Pergamon

Tetrahedron, Vol. 53, No. 28, pp. 9799-9812, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00627-3

Studies on Calix(aza)crowns, I. Synthesis, Alkylation Reactions and Comprehensive NMR Investigation of Capped Calix[4]arenes

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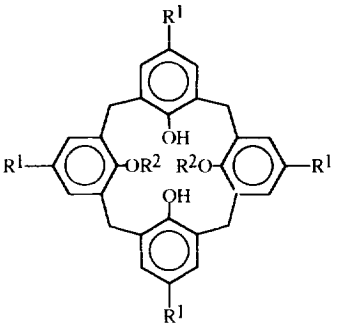
Abstract: Calix[4]arenes capped by diamide bridges in 1,3-position on the lower rim were synthesized. Regioselective alkylations of compounds **2** afforded **3**, **4** O- and N-alkylated derivatives. Comprehensive NMR investigations were made to reveal the conformation of calix(aza)crowns **2**, **3**, **4**.

INTRODUCTION

The easy accessibility and the selective functionalizations at the phenolic hydroxy groups of calix[4]arenes have made this member of the series increasingly attractive for the chemists involved in host-guest chemistry[1] In particular, cation complexing ligands containing calix[4]arene building block have been synthesized to obtain more selective metal ion sensors. These molecules are generally tetra-O-substituted calix[4]arenes capable of alkali-, alkaline earth- and heavy metal ion recognition[2-6] Recently trying to put together the special properties of crowns and calixarenes in one molecule, more elaborate structures are beginning to emerge. Single bridged calixcrowns with poly(oxyethylene) linkage in 1,2[7]- and 1,3 position[8-10], calixspherands[11] (m-teranisyl bridge), double or triple calixarenes with various connecting chains[12-15] or conformationally constrained spacers have been reported[16,17] All of these molecules were prepared by the O-alkylation or acylation of calix[4]arene tetrols with activated bifunctional reagents (oligoethylene glycol ditosylates, diacid dichlorides, bis-bromomethylated teranisyl system).

An alternative strategy has been developed for the synthesis of calix(aza)crowns in wich the 1,3-(distal) positions of p-tert-butylcalix[4]arene are linked with diamide bridges. Rather than use the parent calix[4]arene **1a** with four free phenolic hydroxyl groups , the easily accessible syn-1,3-diacetic acid derivatives were condensed with various diamines to form cyclic diamides[18,19] . Both the diester **1c**[18], and the diacid chloride **1e**[19] afforded **2** single bridged calix(aza)crowns (capped calixarenes) of different ring size (Figure 1.). According to preliminary FAB-MS complexation studies[18] compounds **2** show some complexing ability toward divalent and trivalent metal ions. It should be noted that the effect of methylation of the free OH groups

is very striking, giving rise to much weaker complexation[18]. Since MeO is regarded to be a better ligating function than free OH in neutral medium, the dramatic decrease of complexation may be due to the change in conformation. Actually, while **2a** exists exlusively in the cone conformation, the corresponding dimethyl ether **3a** is a mixture of co/paco/1,3-alt conformers[18]



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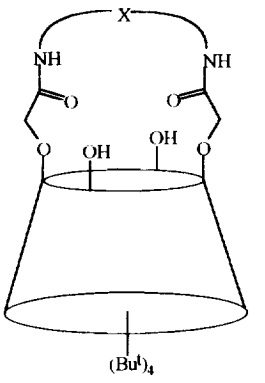


2 (X: various connecting chain)

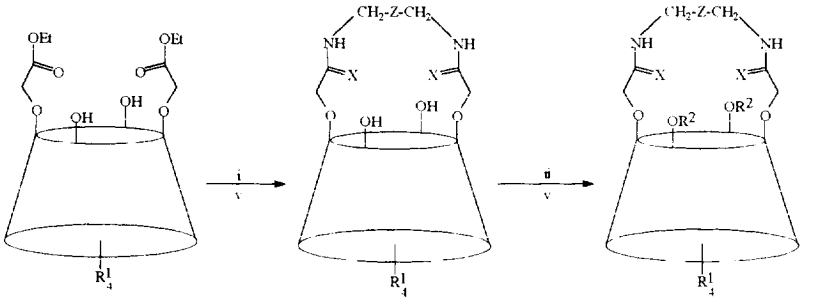
1	R^1	R^2
a	But	H
b	H	H
c	But	CH_2COOEt
d	H	CH_2COOEt
e	But	CH_2COCl

Figure 1.

During our work aiming at synthesizing calix[4]arene ionophores[20,21,22] we also investigated the utility of **1c,d** in amidation reactions with diaminoalkanes and other polyamines as well, in order to obtain novel calix(aza)crowns for further transformation. Moreover, since complete NMR analysis of the 1,3-bridged calix[4]azacrowns have not been reported,we have prepared a series of compounds of type **2** (including known molecules) and **3** to study how the conicity of the calix is influenced by the length of the connecting chain, the alkylation of the phenolic OH and the quality of amide group, respectively.

RESULTS AND DISCUSSION

The amidation of **1c,d** was carried out in toluene-methanol solvent mixture as proposed previously[18] (toluene facilitates the dissolution of **1c,d** while methanol is beneficial to transforming the ethyl ester to the more reactive methyl ester prior to cyclization).The reaction smoothly took place with 1,2-, 1,3-, and 1,4-diamino- alkanes,but longer chained diamines gave no satisfactory result even upon prolonged heating. At the same time polyamines (diethylenetriamine, triethylenetetramine, dipropylenetriamine,tris-(2-aminoethyl)amine) were fairly active in this reaction resulting in the formation of diamide bridged calix[4]arenes (**2a,b,d,e,h, 2i,j,k,l,m**) in cone conformation (Scheme 1.). Although compounds **2a,d** and **2i,k** have already been described[18,19] we were interested to know if the two free phenolic OH or NH in the chain could selectively be alkylated with the retention of the cone conformation. Hitherto the methylation of **2a** was attemped by Reinhoudt at. al. but they failed in preparing **3a** (DMF/NaH, MeI or MeOTs)[18] in this way. Actually, **3a** was obtained in an indirect route and found to be a mixture of conformers[18]



1c,d **2** **3**

i: H_2N-CH_2-Z-CH_2-NH_2, toluene/methanol, RT

ii: R^2Br, aq.NaOH/toluene, $Bu_4N^+Br^-$, t=100°C

v: Lawesson reagent/toluene, t=110°C

2	R^1	X	Z
a	Bu^t	O	-
b	H	O	-
c	Bu^t	S	-
d	Bu^t	O	CH_2
e	H	O	CH_2
f	Bu^t	S	CH_2
g	H	S	CH_2
h	Bu^t	O	CH_2CH_2
i	Bu^t	O	CH_2NHCH_2
j	H	O	CH_2NHCH_2
k	Bu^t	O	$CH_2CH_2NHCH_2CH_2$
l	H	O	$CH_2CH_2NHCH_2CH_2$
m	H	O	$CH_2NHCH_2CH_2NHCH_2$

3	R^1	X	Z	R^2
a	Bu^t	O	-	Me
b	Bu^t	O	-	Pr
c	Bu^t	S	-	Pr
d	Bu^t	O	-	Bu
e	Bu^t	S	-	Bu
f	Bu^t	O	-	i-Bu
g	Bu^t	O	CH_2	Bu
h	Bu^t	O	CH_2CH_2	Bu

Scheme 1.

Cone-selective alkylation of 2 capped calixarenes

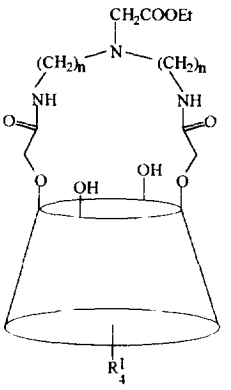
Recently we have developed a simple PTC alkylation of **1a** and several 1,3- syn-dialkylated calix[4]arenes[21]. This method (tolune/50% aqueous NaOH, TBAB catalyst) can advantageously be used for the preparation of p-tert-butylcalix[4]arene tetraethers of cone conformation in case of bulkier groups than ethyl.

When compounds **2a,d,h** were subjected to alkylation with PrBr, BuBr and i-BuBr under PTC conditions[21], exclusively **3b,d,f,g,h** O-alkyl compounds were formed with *cone* selectivity. This observation is somewhat surprising (large excess of alkylating agents and base were used) as lactams are known to be N-alkylated under PTC conditions[23] This method, however, is not suitable to introduce ethoxycarbonyl-methylene groups due to the sensitivity of esters to hydrolysis.For the complete alkylation of **1a** with $BrCH_2COOEt$, K_2CO_3 base in boiling acetone were applied and in long reaction exclusively cone tetraester were obtained[2]. When this reaction was carried out with **2a** we also achieved complete O-alkylation but a mixture of conformers had been formed. Having inspected the ^1H NMR spectrum of the mixture three series of signals could be identified with dominancy of the 1,3-alternate conformer(80%).The minor signals were attributed to cone and partial cone products (20%). The loss of cone-selectivity is not surprising in this case since the K^+ template could not be effective owing to the carboxamide bridge.

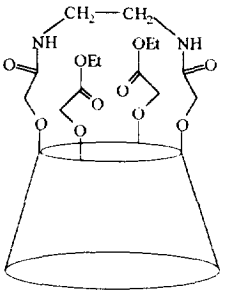
Nevertheless, we succeeded in alkylating **2b** with $BrCH_2COOEt$ in the presence of BaO resulting unexpectedly in the formation of diester **4d** in *cone* conformation. BaO (or CaH_2) is reported to be the base of choice in cone-selective trialkylations[24] of **1b** and 1,3-disubstituted calix[4]arenes,respectively, due to the stable Ba(Ca)- trialkoxy-monophenolate complex formed.In our case the 1,3-carboxamide bridge could prevent the formation of complex mentioned above and the reaction proceeded to completion. It is worth noting that similar alkylation of **2i,j,k** containing one basic NH in the centre of the azacrown ring with ethylbromoacetate afforded only N-alkylated products **4a,b,c** and substitution on the phenolic OH could not be achieved even if large excess of reagents were used at elevated temperature. Compound **2m** with an ethylenediamine unit in the chain, however, gave unseparable mixture of products during alkylation. At the same time, it smoothly cyclized with $(CH_2O)_n$ giving rise to **5** with imidazolidine ring in the centre of the bridge (Figure 2). The structure of compounds **4a–c** is straightforward from the ^1H and ^{13}C chemical shifts of the N-CH_2COOEt moiety. The significant high chemical shifts of the newly introduced methylene (4.36 and 73.5, respectively) in the spectrum of **4d** confirm the O–alkylation. The formation of the imidazolidine ring in **5** is proven by the characteristic NCH_2N signal (3.45 and 74.1, respectively).

The carboxamide functions in calix(aza)crowns **3b,g,h** were attempted to reduce with $LiAlH_4$, SMEAH, or B_2H_6-THF according to published procedures but so far we failed to obtain secondary amines which otherwise could be prepared with difficulties. The failure of reduction was tried to overcome by exchanging the

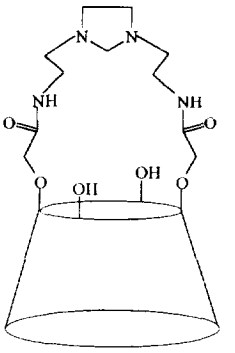
carboxamide oxygen atoms to sulphur followed by desulphuration with Ra-Ni. Although the thioamides **2c,f,g** and **3c,e** could be obtained with Lawesson reagent in standard procedure, attempts to achieve reduced compounds were unsuccesful. Other chemical transformations of the thioamides are currently investigated.



4a,b,c



4d



5

4	R^1	n
a[a]	Bu^t	2
b	H	2
c	Bu^t	3

Figure 2.

Structure determination of capped calix[4]arenes ***2,3***

The characteristic ^1H and ^{13}C chemical shifts are summarized in Table 1–4. For the NMR signal assignment H,H–COSY, HMQC, HMBC and NOESY measurements were utilized in addition to known SCS (substituent chemical shift) effects[25].

Arrows in Fig. 3. indicate proton–proton proximities obtained from the NOESY spectrum of **3d**. This measurement proved the unambiguous assignment of 8–H_{cis} and 8–H_{trans}, and 5-CMe_3 and 11-CMe_3 signals, respectively. The cross–peaks NH / 8–H_{cis} and NH / 28–OCH_2, respectively indicate that the N–H bond is oriented towards the calixarene cavity in the predominating conformation. The methylene protons in the connecting chain *e.g.* 2'–H_2, 5'–H_2, show averaged chemical shifts confirming the rapid conformational motion of this flexible chain.

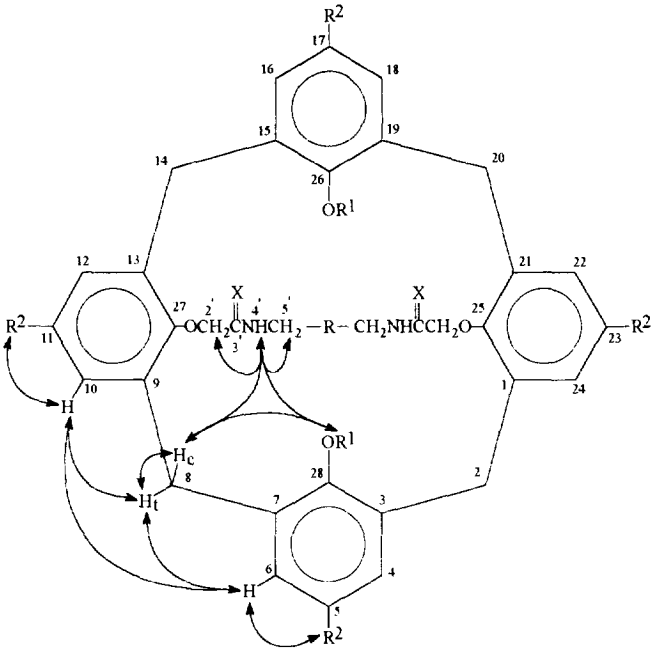


Figure 3.

Differentiation between the quaternary C–27 and C–28 was possible by the correlation of C–27 / 10–H and C–28 / 6–H signals in the HMBC spectra. The long–range ^{3}J(C,H) couplings of 10–H and 6–H protons mark out carbon atoms attached to positions 11 and 5,whereas their ^{2}J(C,H) cross–peaks reveal the δC–9 (135.0) and δC–7 (133.2) chemical shifts. The determination of C–5 and C–11 signals was feasible by the couplings to $C(CH_3)_3$ protons.

Common feature of the ^{1}H NMR spectra of all compounds **2** and **3** is the high difference in the chemical shifts of the diastereotopic 2–H_2 (8–H_2) methylene protons appearing between 4.31–4.06 and 3.52–3.15 ppm, respectively, which are in accordance with the data obtained for **2a** and **2d** (4.14; 3.46 and 4.09;3.46)[18,19] supporting the *cone* conformation (Table 1.,2.). Considering the conic arrangement of the four aryl groups the 2–H_{cis} protons are located in the plane of the neighbouring aromatic rings, whereas the 2–H_{trans} protons are situated above them. Thus the high Δδ values originate from the well-known aromatic anisotropic effect (instead of the usual *axial* and *equatorial* designation; we prefer *cis* and *trans* to denote the real stereochemistry of 2-H protons).

Table 1 ^{1}H Chemical shifts for compounds **2**

H	**2b**	**2c**	**2e**	**2f**	**2g**	**2i**	**2j**	**2k**	**2l**	**2m**
2 c	4.16	4.11	4.12	4.06	4.08	4.16	4.19	4.18	4.23	4.24
2 t	3.52	3.46	3.52	3.47	3.52	3.37	3.44	3.38	3.45	3.44
4,6	7.03	7.06	7.01	7.03	7.01	6.71	6.75	6.68	6.75	6.76
5	6.89		6.84		6.87		6.63		6.65	6.65
5-CMe_3		1.14		1.11		0.88		0.88		
10,12	7.10	7.06	7.10	7.08	7.10	7.13	7.12	7.12	7.13	7.12
11	6.73		6.75		6.75		6.80		6.79	6.80
11-CMe_3		1.24		1.25		1.33		1.33		
2`	4.57	4.90	4.58	4.92	4.94	4.48	4.49	4.48	4.53	4.54
4`NH	8.50	10.07	8.81	10.42	10.35	8.30	8.25	8.41	8.36	8.43
5`	3.70	4.32	3.52	3.84	3.88	3.53	3.54	3.59	3.58	3.54
6`			2.33	2.85	2.86	2.95	2.96	1.77	1.78	2.94
7`								2.77	2.75	2.73 (8`)
OH	8.33	8.20	8.40	8.23	8.32	6.35	6.73	6.13	6.71	6.80

[a] measured at 250 MHz

Table 2 ^{1}H Chemical shifts for compounds **3**

H	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**
2 c	4.29	4.25	4.29	4.24	4.31	4.30	4.24
2 t	3.24	3.24	3.24	3.24	3.24	3.25	3.15
4,6	6.76	6.76	6.75	6.75	6.70	6.62	6.56
5-CMe_3	0.89	0.89	0.89	0.89	0.87	0.86	0.81
10,12	7.19	7.19	7.19	7.19	7.19	7.17	7.08
11-CMe_3	1.35	1.31	1.32	1.31	1.33	1.34	1.25
2`	4.22	4.63	4.22	4.64	4.20	4.44	4.34
4`NH	8.41	9.88	8.39	9.86	8.29	8.54	8.04
5`	3.68	4.37	3.69	4.38	3.67	3.56	3.52
6`						2.33	1.91
OCH_2	3.74	3.73	3.79	3.77	3.55	3.85	3.74
CH_2	1.74	1.72	1.70	1.68	1.95	1.66	1.51
CH_2			1.34	1.31		1.30	1.22
CH_3	0.93	0.90	0.94	0.96	0.99	0.94	0.84

The interesting trend for compounds **3** (δ 4,6–H < δ 10,12–H) can by no means be explained by the different SCS effects of -OR^1 and -$OCH_2CO(S)$ substituents but it is rather attributed to the deformation of the cone conformation caused by the steric requirement of R^1. Replacement of the bulky OR^1 with OH (**3c→2c** and **3e→2c**) gave the same chemical shifts for δ 4,6–H and δ 10,12–H. In the case of **2b–2g** δ 4,6–H and δ 10,12–H values are very close (7.01–7.10 ppm) indicating the almost symmetrical cone conformation, which can be stabilized by strong hydrogen bonds between the phenolic OH groups and the O-atoms attached

to position 27 (δ OH ≈ 8.2-8.4 ppm !). It should be noted that the δ 4,6–H and δ 10,12–H values hardly altered on replacing Bu^t groups by H (**2j** → **2i**, **2l** → **2k**). By increasing chain length (**2i–2m**), ca. Δδ=0.25 ppm diamagnetic shifts of the 4,5,6–H signals can be observed accompanied by significant decrease of δOH values (6.13–6.80 ppm). These changes in the spectra are in accordance with a distorted cone conformation in which the plane of the two opposite aryl groups are getting to be flattened and thus strong hydrogen bonds of OH groups cannot be formed.

The characteristic chemical shift differences of the 5–CMe_3 and 11–CMe_3 signals (Δδ = 0.1 and 0.45, respectively) in the ^1H spectra of compounds **2** and **3** can be utilised for monitoring the extent of conformational distortion (higher difference refers to more distorted conformation).

The NH signals in both series of **2** and **3** appear at remarkable high chemical shifts (8–10 ppm) which are also indicative for intramolecular hydrogen bond with the neighbouring oxygen atom of OH or OR^1 groups. Replacement of the carboxamide oxygen with sulphur is associated with ca. 1.5 ppm increase of δNH values (**2b** → **2c**, **2e** → **2g**, **3b** → **3c**, **3d** → **3e**) referring to the stronger hydrogen bondings.

Gutsche suggested the Δδ values observed for the chemical shifts of the protons in the methylene bridge (2–H_{cis} and 2–H_{trans}) can be used for the assessment of the distortion from the symmetrical cone conformation[26]. Our results in agreement with Arduini's opinion[27] underline that this argument did not hold in case of bridged systems such as compounds **2** and **3**.

In the ^{13}C spectra of compounds **2** and **3** (Table 3., 4.) significant downfield shifts (about 5 ppm) of δ C–3 signals upon alkylation of OH groups were observed. This phenomenon is in contradiction with the known substituent effects[25]. At the same time a ca. 2.5 ppm downfield shifts of the relatively remote C–9 signals can also be recognised. Neither of them is originated from the effect of alkyl substitution but rather arises from the distortion of the symmetrical cone conformation discussed above.

The signals of the ipso C–28 carbon atoms are shifted ca. 2–2.5 ppm to downfield when alkylated (**3b–3g**) which is in accordance with expectation. In compounds **2j,l,m** this effect is overcompensated, probably by the lack of hydrogen bonds.

A comparison between the chemical shifts of amide and thioamide derivatives revealed significant downfield shifts of 2'–H (~0.4), 5'–H (~0.6) and C–2' (~6), C–3'(~30), C–5'(~4) signals, respectively. As to the pattern of hydrogen bondings, the participation of C=O or C=S groups, at least in solution, can be excluded since the respective C–3' signals appear at almost identical chemical shifts (168–169 ppm, and 195–196 ppm) in the whole series of **2, 3.**

Our molecules possessing donor and acceptor sites for hydrogen bonding can behave as polydentate ligands capable of complexing neutral molecules containing OH or NH groups. Preliminary investigations with

aliphatic alcohols and amines support this expectation. ^1H relaxation time measurements are in progress to collect informations on the structure of complexes.

Table 3. ^{13}C Chemical shifts for compounds **2**

C	2b	2c	2e	2f	2g	2j	2l	2m
2,8	31.8	32.1	31.8	32.1	31.5	31.1	31.3	31.4
3,7	127.8	126.7	127.4	126.7	127.3	128.0	128.2	128.4
4,6	129.6	126.0	129.7	126.0	129.3	129.0	129.1	129.1
5	121.1	143.3	121.2	143.5	121.0	120.2	120.3	120.4
5C		33.9		33.9				
$5CMe_3$		31.1		32.0				
9,13	133.4	132.6	133.2	132.4	132.8	132.1	132.1	132.3
10,12	130.0	126.3	130.1	126.3	129.7	129.4	129.4	129.5
11	127.4	146.6	127.4	147.0	127.1	126.1	125.9	126.0
11C		34.3		34.3				
$11CMe_3$		31.5		31.5				
27	152.4	149.4	152.4	149.3	151.7	152.4	152.3	152.7
28	149.4	148.9	149.8	148.9	148.8	151.3	151.9	152.2
2`	75.1	80.8	74.9	80.3	80.4	74.9	75.0	75.2
3`	167.9	196.7	168.5	195.9	195.7	168.2	168.1	168.7
5`	39.7	43.2	36.5	40.4	40.5	40.2	37.4	39.4
6`			23.9	19.5	19.6	49.0	28.3	47.6
7`							46.0	47.6(8`)

Table 4. ^{13}C Chemical shifts for compounds **3**

C	3b	3c	3d	3e	3f	3g
2,8	30.2	30.4	30.2	30.4	30.1	31.1
3,7	133.2	133.2	133.2	133.2	133.2	132.6
4,6	125.8	125.9	125.8	125.9	125.9	125.6
5	145.5	145.7	145.5	145.6	145.3	145.5
5C	34.1	34.2	34.2	34.2	34.1	34.1
$5CMe_3$	31.5	30.4	31.5	31.5	31.5	31.5
9,13	135.0	135.1	135.0	135.1	135.0	134.7
10,12	126.0	126.0	126.0	126.0	126.2	126.4
11	147.1	147.3	147.1	147.3	147.0	146.7
11C	34.6	34.6	34.6	34.6	34.6	34.5
$11CMe_3$	32.1	32.0	32.1	32.1	32.1	32.0
27	151.7	151.2	151.7	151.2	151.9	153.4
28	151.3	151.1	151.3	151.2	151.8	151.1
2`	75.1	81.4	75.1	81.4	75.4	74.7
3`	169.9	198.9	169.9	198.9	169.7	170.2
5`	39.0	43.0	39.0	43.0	38.9	38.2
6`						24.9
OCH_2	79.1	79.3	77.3	77.6	84.8	77.3
CH_2	23.3	23.4	32.1	33.3	28.6	31.6
CH_2			19.5	19.5		19.4
CH_3	10.6	10.6	14.4	14.4	20.5	14.4

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ at 500/125 MHz on Bruker Avance DRX-500 spectrometer. Chemical shifts are given on the δ-scale. Precoated silica gel plates (Merck 60 F_{254}) were used for analytical TLC. All chemicals were reagent grade and used without further purifications. Compounds **1c,d**[28] and **2a**[18] were prepared as described in the literature whereas **2b,d,e,h,i,j,k,l,m** were obtained with a slight modification of the procedure reported in ref.[18] This method is found to be superior to that of applying acid chloride **1e** in high dilution[19] since it can simply be performed and provide good yields. The diamines used are commercially available (Fluka).

General procedure for the synthesis of calix(aza)crowns 2

A solution of diethylester **1c,d** (10 mmol) and the appropriate diamine (15 mmol for **2b,d** and 30 mmol for the rest) in a mixture of methanol (100 ml) and toluene (100 ml) were allowed to stand at room temperature for 48-72 h. After completion of the reaction the solution was concentrated at reduced pressure.The remaining solid residue was suspended in methanol or water, filtered and recrystallized. The analytical samples were dried at 80 ° C in 0.1 Torr pressure.The following compounds were thus prepared (including the known **2d,i,k** which were reported with different mp.'s and lower yields).

2b: yield:89%, mp: 351-352°C (MeOH), Anal. calcd. for: $C_{34}H_{32}N_2O_6$ (564.64): C 72.33, H 5.71, N 4.96 Found: C 72.51, H 5.76, N 4.90

2e: yield:87%, mp: >380°C (MeOH), Anal. calcd. for: $C_{35}H_{34}N_2O_6$ (578.66): C 72.65, H 5.92, N 4.84, Found: C 72.22, H 5.83, N 4.80

2d: yield:82%, mp: 283-284 ° C (EtOH) (lit mp: 194-200 ° C[19]), Anal calcd for $C_{51}H_{66}N_2O_6$ (803.09): C 76.28, H 8.28, N 3.49, Found C 76.52, H 8.23, N 3.45

2i: yield:63%, mp: 183-185°C (EtOH) (lit mp 181-183 °C[18]), Anal. calcd. for: $C_{52}H_{69}N_3O_6$ (832.13): C 75.06, H 8.36, N 5.05 Found: C 74.88, H 8.41, N 4.99

2j: yield:82%, mp: 264-265°C (BuOH), Anal. calcd. for: $C_{36}H_{37}N_3O_6$ (607.70): C 71.15, H 6.14, N 6.91 Found: C 70.79, H 6.22, N 6.97

2k: yield:74%, mp: 255-256°C (MeOH) (lit mp 155-157 °C[18]), Anal. calcd. for: $C_{54}H_{73}N_3O_6$ (860.19): C 75.40, H 8.55, N 4.88 Found: C 75.18, H 8.61, N 4.82

2l: yield:81%, mp: 272-274°C (BuOH), Anal. calcd. for: $C_{38}H_{41}N_3O_6$ (635.76): C 71.79, H 6.50, N 6.61 Found: C 71.99, H 6.58, N 6.65

2m: yield:49%, mp: 203-205°C (MeOH), Anal. calcd. for: $C_{38}H_{42}N_4O_6$ (650.77): C 70.13, H 6.50, N 8.61 Found: C 70.48, H 6.45, N 8.65

General procedure for the PTC alkylation of ***2a,d,h***

Compounds **2a,d,h** (1 mmol), toluene (25 ml), 50% w/w aq.NaOH (0.5 ml), R^2Br (6 mmol) and tetrabutylammonium bromide catalyst (0.03 g, 0.1 mmol) were vigorously stirred at 90-100 °C for 6 h. After cooling, water (10 ml) was added and the phases were separated. The organic phase was washed with dilute HCl (20 ml) and water, subsequently.The toluene solution was dried (Na_2SO_4), evaporated to dryness then the residue was triturated with methanol to give compounds **3** as white solids in substantially poor state.

3b: yield:82%, mp: 302-305°C (BuOH), Anal. calcd. for: $C_{56}H_{76}N_2O_6$ (873.23): C 77.03, H 8,77, N 3.21 Found: C 77.21, H 8.72, N 3.17

3d: yield:88%, mp: 285-287°C (BuOH), Anal. calcd. for: $C_{58}H_{80}N_2O_6$ (901.28): C 77.29, H 8.95, N 3.11 Found: C 77.01, H 9.00, N 3.06

3f: yield:44%, mp: 323-325°C (MeOH), Anal. calcd. for: $C_{58}H_{80}N_2O_6$ (901.28): C 77.29, H 8.95, N 3.11 Found: C 77.46, H 8.89, N 3.08

3g: yield:77%, mp: 261-263°C (MeOH), Anal. calcd. for: $C_{59}H_{82}N_2O_6$ (915.31): C 77.42, H 9.03, N 3.06 Found: C 77.22, H 9.06, N 3.11

3h: yield:40%, mp: 228-230°C (MeOH), Anal. calcd. for: $C_{60}H_{84}N_2O_6$ (929.33): C 77.55, H 9.11, N 3.01 Found: C 77.33, H 9.18, N 2.98

General procedure for the synthesis of thioamides ***2c,f,g*** *and* ***3c,e***

Compounds **2a,d,e** and **3b,d** (1 mmol) and Lawesson reagent (0.5 g, 1.25 mmol) were refluxed in toluene (20 ml) for 6-8 h. When the reaction had been completed the solution was evaporated at reduced pressure, the residue was triturated with methanol and filtered. Pale yellow solids were obtained which was purified by recrystallization (**2f** was chromatographed on silica gel with hexane-EtAc=8:2 eluent).

2c: yield:91%, mp: 271-272°C (MeOH), Anal. calcd. for: $C_{50}H_{64}N_2O_4S_2$ (821.20): C 73.13, H 7.86, N 3.41 Found: C 73.36, H 7.80, N 3.45

2f: yield:96%, mp: 258-260°C, Anal. calcd. for: $C_{51}H_{66}N_2O_4S_2$ (835.22): C 73.34, H 7.96, N 3.35, Found: C 74.62, H 8.02, N 3.39

2g: yield:76%, mp: 288-290°C (MeOH), Anal. calcd. for: $C_{35}H_{34}N_2O_4S_2$ (610.80): C 68.83, H 5.61, N 4.59, Found: C 68.46, H 5.67, N 4.55

3c: yield:85%, mp: 283-286°C (BuOH), Anal. calcd. for: $C_{56}H_{76}N_2O_4S_2$ (905.36): C 74.29, H 8.46, N 3.09, Found: C 74.58, H 8.41, N 3.12

3e: yield:96%, mp: 276-278°C (BuOH), Anal. calcd. for: $C_{58}H_{80}N_2O_4S_2$ (933.41): C 74.63, H 8.64, N 3.00, Found: C 74.23, H 8.70, N 3.04

General procedure for the alkylation of ***2i,j,k*** *with ethylbromoacetate*

Compounds **2i,j,k** (1 mmol), $BrCH_2COOEt$ (0.34 g, 2 mmol) and BaO (0.31 g, 2 mmol)were stirred in acetone (20 ml) at reflux temperature for 7 h. After completion of the reaction the mixture was evaporated at reduced pressure, the residue was triturated with water, extracted with $CHCl_3$ (50 ml) and washed with water, subsequently.The organic phase was dried (Na_2SO_4), evaporated to dryness and the residue was purified by recrystallization to give **4a,b,c** as white crystals.

For the preparation of **4d**, **2b** (1mmol) ,$BrCH_2COOEt$ (1.26 g, 8 mmol) and BaO (0.46 g, 3 mmol) were used in DMF (20 ml) at 80 ° C and similar work up was applied.

4a: yield:65%, mp: 227-229°C (MeOH), ^1H NMR δ: 8.29 (t,2H,NH), 7.12, (s,4H,ArH), 6.74 (s,4H,ArH) 6.63 (s,2H,OH), 4.51 (s,4H,CH_2O), 4.17 and 3.37 (d,J=13.4,8H,$ArCH_2Ar$,cone), 4.08 (q,2H,OCH_2), 3.51 (d,4H,NCH_2), 3.44 (s,2H,NCH_2), 2.99 (d,4H,NCH_2), 1.32 and 0.89 (s,18H each,Bu^t), 1.21 (t,3H,CH_3) ^{13}C NMR δ: 171.2, 168.7 (C=O), 149.9, 148.7, 148.0, 142.9, 131,7 127.8, 125.9, 125.3 (Ar), 74.6 (OCH_2CO), 60.3 (NCH_2CO), 55.7 (OCH_2), 54.9, 38.9 (NCH_2) 33.9, 31.6, 30.8 (Bu^t), 31.4 ($ArCH_2$), 14.2 (CH_3). Anal. calcd. for: $C_{56}H_{75}N_3O_8$ (918.22): C 73.25, H 8.23, N 4.58 Found: C 73.00, H 8.20, N 4.64

4b: yield:76%, mp: 259-261°C (BuOH), ^1H NMR δ: 8.28 (t,2H,NH), 7.12, (d,4+2H,ArH,OH), 6.78 (m,6H,ArH), 6.64 (t,2H,ArH), 4.52 (s,4H,CH_2O), 4.22 and 3.44 (d,J=13.5,8H,$ArCH_2Ar$,cone), 4.05 (q,2H,OCH_2), 3.52 (q,4H,NCH_2), 3.43 (s,2H,NCH_2), 2.97 (t,4H,NCH_2), 1.19 (t,3H,CH_3) ^{13}C NMR δ: 171.3, 168.4 (C=O), 152.5, 151.2, 132.2, 129.4, 128.9, 127.8, 126.1, 120.2 (Ar), 74.8 (OCH_2CO), 60.3 (NCH_2CO), 55.9 (OCH_2), 55.0, 39.0 (NCH_2) 31.2 ($ArCH_2$), 14.2 (CH_3). Anal. calcd. for: $C_{40}H_{43}N_3O_8$ (693.79): C 69.25, H 6.25, N 6.06, Found: C 69.60, H 6.19, N 6.02

4c: yield:53%, mp: 243-245°C (MeOH-EtOH), ^1H NMR δ: 8.27 (t,2H,NH), 7.12, (s,4H,ArH), 6.67 (s,4H,ArH), 6.08 (s,2H,OH), 4.47 (s,4H,CH_2O), 4.18 and 3.38 (d,J=13.5,8H,$ArCH_2Ar$,cone), 4.02 (q,2H,OCH_2), 3.54 (q,4H,NCH_2), 3.37 (s,2H,NCH_2), 2.79 (t,4H,NCH_2), 1.77 (m,4H,CH_2), 1.33 and 0.86 (s,18H each,Bu^t), 1.17 (t,3H,CH_3), ^{13}C NMR δ: 171.5, 168.3 (C=O), 149.6, 149.5, 147.8, 143.2, 131,5 128.4, 126.0, 125.6 (Ar), 74.9 (OCH_2CO), 60.4 (NCH_2CO), 56.3 (OCH_2), 51.1, 37.4 (NCH_2) 34 0, 33.9, 31.6, 30.8

(Bu^t), 31.5 ($ArCH_2$), 26.9 (CH_2), 14.2 (CH_3). Anal. calcd. for: $C_{58}H_{79}N_3O_8$ (946.28): C 73.62, H 8.41, N 4.44, Found: C 73.22, H 8.47, N 4.48

4d: yield:61%, mp: 243-245°C (BuOH), ^{1}H NMR δ: 8.33 (t,2H,NH), 7.16 (d,4H,ArH), 7.00 (d,4H,ArH), 6.89 (t,2H,ArH), 6.73 (t,2H,ArH), 4.67 and 3.40 (d,J=12.6,8H,$ArCH_2Ar$,cone), 4.56 and 4.36 (s,4H each,CH_2O), 4.21 (q,4H,OCH_2), 3.64 (t,4H,NCH_2), 1.27 (t,6H,CH_3), ^{13}C NMR δ: 169.2, 169.0 (C=O), 155.0, 152.9, 135.2, 134.0, 129.2 129.0, 125.1, 124.9 (Ar), 74.4, 73.5 (OCH_2CO), 61.4 (OCH_2), 54.9, 38.4 (NCH_2), 30.1 ($ArCH_2$), 14.2 (CH_3). Anal. calcd. for: $C_{42}H_{44}N_2O_{10}$ (736.82): C 68.47, H 6.02, N 3.80, Found: C 68.15, H 6.07, N 3.76

*Ring closure of **2m** with formaldehyde (**5**)*

Compound **2m** (0.49 g, 0.75 mmol), $(CH_2O)_n$ (0.07 g, 2.3 mmol), and pTsOH (0.01 g) were refluxed in CH_2Cl_2 for 4 h. The solution was washed with 5% aq. Na_2CO_3 (15 ml), dried and evaporeted.The residue was suspended in methanol and filtered to give **5** (0.37 g, 75%), mp: >400°C (BuOH), ^{1}H NMR δ: 8.07 (t,2H,NH), 7.13, (d,4H,ArH), 6.81 (t,2H,ArH), 6.61 (m,6H,ArH), 5.55 (s,2H,OH), 4.43 (s,4H,CH_2O), 4.29 and 3.41 (d,J=13.9,8H,$ArCH_2Ar$,cone), 3.55 (q,4H,NCH_2), 3.45 (s,2H,NCH_2N), 2.73 (t,4H,NCH_2), 2.59 (s,4H,CH_2N), ^{13}C NMR δ: 168.0 (C=O), 152.9, 152.7, 132.2, 129.1, 129.0 125.3, 119.9 (Ar), 74.6 (OCH_2CO), 74.1 (NCH_2N), 52.6, 51.7, 37.2 (NCH_2), 30.8 ($ArCH_2$). Anal. calcd. for: $C_{39}H_{42}N_4O_6$ (662.78): C 70.68, H 6.39, N 8.45, Found: C 70.98, H 6.34, N 8.49

ACKNOWLEDGEMENT

We are indebted to the Hungarian National Science Foundation (OTKA, Project No. T 017327 and T 016583) for support of this research.

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(*Received in UK* 2 *April* 1997; *revised* 28 *May* 1997; *accepted* 29 *May* 1997)