprising different crown rings may be accessible which are not available otherwise.

None of the glycols gave biscrowns with CA even under these vigorous conditions. The differences in the reactivity of TCA and CA towards the second Mitsunobu coupling can be rationalised in terms of the acidities of the OH groups remaining after the first reaction. With TCA these values ($pK_{a3,4}$ = 11.6–12)[18] reach the lower limit where the reaction is still predicted to take place.[14] In the case of CA, due to the acidities being weaker by more than one order of magnitude (estimated $pK_{a3,4}$ <13),[18] the second ring closure failed.

Of the compounds prepared during this study,[19] monocrowns CA**1**10, **2**,[20,21] **3**,[22] and TCA**3**[9] have been described already and it has been established they exist, just like the new thiacalix[4]monocrowns TCA**2** and **4**–**6**, in *cone* conformations. It is worth noting here that the traditional base promoted syntheses of the calix[4]monocrown-4 CA**2** and the thiacalix[4]monocrown-5 TCA**3** have been reported to provide comparable or lower yields in extremely long reactions.[9,19] In addition, the other monocrowns TCA**2**, **4**–**6** of the thiacalixarene series and CA**4**, **5** of the calixarene series have not been available until now by any method. Thiacalix[4]biscrown TCA**8** has also been synthesised earlier[5,6,9] and found to exist, just like the new derivative TCA**7**, in the 1,3-*alt* conformation. Here we should emphasise that, to our knowledge, TCA**4**

and **5** are the only representatives of thiacalixarene azacrowns.

Two interesting questions remain to be answered: (1) why are these reactions which involve a double alkylation during cyclisation much faster when compared to dialkylation with simple alcohols?[12] (2) Why is the formation of a crown ring preferred in most cases to intermolecular coupling?

Presently, we have no firm evidence but we assume that, after the substitution of the first OH group by a glycol chain, the podand-like arm of the intermediate thereby formed, acting as a tether, keeps the second cationic phosphonium species in a beneficial molecular environment (together with the calixarene perhaps) facilitating by this means a rapid intramolecular coupling. Glycols with medium chain lengths (**2**–**5**) can bridge the obviously preferred diametrical positions in both CA and TCA. The effect of the cavity sizes (TCA>CA) on the outcome of reactions is reflected mainly in the results obtained with the shortest glycol **1** (CA: 1,2-intra, TCA: 1,3-inter) and the longest glycol **6** (TCA: 1,3-intra, CA: no ring closure), respectively. The latter is supposed to be too long to cyclise with CA in a non-templated reaction.

In conclusion, the Mitsunobu cyclisation with oligoethylene glycols has been demonstrated to represent an attractive alternative for the synthesis of 1,3-monocrown-4,-5-, and 6-ethers including monoazacrowns in both calix[4]arene series. The main advantages of the method are the extremely short reaction times, mild conditions and similar yields in comparison to the traditional base promoted ring closures. In addition, the preparation of glycol ditosylate cyclising agents can be avoided. Notwithstanding the disadvantages (the commercially unavailable and dangerous DEAD, large amount of ballast TPPO, DEHD formed from the reagents), the method allows access to calixcrowns in multigram scale.

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19. NMR spectra were recorded at 298 K in $CDCl_3$ at 500/125 MHz on a Bruker-Avance DRX-500 instrument. *General procedure for the reactions of CA and TCA with oligoethylene glycols*: To the stirred mixture of **TCA** (0.72 g, 1 mmol) or **CA** (0.65 g, 1 mmol) TPP (0.8 g, 3mmol), glycol (1.5 mmol) in 20 ml toluene, a 40% toluene solution of DEAD (1.3 ml, 3 mmol) was added at room temperature and allowed to react for 0.5 h. The solvent was then removed under reduced pressure and worked up differently: (1) TCA derivatives were triturated with MeOH (20 ml) and filtered to give white solids (thus TCA**1** was obtained in pure form) which were purified by chromatography on silica (eluent: hexane–EtOAc = 9:1, TCA**2**–**7**), (2) CA**1** and **2** were extracted from the residue with hexane (3×10 ml) followed by evaporation and subsequent trituration with MeOH (CA**1**) or chromatography (eluent: hexane–EtOAc = 8:2). The residue containing CA**3**–**5** was directly chromatographed (eluent: hexane–EtOAc = 8:2 and 9:1, respectively).
Compounds CA**1**,[10] **2**,[20,21] **3**,[22] TCA**3**[9] and TCA**8**[5] were identical in every respect with the reference samples prepared by base promoted cyclisations.
Compound TCA**1**. Mp 340–342°C; ^{1}H NMR: δ 8.42 (s, 4H, O*H*), 7.57 (s, 8H, Ar*H*), 6.86 (s, 8H, Ar*H*), 5.08 (bs, 8H, OCH_2), 4.19 (bs, 8H, OCH_2), 1.32 (s, 36H, Bu^t), 0.74 (s, 36H, Bu^t); ^{13}C NMR: δ 156.2, 155.6, 142.1, 134.7, 129.7, 129.1, 128.3 (Ar), 72.1, (O*C*H$_2$), 34.5 (*C*(CH$_3$)$_3$), 34.3 (*C*(CH$_3$)$_3$), 31.9 (C(*C*H$_3$)$_3$), 31.1 (C(*C*H$_3$)$_3$); FAB-

MS m/z (%): 1581 $[M+H]^+$(69), 1598 $[M+NH_4]^+$(49), 1619 $[M+K]^+$(100); anal. calcd for $C_{88}H_{108}O_{10}S_8$ (1582.29): C, 66.80; H, 6.88, found: C, 66.43; H, 6.82%.

Compound TCA**2**. Mp 272–273°C; ^{1}H NMR: δ 8.51 (s, 2H, O*H*), 7.68 (s, 4H, Ar*H*), 7.19 (s, 4H, Ar*H*), 4.77 (t, 4H, $J=5.6$, OCH_2), 4.28 (t, 4H, $J=5.6$, OCH_2), 3.94 (bs, 4H, OCH_2), 1.36 (s, 18H, Bu^t), 0.93 (s, 18H, Bu^t); ^{13}C NMR: δ 157.1, 156.4, 147.8, 142.4, 134.7, 134.0, 128.9, 121.8 (Ar), 74.6, 71.3, 70.5 (O*C*H$_2$), 34.3 (*C*(CH$_3$)$_3$), 34.2 (*C*(CH$_3$)$_3$), 31.7 (C(*C*H$_3$)$_3$), 31.0 (C(*C*H$_3$)$_3$); anal. calcd for $C_{46}H_{58}O_6S_4$ (835.20): C, 66.15; H, 7.00, found: C, 65.89; H, 7.04%.

Compound TCA**3**. Mp 240–243°C; ^{1}H NMR: δ 8.04 (s, 2H, O*H*), 7.67 (s, 4H, Ar*H*), 6.93 (s, 4H, Ar*H*), 4.74 (t, 4H, $J=4.7$, OCH_2), 4.15 (t, 4H, $J=4.7$, OCH_2), 3.89 (bs, 4H, OCH_2), 3.81 (bs, 4H, OCH_2), 1.34 (s, 18H, Bu^t), 0.78 (s, 18H, Bu^t); ^{13}C NMR: δ 156.0, 155.9, 147.9, 142.5, 134.7, 132.7, 129.2, 122.3 (Ar), 73.2, 71.1, 70.3, 70.0 (O*C*H$_2$), 34.5 (*C*(CH$_3$)$_3$), 34.3 (*C*(CH$_3$)$_3$), 31.8 (C(*C*H$_3$)$_3$), 31.1 (C(*C*H$_3$)$_3$); FAB-MS m/z (%): 901 $[M+Na]^+$(100), 917 $[M+K]^+$(30); anal. calcd for $C_{48}H_{62}O_7S_4$ (879.25): C, 65.57; H, 7.11, found: C, 65.23; H, 7.01%.

Compound TCA**4**. Mp 236–238°C; ^{1}H NMR: δ 8.14 (s, 2H, O*H*), 7.70 (s, 4H, Ar*H*), 7.20 (bs, 2H, Ar*H*), 6.97 (s, 4H, Ar*H*), 6.75 (bs, 2H, Ar*H*), 6.65 (bs, 1H, Ar*H*), 4.73 (bs, 4H, OCH_2), 4.09 (bs, 4H, OCH_2), 3.93 (bs, 4H, OCH_2), 3.75 (bs, 4H, OCH_2), 1.37 (s, 18H, Bu^t), 0.81 (s, 18H, Bu^t); ^{13}C NMR: δ 156.0, 155.7, 148.0, 142.5, 134.8, 132.7, 129.3, 129.2, 122.2, 115.9, 111.7 (Ar), 74.0, 70.0, 69.2 (O*C*H$_2$), 51.4 (N*C*H$_2$), 34.5 (*C*(CH$_3$)$_3$), 34.3 (*C*(CH$_3$)$_3$), 31.9 (C(*C*H$_3$)$_3$), 31.1 (C(*C*H$_3$)$_3$); anal. calcd for $C_{54}H_{67}O_6NS_4$ (954.36): C, 67.96; H, 7.08, found: C, 67.75; H, 7.04%.

Compound TCA**5**. Mp 138–142°C; ^{1}H NMR: δ 8.07 (s, 2H, O*H*), 7.68 (s, 4H, Ar*H*), 7.36 (m, 2H, Ar*H*), 7.23 (m, 3H, Ar*H*), 6.92 (s, 4H, Ar*H*), 4.72 (t, 4H, OCH_2), 4.06 (t, 4H, OCH_2), 3.83 (t, 4H, OCH_2), 3.73 (s, 2H, NCH_2Ar), 2.92 (t, 4H, NCH_2), 1.34 (s, 18H, Bu^t), 0.77 (s, 18H, Bu^t); ^{13}C NMR: δ 155.9, 155.7, 147.7, 142.3, 136.3, 134.6, 132.5, 129.1, 128.7, 128.1, 126.8, 122.1, 120.5, (Ar), 73.3, 69.8, 69.7 (O*C*H$_2$), 61.1 (N*C*H$_2$Ar), 53.2 (N*C*H$_2$), 34.4 (*C*(CH$_3$)$_3$), 34.2 (*C*(CH$_3$)$_3$), 31.7 (C(*C*H$_3$)$_3$), 31.0 (C(*C*H$_3$)$_3$); anal. calcd for $C_{55}H_{69}O_6NS_4$ (968.39): C, 68.22; H, 7.18, found: C, 67.93; H, 7.11%.

Compound TCA**6**. Mp 124–128°C; ^{1}H NMR: δ 8.10 (s, 2H, O*H*), 7.65 (s, 4H, Ar*H*), 6.92 (s, 4H, Ar*H*), 6.69 (m, 4H, Ar*H*), 4.78 (t, 4H, OCH_2), 4.26 (m, 8H, OCH_2), 4.09 (t, 4H, $J=4.60$, OCH_2), 1.33 (s, 18H, Bu^t), 0.77 (s, 18H, Bu^t); ^{13}C NMR: δ 155.9, 155.8, 142.5, 136.4, 134.6, 132.7, 129.2, 122.2, 122.0, 116.1 (Ar), 73.8 (ArO*C*H$_2$), 71.3, 70.4, 70.1 (O*C*H$_2$), 34.5 (*C*(CH$_3$)$_3$), 34.3 (*C*(CH$_3$)$_3$), 31.8 (C(*C*H$_3$)$_3$), 31.0 (C(*C*H$_3$)$_3$); anal. calcd for $C_{54}H_{66}O_8S_4$ (971.35): C, 66.77; H, 6.85, found: C, 66.22; H, 6.88%.

Compound TCA**7**. Mp 275–277°C; ^{1}H NMR: δ 7.74 (s, 8H, Ar*H*), 3.97 (t, 8H, $J=3.35$, OCH_2), 3.47 (t, 8H, $J=3.4$, OCH_2), 2.59 (bs, 8H, OCH_2), 1.34 (s, 36H, Bu^t); ^{13}C NMR: δ 156.0, 144.8, 127.4, 127.1 (Ar), 69.9, 68.5, 67.3 (O*C*H$_2$), 33.3 (*C*(CH$_3$)$_3$), 30.3 (C(*C*H$_3$)$_3$); anal. calcd for $C_{52}H_{68}O_8S_4$ (949.34): C, 65.79; H, 7.22, found: C, 65.32; H, 7.17%.

Compound CA**4**. Mp 207–210°C (eluent: hexane–EtOAc=9:1); ^{1}H NMR: δ 7.20 (m, 2+2H, O*H*, Ar*H*), 7.13 (s, 4H, Ar*H*), 6.95 (m, 6H, Ar*H*), 6.62 (t, 1H, $J=7.5$, Ar*H*), 4.43 (d, 4H, $J=12.6$, ArCH_2), 4.14 (bs, 4H, OCH_2), 3.94 (m, 8H, OCH_2), 3.63 (t, 4H, OCH_2), 3.29 (d, 4H, $J=12.8$, ArCH_2), 1.30 (s, 18H, Bu^t), 0.93 (s, 18H, Bu^t); ^{13}C NMR: δ 150.7, 149.7, 147.6, 146.9, 141.3, 132.7, 129.4, 127.9, 125.5, 125.1, 115.9, 111.6 (Ar), 76.4, 70.5, 69.6 (O*C*H$_2$), 51.9 (N*C*H$_2$), 34.3, 34.2 (*C*(CH$_3$)$_3$), 32.1, 31.4 (C(*C*H$_3$)$_3$), 31.7 (Ar*C*H$_2$Ar); anal. calcd for $C_{58}H_{75}O_6N$ (882.23): C, 78.96, H, 8.57, found: C, 78.67, H, 8.65%.

Compound CA**5**. Mp 200–202°C; ^{1}H NMR: δ 7.33–7.21 (m, 5H, *ArH*), 7.19 (s, 2H, O*H*), 7.13 (s, 4H, Ar*H*), 6.75 (s, 4H, Ar*H*), 4.35 (d, 4H, $J=13$, ArCH_2), 4.05 (bs, 4H, OCH_2), 4.00 (bs, 4H, OCH_2), 3.94 (t, 4H, OCH_2), 3.70 (bs, 2H, OCH_2), 3.29 (d, 4H, $J=13$, ArCH_2), 2.88 (t, 4H, OCH_2), 1.32 (s, 18H, Bu^t), 0.90 (s, 18H, Bu^t); ^{13}C NMR: δ 150.8, 149.8, 146.8, 141.2, 140.0, 132.5, 128.7, 128.2, 127.9, 126.8, 125.5, 125.0 (Ar), 77.1, 71.3, 70.6 (O*C*H$_2$), 60.8 (N*C*H$_2$Ar), 55.1 (N*C*H$_2$), 34.2 (*C*(CH$_3$)$_3$), 32.1, 31.3 (C(*C*H$_3$)$_3$), 31.7 (Ar*C*H$_2$Ar); anal. calcd for $C_{59}H_{77}O_6N$ (896.26): C, 79.07, H, 8.66, found: C, 79.24, H, 8.53%.

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