Journal of Inclusion Phenomena and Molecular Recognition in Chemistry **27:** 21–30, 1997.

Synthesis of a Calix[4]arene Containing 'Hard' and 'Soft' Metal Ion Binding Sites

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(Received: 28 February 1996; in final form: 10 June 1996)

Abstract. Co-receptor 1,3-calix[4]-di(aza-benzo)crown-crown-6 (**1-H**) designed with one calix[4]arene in a 1,3-alternate conformation and 'hard' and 'soft' metal ion binding sites has been prepared according to three pathways (**A–C**). Pathway **B**, consisting of two different 1 + 1 condensations with ditosylate derivatives, was shown to be the most efficient.

Key words: Co-receptors, 'hard' and 'soft', calix[4]arene 1,3-alternate conformation, crown ether, diazabenzo crown-ether, Schiff base.

1. Introduction

Co-receptors refer to polytopic receptor molecules combining two or more binding subunits within the same macropolycyclic architecture [1]. A recent review article reports the supramolecular chemistry of those co-receptors which contain combinations of 'hard' and 'soft' metal cations in the same molecular structure [2]. When dissymetric, 'hard' and 'soft' receptors provide entries to molecular behavior such as cooperativity, allostery, regulation and transfer signal [1]. For example, the combination of two different polyether loops combining oxygen/sulfur donor atoms leads to ligands with a charge-differentiating effect of the binding compartments [3]. Lateral macrobicyclic cryptands have been designed by association of 'hard' azoxamacrocycles with 'soft' 2,6-dimethylthio pyridine. The resulting heteroditopic cryptates are well suited for inducing processes of 'push-pull' dimetallic substrate activation [4]. Similarly, a lateral macrobicyclic 'hard' and 'soft' cryptand containing an *o*-phenanthroline subunit and an aza-crown ether has been prepared for forming copper(I) and rhodium(I)-alkali complexes [5]. More recently, the synthesis of diazatetraoxacyclooctadecane derivatives bearing two catechol groups has been designed to bind simultaneously alkaline and transition metal cations [6]. 'Hard-soft' ditopic metal binding sites have been attached to a calix[4]arene in the cone conformation. It has been established that silver cation can coexist with sodium in the ionophoric cavity [7]. A metallomacrocycle has been designed from calix[4]arene in the l,3-alternate conformation with a salophene unit on one side

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and a crown ether on the other which transports simultaneously cations and anions through supported liquid membranes [8]. The synthesis of an unsymmetrically doubly bridged calix[4]arene constrained in a 1,3-alternate conformation by one crown ether and one diaza-benzo crown ether bridging has been reported [9].

We report herein the synthesis of 1,3-calix[4]-di(aza-benzo)crown-crown-6 (**1-H**). In order to evaluate the most convenient synthesis, three pathways **A–C** were investigated which are shown in Scheme I. Pathways **A** and **B**, with calix[4]arene as starting material consist in performing two successive 1 + 1 condensations with two different ditosylate derivatives. Pathway **C** begins with the selective 1,3-di-O-alkylation of calix[4]arene with two groups bearing aldehyde functionalities. The following step consists of a 1 + 1 condensation with the ditosylated reagent. The final step is the ring closure by formation and reduction of the Schiff base obtained from the reaction of the two aldehyde functions with a diamino derivative.

2. Experimental

2.1. Materials for Synthesis

2-(2-Bromoethoxy)benzaldehyde [10], calix[4]arene [11] and calix[4]-crown-6 (yield 50%) [12] were prepared as described elsewhere. Pentaethylene glycol di-p-toluene sulfonate, salicyladehyde, 2-chloroethanol, 1,3-diamino-propane, potassium carbonate, potassium *tert*-butoxide, sodium borohydride, lithium aluminium hydride and the solvents were commercial reagents and used without further purification.

2.2. Analytical Procedures

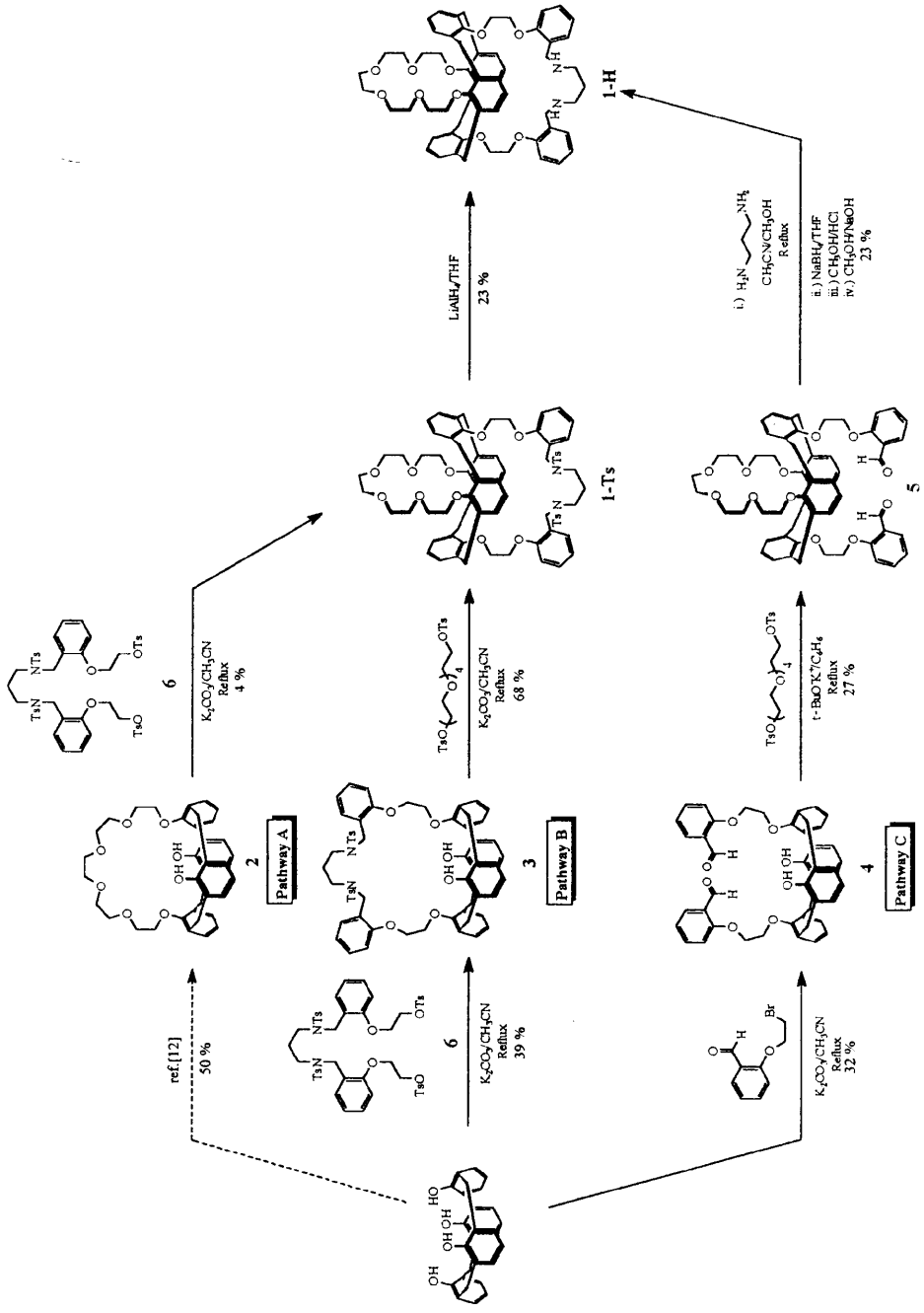
Melting points were measured on a Büchi 500 apparatus in capillaries sealed under nitrogen. Silica columns were prepared with Kieselgel Merck (Art. 9385). The eluent is specified in the experimental procedure. The ^{1}H-NMR spectra were recorded at 200 MHz on a Bruker SY200 spectrometer. The FAB mass spectra were obtained on a VG-Analytical ZAB HF apparatus.

2.3. Synthetic Procedures

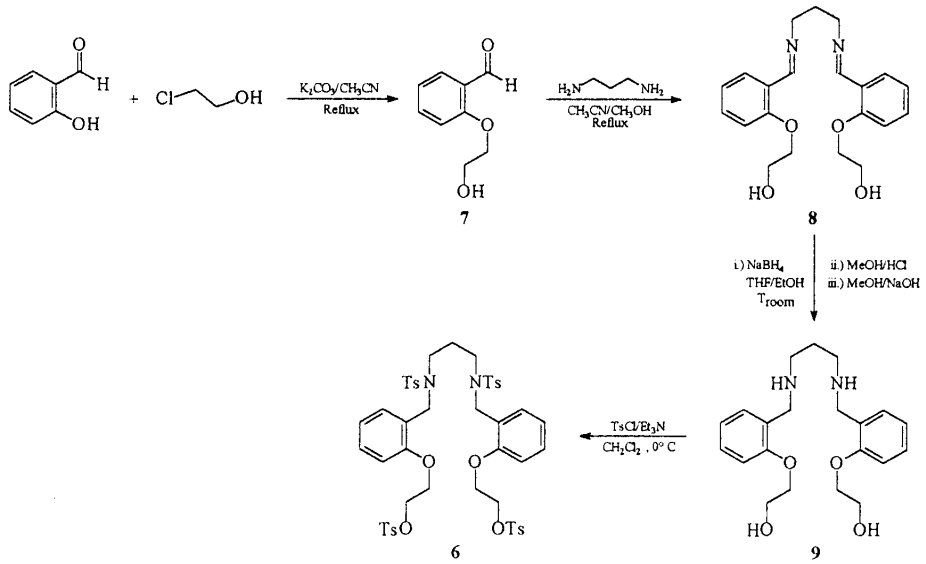
2.3.1. *Preparation of Tetra(N, O)tosylate (**6**) According to Scheme II*

Preparation of 2-(2-hydroxyethoxy)benzaldehyde (**7**)

2-Chloroethanol (32.20 g, 400 mmol) dissolved in acetonitrile (100 mL) was added dropwise to a mixture of salicylaldehyde (48.84 g, 400 mmol), potassium carbonate (55.28 g, 400 mmol), and acetonitrile (1300 mL). The contents were stirred with reflux under nitrogen for 24 h. Then, the reaction mixture was cooled to room temperature and filtered. The filtrate was evaporated to dryness to yield a reddish brown residue (45.66 g) which was chromatographed on a silica column by using 90:10



Scheme I. Synthesis pathways **A–C** of 1,3-calix[4]-di(aza-benzo)crown-crown-6 (**1-H**).



Scheme II. Synthesis of tetra(N, O)tosylate derivative (**6**).

dichloromethane : acetone as eluent. Pure 2-(2-hydroxyethoxy)-benzaldehyde (**7**) was obtained as a transparent yellow oil. Yield 22%. ^{1}H-NMR ($CDCl_3$) δ in ppm from TMS: 10.43 (s, 1 H, ArCO*H*), 7.83 (d, J_{H-H} = 7.6 Hz, 1H, ArH_6), 7.54 (t, J_{H-H} = 8.7 Hz, 1H, ArH_4), 7.05 (t, J_{H-H} = 7.6 Hz, 1H, ArH_5), 7.01 (d, J_{H-H} = 8.3 Hz, 1H, ArH_3), 4.20 (m, 2H, ArOCH_2), 4.04 (m, 2H, CH_2OH), 2.85 (t, J_{H-H} = 5.8 Hz, 1H, CH_2O*H*).

Preparation of 2,2′-[(1,1′-(1,3-propylenediimino))-2,2′-diphenoxy]diethanol (**8**)

1,3-Diamino-propane (0.74 g, 10 mmol) dissolved in methanol (35 mL) was added dropwise to a solution of benzaldehyde derivative (**7**) (3.33 g, 20 mmol) in acetonitrile (160 mL). The contents were stirred with reflux under nitrogen for 24 h. Then, the reaction mixture was cooled to room temperature and evaporated to dryness to afford a transparent orange oil (4.05 g) which was used without further purification.

Preparation of 2,2′-[(1,1′-(1,3-propylenediamine))-2,2′-diphenoxy]diethanol (**9**)

Compound (**8**) (4.04 g) dissolved in ethanol (150 mL) was added dropwise to a suspension of sodium borohydride (3.17 g, 80 mmol) and tetrahydrofuran (150 mL). The contents were stirred at room temperature under nitrogen for 4 h. Then, water (200 mL) was added and the reaction mixture was stirred for 1 h. After evaporation to dryness, the residue was dissolved in methanol (50 mL) and treated with 6 M hydrochloric acid (10 mL) for 30 min. The mixture was evaporated

to dryness to afford a residue which was dissolved again in methanol (50 mL) and treated with an excess of sodium hydroxide for 30 min. After evaporation to dryness, the residue was extracted with dichloromethane (100 mL) and water (100 mL). The organic layer was dried over sodium sulfate and concentrated to afford a lightly yellow oil. The product was almost pure on ^{1}H-NMR and used without further purification. ^{1}H-NMR ($CDCl_3$) δ in ppm from TMS: 7.28–7.25 (m, 4H, ArH), 7.20–7.12 (m, 4H, ArH), 4.19–4.15 (m, 4H, ArOCH_2), 3.75 (bs, 8H, CH_2OH and ArCH_2N), 3.57 (bs, 4H, CH_2OH and NH), 2.68 (t, J_{H-H} = 6.8 Hz, 4H, NCH_2CH$_2$CH_2N), 1.74 (qpt, J_{H-H} = 6.8 Hz, 2 H, NCH$_2$CH_2CH$_2$N).

2.3.2. *Preparation of N,N′-O,O′-2,2′-[(1,1′-(1,3-propylenediamine))-2,2′-diphenoxy]diethoxy tetratosylate* (**6**)

Triethylamine (4.64 g, 46 mmol) dissolved in dichloromethane (10 mL) was added dropwise over 30 min to a solution of (**9**) (3.41 g, 9 mmol) and p-toluene-sulfonyl chloride (6.99 g, 37 mmol) in dichloromethane (22 mL) at 0 °C. The reaction mixture was stirred at room temperature under nitrogen for 24 h. Then, 1 M hydrochloric acid (50 mL) was added and the contents were stirred for 30 min. The organic phase was dried over sodium sulfate and evaporated to yield a deep red residue (11.68 g). The residue was chromatographed on a silica column by using 99:1 chloroform: acetone as eluent. Tetra(N,O)tosylated derivative (**6**) was obtained pure as a transparent oil. Yield 81%. *Anal. Calc.* for (**6**) $C_{59}H_{54}N_2O_{12}S_4$: C, 59.38; H, 5.50; *Found*: C, 59.40; H, 5.38%. ^{1}H-NMR ($CDCl_3$) δ in ppm from TMS: 7.77 (d, J_{H-H} = 8.2 Hz, 4H, AB system of N—Ts), 7.59 (d, J_{H-H} = 8.2 Hz, 4H, AB system of O—Ts), 7.28–7.11 (m, 12H, ArH), 6.83 (t, J_{H-H} = 7.4 Hz, 2H, ArH), 6.67 (d, J_{H-H} = 8.0 Hz, 2H, ArH), 4.32–4.27 (m, 4H, ArOCH_2), 4.13 (s, 4H, ArCH_2N), 4.09–4.05 (m, 4H, CH_2OTs), 2.97 (t, J_{H-H} = 7.3 Hz, 4H, TsNCH_2), 2.41 (s, 12 H, ArCH_3), 1.52–1.42 (m, 2H, NCH$_2$CH_2CH$_2$N).

2.3.3. *Preparation of Calixarene Derivative (1-***H***) by Pathway* **A**

Preparation of 25,27-[2,2′-[1,1′-(N,N′-(1,3-propylenediamine)ditosylate)]-2,2′-diphenoxy]diethyl]-calix[4]arene crown-6 (**1-Ts**)

A mixture of calix[4]-crown-6 (**2**) (0.63 g, 1 mmol), potassium carbonate (0.69 g, 5 mmol) in acetonitrile (60 mL) was stirred for 3 h. Then, a solution of tetra(N, O)tosylate (**6**) (1.00 g, 1 mmol) in acetonitrile (15 mL) was added dropwise. The reaction mixture was stirred with reflux under nitrogen for 2 days. The solvents were evaporated to dryness to yield a residue which was extracted with dichloromethane (150 mL) and 1 M hydrochloric acid (150 mL). The organic phase was dried over sodium sulfate and evaporated. The residue was chromatographed on a silica column by using 85 : 15 chloroform : acetone as eluent to provide calix[4]-di(-aza-benzo)crown-crown-6 (**1-Ts**) as a white solid. M.p. 240–241 °C. Yield 4%. *Anal. Calc*. for (**1-Ts**) $C_{73}H_{80}N_2O_{14}S_2$: C, 68.84; H, 6.34; *Found:* C, 68.91;

H, 6.20%. ^{1}H-NMR ($CDCl_3$) δ in ppm from TMS: 7.75 (d, J_{H-H} = 8.1 Hz, 4H, AB system of N—Ts), 7.34 (d, J_{H-H} = 8.1 Hz, 4H, AB system of N—Ts), 7.14 (d, J_{H-H} = 7.4 Hz, 4H, m-ArH of calix), 7.04–6.86 (m, 10 H, ArH), 6.71 (t, J_{H-H} = 7.4 Hz, 2H, ArH), 6.57 (t, J_{H-H} = 7.4 Hz, 2H, p-ArH of calix), 6.38 (d, J_{H-H} = 8.1 Hz, 2H, ArH), 4.12 (s, 4H, ArCH_2N), 3.91 (s, 8H, ArCH_2Ar), 3.71–3.43 (m, 24H, O CH_2CH_2O), 3.12–2.99 (m, 8H, NCH_2 CH_2 and OCH_2 CH_2O), 2.41 (s, 6H, ArCH_3), 1.31–1.26 (m, 2H, CH_2C$H_2$$CH_2$). FAB m/z: 1273.4 (for $C_{73}H_{80}N_2O_{14}S_2$).

Preparation of 25,27-[2,2′-(1,1′-(1,3-propylenediamine))-2,2′-diphenoxy]diethyl]-calix[4]arene crown-6 (**1-H**)

Lithium aluminium hydride (0.10 g, 2.50 mmol) was added to a solution of (**1-Ts**) (0.13 g, 0.10 mmol) in freshly distilled tetrahydrofuran (3 mL). The contents were stirred with reflux under nitrogen for 24 h. Then, the same quantity of lithium aluminium hydride was added and the reaction mixture was stirred with reflux for an additional 24 h. After cooling to room temperature, water (5 mL) and an excess of lithium hydroxide was added and the contents were stirred for 30 min. The mixture was dried over magnesium sulfate and washed with chloroform. The filtrate was concentrated and the residue was chromatographed on a silica column by using 70 : 15 : 15 dichloromethane : acetone : methanol as eluent to provide calix[4]-di(aza-benzo)crown-crown-6 (**1-H**) as a white solid. M.p. 133–134 °C. Yield 23%. *Anal. Calc.* for (**1-H**) $C_{59}H_{68}N_2O_{10}$. 0.5 $CHCl_3$: C, 69.76; H, 6.75; *Found:* C, 70.21; H, 6.77%. ^{1}H-NMR ($CDCl_3$) δ in ppm from TMS: 7.22 (d, J_{H-H} = 7.3 Hz, 2 H, ArH), 7.10–7.07 (m, 6 H, ArH), 7.01 (d, J_{H-H} = 7.5 Hz, 4H, m-ArH of calix), 6.90–6.81 (m, 4H, ArH), 6.69–6.63 (m, 4H, ArH), 3.78–3.36 (m, 40H, ArCH_2Ar, ArCH_2N and O CH_2 CH_2O), 2.59 (t, J_{H-H} = 6.8 Hz, 4H, C$H_2$$CH_2CH_2$), 1.79–1.55 (m, 2H, CH_2C$H_2$$CH_2$). FAB m/z: 965.5 (for $C_{59}H_{68}N_2O_{10}$).

2.3.4. *Preparation of Calixarene Derivative* (**1-H**) *by Pathway* **B**

Preparation of 25,27-[2,2′-[1,1′-(N,N′-(1,3-propylenediamine)ditosylate]-2,2′-diphenoxy]diethyl]-calix[4]-arene (**3**)

Tetra(N, O)tosylated derivative (**6**) (1.37 g, 1.38 mmol) dissolved in acetonitrile (50 mL) was added dropwise to a mixture of calix[4]arene (0.58 g, 1.38 mmol), potassium carbonate (0.20 g, 1.38 mmol), and acetonitrile (500 mL). The contents were stirred with reflux under nitrogen for 2 weeks. Then, the solvent was evaporated to afford a residue which was extracted with dichloromethane (250 mL) and 1 M hydrochloric acid (250 mL). The organic phase was dried over sodium sulfate and evaporated to yield an orange residue which was chromatographed on a silica column by using 56:40:4 dichloromethane : hexane : acetone as eluent. Calix[4]arene derivative (**3**) was obtained as a white solid. M.p. 268–269 °C. Yield 39%. ^{1}H-NMR ($CDCl_3$) δ in ppm from TMS: 7.61 (d, J_{H-H} = 8.2 Hz, 4 H, AB system of

N—Ts), 7.36 (s, 2 H, ArO*H*), 7.28–7.20 (m, 6 H, Ar*H*), 7.15 (t, J_{H-H} = 7.7 Hz, 2 H, Ar*H*), 6.85–6.54 (m, 16H, Ar*H*), 4.38 (d, J_{H-H} = 13.1 Hz, 4H, ArCH_AH_BAr), 4.28 (s, 4H, $Ar_{Calix}OCH_2CH_2OAr$), 4.27 (s, 4H, Ar_{Calix} OCH_2CH_2OAr), 4.20 (s, 4H, ArCH_2N), 3.15 (d, J_{H-H} = 13.1 Hz, 4H, ArCH_AH_BAr), 2.75 (t, J_{H-H} = 7.6 Hz, 4H, NCH_2CH_2), 2.47 (s, 6H, ArCH_3), 1.41–1.25 (m, 2H, $CH_2CH_2CH_2$).

Preparation of (**1-Ts**)

A mixture of (**3**) (0.12 g, 0.10 mmol), potassium carbonate (0.14 g, 1.00 mmol), and acetonitrile (40 mL) was stirred at room temperature for 3 h. Then, pentaethylene glycol di-*p*-toluenesulfonate (0.05 g, 0.10 mmol) dissolved in acetonitrile (10 mL) was added dropwise. The reaction mixture was then stirred with reflux under nitrogen for 7 days. Then, the solvents were evaporated to dryness to yield a residue which was extracted with dichloromethane (25 mL) and 1 M hydrochloric acid (25 mL). The organic phase was separated, dried over sodium sulfate and evaporated to give a residue which was chromatographed on a silica column by using 85:15 dichloromethane: acetone as eluent. The calix[4]- di(aza-benzo)crown-crown-6 (**1-Ts**) was obtained as a white solid. M.p. 241–242 °C. Yield 68%.

The preparation of (**1-H**) by pathway **B** was carried out in the same manner as in pathway **A**. Yield 21%.

2.3.5. *Preparation of Calixarene Derivative* (**1-H**) *by Pathway* **C**

Preparation of 25,27-di((2-ethoxy)benzaldehyde)calix[4]arene (**4**)

A mixture of calix[4]arene (12.73 g, 30 mmol), potassium carbonate (4.15 g, 30 mmol) and acetonitrile (400 mL) was stirred at room temperature overnight. Then, 2-(2-bromoethoxy)benzaldehyde (13.75 g, 60 mmol) dissolved in acetonitrile (50 mL) was added dropwise over 30 min. The reaction mixture was stirred with reflux under nitrogen for 2 weeks, the solvents were evaporated to dryness. The residue was extracted with dichloromethane (250 mL) and 1 M hydrochloric acid (250 mL). The organic layer was dried over sodium sulfate and evaporated to yield an orange solid which was chromatographed on a silica column by using dichloromethane as eluent. The calixarene-dialdehyde derivative (**4**) was obtained as a white solid. M.p. 209—210 °C. Yield 32%. *Anal. Calc.* for (**4**) $C_{46}H_{40}O_8 : 2CH_2Cl_2 : 2H_2O$: C, 62.32; H, 5.23; *Found:* C, 62.88; H, 5.59%. ^{1}H-NMR ($CDCl_3$) δ in ppm from TMS: 10.53 (s, 2H, ArCO*H*), 7.91 (s, 2H, ArO*H*), 7.87 (d, J_{H-H} = 7.6 Hz, 2H, Ar*H*), 7.50 (t, J_{H-H} = 8.7 Hz, 2H, Ar*H*), 7.06–6.99 (m, 6H, Ar*H*), 6.95–6.91 (m, 6H, Ar*H*), 6.77 (t, J_{H-H} = 7.5 Hz, 2H, *p*-Ar*H* of calix), 6.64 (t, J_{H-H} = 7.5 Hz, 2H, *p*-Ar*H* of calix), 4.40 (d, J_{H-H} = 2.0 Hz, 8H, ArOCH_2 CH_2OAr), 4.35 (d, J_{H-H} = 13.0 Hz, 4H, ArCH_AH_BAr), 3.41 (d, J_{H-H} = 13.0 Hz, 4H, ArCH_AH_BAr).

Preparation of 25,27-di((2-ethoxy)benzaldehyde)-calix[4]arene crown-6 (**5**)

A mixture of (**4**) (2.88 g, 4 mmol) and potassium *tert*-butoxide (0.91 g, 8 mmol) in benzene (250 mL) was stirred at room temperature for 3 h. Then, pentaethylene glycol di-p-toluenesulfonate (2.19 g, 4 mmol) dissolved in benzene (75 mL) was added dropwise. The reaction mixture was stirred with reflux under nitrogen for 1 hour. After cooling to room temperature, the mixture was extracted with 1 M hydrochloric acid (250 mL). The organic phase was dried over sodium sulfate and evaporated. The residue was chromatographed on a silica column by using 60 : 20 : 20 chloroform : hexane : acetone. The calix[4]arene-dialdehyde-crown-6 (**5**) was obtained as a transparent oil. Yield 27%. *Anal. Calc.* for (**5**) $C_{56}H_{58}O_{12}$: C_6H_{14}: C, 73.77; H, 7.20; *Found:* C, 73.28; H, 7.24%. ^{1}H-NMR ($CDCl_3$) δ in ppm from TMS: 10.36 (s, 2 H, ArCOH), 7.85 (d, J_{H-H} = 7.6 Hz, 2 H, ArH), 7.45 (t, J_{H-H} = 7.0 Hz, 2H, ArH), 6.98–6.78 (m, 14H, ArH), 6.68 (t, J_{H-H} = 7.4 Hz, 2H, p-ArH of calix), 3.83 (s, 16H, ArOCH_2CH_2OAr and ArOCH_2CH_2O), 3.72 (s, 8 H, ArCH_2Ar), 3.68–3.59 (m, 4H, ArOCH$_2$CH$_2$OCH_2), 3.55–3.52 (m, 4H, ArOCH$_2$CH$_2$OCH$_2$CH_2), 3.41–3.35 (m, 4H, ArOCH$_2$CH$_2$OCH$_2$CH$_2$OCH_2). FAB m/z: 945.4 (for $C_{56}H_{58}O_{12}Na^+$).

Preparation of 25,27-[2,2′-(1,1′-(1,3-propylenediamine))-2,2′-diphenoxy]diethyl]-calix[4]arene (**1-H**)

1,3-Diamino-propane (0.10 g, 1.30 mmol) dissolved in methanol (22 mL) was added dropwise to a solution of calix[4]-dialdehyde-crown-6 (**5**) (1.22 g, 1.30 mmol) in acetonitrile (110 mL). The contents were stirred with reflux under nitrogen for 24 h. Then the solvents were evaporated to dryness to afford an orange residue. The residue was directly dissolved in tetrahydrofuran (50 mL) and added into a suspension of sodium borohydride (0.86 g, 22.82 mmol) in tetrahydrofuran (150 mL). The contents were stirred at room temperature for 4 h and then water (200 mL) was added. The mixture was stirred for 1 h and then the solvents were evaporated to dryness to give a residue which was extracted with dichloromethane (200 mL) and water (200 mL). The organic phase was dried over sodium sulfate and evaporated. The residue was dissolved in dichloromethane (10 mL) and methanol (50 mL). 6 M Hydrochloric acid (10 mL) was added and the contents were stirred for 1 h. After removal of the solvents, the residue was extracted with dichloromethane (200 mL) and water (200 mL). The organic layer was dried over sodium sulfate and concentrated. The residue was dissolved in dichloromethane (10 mL) and methanol (50 mL) and treated with an excess of sodium hydroxide with stirring for 1 h. The contents were concentrated and the residue was extracted in dichloromethane (150 mL) and water (150 mL). The organic phase was separated, dried over sodium sulfate and evaporated. The residue was dissolved in the smallest amount of dichloromethane and precipitated by the addition of methanol. The white solid was filtered off and washed with methanol. M.p. 133–134 °C (Methanol). Yield 23%.

3. Results and Discussion

In order to improve the yield, the synthesis of 1,3-alternate calix[4]-di(aza-benzo)-crown-crown-6 (**1-H**) was accomplished by 3 pathways (**A-C**) as shown in Scheme I. In pathway **A**, calix[4]-crown-6 (**2**) was treated with tetra(N, O)tosylated derivative (**6**) (for the synthesis of (**6**) see Scheme II) in the presence of 5 equiv. of potassium carbonate in refluxing acetonitrile for 2 days. Calix[4]-di(aza-benzo)-crown-crown-6-ditosylate (**1-Ts**) was isolated by column chromatography in 4% yield and was deduced to be in the 1,3-alternate conformation due to the presence of one singlet at 3.91 ppm for the methylene protons of the calix macroring. The calix[4]-di(aza-benzo)-crown-crown-6-ditosylate (**1-Ts**) was detosylated by treatment with 25 equiv. of lithium aluminium hydride in refluxing tetrahydrofuran for 24 h. After treatment with hydrochloric acid and sodium hydroxide respectively, detosylated calix[4]arene derivative (**1-H**) was purified by column chromatography in 23% yield. The analytical data were in agreement with the desired structure. The total yield of this pathway was 0.5% (calculated from calix[4]arene by taking into account the preparation of (**2**) [12] in 50% yield; 50% $\times$ 4% $\times$ 23% $\times$ 100). Alternative pathway **B** began by reacting calix[4]arene with 1 equiv. of tetra(N, O)tosylate derivative (**6**) in the presence of 1 equiv. of potassium carbonate in refluxing acetonitrile for 2 weeks. After purification by column chromatography, calix[4]-di(aza-benzo)-crown ditosylate (**3**) was obtained in 39% yield in the cone conformation according to the appearance of a well-resolved AB system of methylene protons of the calix macroring at 4.38 and 3.15 ppm which also meant that the condensation has occurred at 1,3-positions. The calix[4]-di(aza-benzo)-crown (**3**) was then bridged with 1 equiv. of pentaethylene glycol di-p-toluenesulfonate in the presence of 10 equiv. of potassium carbonate in refluxing acetonitrile for 7 days. The isolation was carried out by column chromatography and calix[4]-di(aza-benzo)-crown-crown-6-ditosylate (**1-Ts**) was obtained in 68% yield. Detosylation was performed in the same manner as in pathway **A**. The total yield of preparation of (**1-H**) by pathway **B** was 6% (39% $\times$ 68% $\times$ 23% $\times$ 100). By a different strategy from pathways **A** and **B**, pathway **C**, started with the O-dialkylation of calix[4]arene with 2 equiv. of 2-(2-bromoethoxy)benzaldehyde in the presence of 1 equiv. of potassium carbonate in refluxing acetonitrile for 2 weeks. Pure calix[4]-dialdehyde (**4**) was obtained by column chromatography in 32% yield. By means of ^{1}H-NMR, it was found that calix[4]-dialdehyde (**4**) was functionalized at the 1,3-positions and fixed in the cone conformation by the appearance of a AB system at 4.35 and 3.41 ppm of methylene protons of the calix macroring. The calix[4]arene dialdehyde (**4**) was condensed with 1 equiv. of pentaethylene glycol di-p-toluenesulfonate in the presence of 2 equiv. of potassium *tert*-butoxide in refluxing benzene for 1 h. After purification by chromatography, calix[4]-dialdehyde-crown-6 (**5**) was obtained in 27% yield and deduced to be in the 1,3-alternate conformation due to the presence of a singlet at 3.72 ppm of methylene protons. The calix[4]-dialdehyde-crown-6 (**5**) was bridged by 1 equiv. of 1,3-diaminopropane in a refluxing mixture of 1 : 1 ace-

tonitrile : methanol for 24 h. After removal of the solvents, the residue was reduced by 20 equiv. of sodium borohydride in tetrahydrofuran at room temperature for 4 h. Calix[4]-di(aza-benzo)-crown-crown-6 (**1-H**) was precipitated by methanol from dichloromethane in 23% yield. The analytical data were in agreement with the proposed structure in which the two bridges are situated at the opposite sides of calix[4]arene in the 1,3-altemate conformation. The total yield of preparation of (**1-H**) by pathway **C** was 3% (32% × 27% × 23% × 100).

The synthesis of calix[4]-di(aza-benzo)-crown-crown-6 (**1-H**) by pathway **B** is the most efficient due to, in pathway **A**, the second cyclisation step of calix-crown-6 (**2**) with (**6**) giving only 4% yield.

Preliminary complexation studies of (**1-H**) were carried out by mean of ^{1}H-NMR. In the presence of an excess of cesium picrate in a $CDCl_3$ solution of (**1-H**), a downfield shift of the signals of the crown-ether chain from 3.78–3.36 ppm to 3.96–3.58 ppm was observed. This was interpreted as the complexation of cesium cation in the 'hard' polyether chain. When a solution of (**1-H**) in 1 : 1 $CDCl_3 : CD_3OD$ was reacted with an excess of zinc perchlorate a downfield shift of the triplet of—$NCH_2CH_2CH_2N$— from 2.59 ppm to 2.91 ppm (broad triplet) was observed. This was indicative of complexation of the zinc by nitrogen atoms as already observed for a very similar calix compound [10].

Further studies of the complexation of (**1-H**) to form hetero binuclear complexes are currently under investigation and will be presented in full in due course. We are also investigating the binding properties of other receptors related to (**1-H**). Our objectives include: (a) alkylations of N-H into N-R with binding groups able to complex lanthanides; (b) preparing calixarene derivatives containing both cryptand and crown ether chains to provide allosteric systems.

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