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Calix[4]arene Phosphonates - Recognition of Amino Alcohols in Water

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ABSTRACT: *The water-soluble calix[4]arenes based cavitands were obtained in good yield by introduction of phosphonic acids groups at the upper rim; we describe the design, synthesis, and formation of the complexes with ephedrine, norephedrine, and noradrenaline hydrochloride in the phosphate buffer at pD 7.3.* © 2004 Wiley Periodicals, Inc. Heteroatom Chem 15:155–161, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10229

INTRODUCTION

Calix[4]arenes have become an interesting platform for further synthetic elaboration into host molecules [1,2]. A lot of work has been done to modify either the lower or the upper rim positions to create host molecules mainly for the attraction of simple cations, anions, and small organic molecules [3]. However, water solubility is required for in vivo application of appropriately functionalized host [4]. Water soluble calixarenes, in most cases, have been achieved by the introduction of charged functional groups like carboxylic, sulfonic, and phosphonic or phosphoric. After the first reports of Ungaro [5] and Shinkai [6], a variety of new compounds have been obtained and their binding properties in aqueous solution have been demonstrated, which was summarized in review [7]. In our opinion the introduction of phosphonate groups into the calix[4]arene seems to be the most promising approach. In contrast to the carboxylate or sulfonate group, the phosphonate group can be easily modified with preservation of hydrophilic properties.

Kalchenko [8] has described water soluble calix[4]arenes bearing one, two, or four proton-ionizable dihydroxyphosphoryl groups at the lower rim, and their salt formation with L-(−)-α-phenylethylamine and (1*S*,2*R*)-(+)-ephedrine. These salts in deuteromethanol solution at room temperature exist as tight ion pair. However, increasing the temperature or addition of deuterated water leads to appreciable dissociation of the ion pairs. On the other hand, Coleman [9] reported a series of amphiphilic calix[4]arenes having four hydrophobic acyl chains at the upper rim as well as two hydrophilic dihydroxyphosphoryloxy groups at the lower rim self-assemble at the air-water interface as stable Langmuir monolayers. Calix[4]arenes substituted at the upper rim by hydroxyethoxyphosphoryl groups and their self-assembly to capsules with tetra-cationic counterparts in polar solvents has been recently described by Schrader [10]. Unfortunately the 1:1 complexes were often insoluble in water and in some cases precipitated even from methanol. Calix[4]arenes bearing α-amino or α-hydroxyphosphonic acid fragments were also described. Their self-assembly [11] and transport [12] of bioactive guest through cell membrane were reported.

As one can see, the amphiphilic calix[4]arenes bearing phosphonic acids groups at the lower or upper rim can form salts with amines, self-assemble

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at the air–water interface as monolayers, or self-assemble to capsules with tetra-cationic counterparts in polar solvents respectively. There is no report concerning host-guest interaction in aqueous solution of water soluble calix[4]arene having phosphonic acid groups at the upper rim.

In our study the main attention is focused on the structure influence of ammonium type guests on the binding with calix[4]arenes bearing phosphonic acids groups at the upper rim. The placing of the phosphonic acid groups directly at the upper rim of calix[4]arene seems to be crucial for binding process in aqueous solution. The ionic host-guest interaction can be supported by hydrophobic effect of calix[4]arene cavity, therefore we decided to verify our expectation by experiment.

EXPERIMENTAL

All moisture sensitive reactions were performed under argon atmosphere. Melting points are uncorrected. NMR spectra were recorded on a Varian Gemini 500 MHz spectrometer. IR spectra were measured on a Bruker IFS66. ESI-MS spectra were recorded on a MARINER PerSeptve Biosystem. Reactions were monitored by TLC on precoated silica gel plates (SiO_2, E. Merck, $60F_{254}$). Flash column chromatography were performed on silica gel 60 (SiO_2, E. Merck, particle size 0.040–0.064 mm 230–400 mesh). All measurements of complexation in water were performed in deuterated phosphate buffer (0.2 M) pD 7.3. The guest concentration was kept constant (1×10^{-3} M) while the host concentration was varied from 2×10^{-3} to 20×10^{-3} M. Chemical shifts (δ, ppm) were internally referenced to TMSP-d_4. Diphenyl ether (Aldrich), lithium bromide (Lancaster), (1*R*,2*S*)-(−)-ephedrine hydrochloride, (1*R*,2*S*)-(−)-norephedrine hydrochloride, (*R*)-(−)-noradrenaline hydrochloride, 2-phenylethylamine hydrochloride, benzylamine hydrochloride, 1,2-phenylenediamine dihydrochloride, ethanolamine hydrochloride (Aldrich) were reagents grade and used without further purification. Acetonitrile was distilled from calcium hydride and kept over molecular sieves (4 Å). The trimethylsilyl bromide and trimethyl phosphite were distilled before use.

General Procedure for **11, 13** *and* **12, 14**

A suspension of bromide **7–10** (7.0 mmol) and anhydrous $NiCl_2$ (0.362 g, 2.8 mmol, for **7** and **9**) or (0.181 g, 1.4 mmol, for **8** and **10**) in diphenyl ether (100 ml) was heated to 210–220°C and treated, dropwise, over a period of 15 min with trimethyl phosphite (10.4 g, 84 mmol, for **7** and **9**) or (5.2 g, 42 mmol, for **7** and **9**). The temperature of reaction mixture was maintained at 210–220°C for an additional 2 h. After the evaporation of the solvent under reduced pressure the residue was purified by column chromatography on silica, using $CHCl_3/CH_3OH$ as eluent to give pure product as a white solid.

5,11,17,23-Tetrakis-(dimethoxyphosphoryl)-25,26,27,28-tetrapropoxycalix[4]arene **11**. Yield (85%); m.p. 195–200°C; R_f ($CHCl_3/CH_3OH$, 15:1) 0.24; IR (KBr) $\nu = 1461, 1273, 1022, 774, 825$ cm^{-1}; ^{1}H NMR ($CDCl_3$) $\delta = 0.98$ (t, $J = 7.3$ Hz, 12H, $OCH_2CH_2C\underline{H}_3$), 1.95–2.00 (m, 8H, $OCH_2C\underline{H}_2CH_3$), 3.26 (d, $J = 13.2$ Hz, 4H, $ArC\underline{H}_2Ar$), 3.50 (d, $J = 11.2$ Hz, 24H, $POC\underline{H}_3$), 3.88 (t, $J = 7.8$ Hz, 8H, $OC\underline{H}_2CH_2CH_3$), 4.44 (d, $J = 13.2$ Hz, 4H, $ArC\underline{H}_2Ar$), 7.19 (d, $J = 13.2$ Hz, 8H, Ar); ^{13}C NMR ($CDCl_3$) $\delta = 10.0$ ($OCH_2CH_2\,\underline{C}H_3$), 23.1 ($OCH_2\underline{C}H_2CH_3$), 30.4 ($Ar\underline{C}H_2Ar$), 52.4 (d, $J = 5.3$ Hz, $PO\underline{C}H_3$), 77.3 ($O\underline{C}H_2CH_2CH_3$), 120.4 (d, $J = 190$ Hz), 132.3 (d, $J = 9.9$ Hz), 134.8 (d, $J = 16.0$ Hz), 159.6 (d, $J = 3.9$ Hz); ^{31}P NMR ($CDCl_3$) $\delta = 22.64$; LR-ESI-MS: $m/z = 1025$ ($[M+H]^+$, 10%, $C_{48}H_{69}O_{16}P_4$ required 1025), 1047($[M + Na]^+$, 100).

5,17-Bis(dimethoxyphosphoryl)-25,26,27,28-tetrapropoxycalix[4]arene **12**. Yield (68%); m.p. 230–235°C; R_f ($CHCl_3/CH_3OH$, 25:1) 0.45; IR (KBr) $\nu = 1462, 1258, 1020, 771, 828$ cm^{-1}; ^{1}H NMR ($CDCl_3$) $\delta = 0.91$ (t, $J = 7.3$ Hz, 6H, $OCH_2CH_2C\underline{H}_3$), 1.08 (t, $J = 7.3$ Hz, 6H, $OCH_2CH_2C\underline{H}_3$), 1.88–1.96 (m, 8H, $OCH_2C\underline{H}_2CH_3$), 3.22 (d, $J = 13.2$ Hz, 4H, $ArC\underline{H}_2Ar$), 3.71 (t, $J = 6.8$ Hz, 4H, $OC\underline{H}_2CH_2CH_3$), 3.77 (d, $J = 11.2$ Hz, 12H, $OC\underline{H}_3$), 4.05 (t, $J = 7.8$ Hz, 4H, $OC\underline{H}_2CH_2CH_3$), 4.46 (d, $J = 13.2$ Hz, 4H, $ArC\underline{H}_2Ar$), 6.17 (d, $J = 7.3$ Hz, 4H, Ar), 6.29 (t, $J = 7.3$ Hz, 2H, Ar), 7.50 (d, $J = 13.2$ Hz, 4H, Ar); ^{13}C NMR ($CDCl_3$) $\delta = 9.8$, 10.6 ($OCH_2CH_2\underline{C}H_3$), 23.1, 23.4 ($OCH_2\underline{C}H_2CH_3$), 30.8 ($Ar\underline{C}H_2Ar$), 52.6 (d, $J = 5.3$ Hz, $O\underline{C}H_3$), 76.7, 77.0 ($O\underline{C}H_2CH_2CH_3$), 119.1 (d, $J = 191.5$ Hz), 122.4, 127.7, 132.5 (d, $J = 10.7$ Hz), 132.7, 137.0 (d, $J = 16.8$ Hz), 155.2, 161.7 (d, $J = 3.9$ Hz); ^{31}P NMR ($CDCl_3$) $\delta = 24.17$; HR-ESI-MS $m/z = 809.3580$ ($[M + H]^+$, $C_{44}H_{59}O_{10}P_2$ required 809.3584).

5,11,17,23-Tetrakis-(dimethoxyphosphoryl)-25,26,27,28-tetrakis-(2-methoxyethoxy)calix[4]arene **13**. Yield (31%); m.p. 175–177°C; R_f ($CHCl_3/CH_3OH$, 10:1) 0.26; IR (KBr) $\nu = 1469, 1274, 1022, 772, 826$ cm^{-1}; ^{1}H NMR ($CDCl_3$) $\delta = 3.31$ (d, $J = 13.1$ Hz, 4H, $ArC\underline{H}_2Ar$), 3.41 (s, 12H, $CH_2OC\underline{H}_3$), 3.56 (d, $J = 11.0$ Hz, 24H, $POC\underline{H}_3$), 3.83 (t, $J = 4.9$ Hz, 8H, $OCH_2C\underline{H}_2OCH_3$), 4.23 (t, $J = 4.89$ Hz, 8H, $OC\underline{H}_2CH_2OCH_3$), 4.60 (d, $J = 13.1$ Hz,

4H, ArC$\underline{H}_2$Ar), 7.25 (d, $J = 13.1$ Hz, 8H, Ar); ^{13}C NMR ($CDCl_3$) $\delta = 30.4$ (ArC$\underline{H}_2$Ar), 52.5 (d, $J = 5.3$ Hz, PO$\underline{C}H_3$), 58.6 ($OCH_2CH_2O\underline{C}H_3$), 71.5 ($OCH_2\underline{C}H_2OCH_3$), 73.6 ($O\underline{C}H_2CH_2OCH_3$), 120.8 (d, $J = 190$ Hz), 132.4 (d, $J = 9.9$ Hz), 135.0 (d, $J = 16.0$ Hz), 159.4 (d, $J = 3.9$ Hz); ^{31}P NMR ($CDCl_3$) $\delta = 22.59$; LR-ESI-MS $m/z = 1089.5$ ($[M + H]^+$, 15%, $C_{48}H_{69}O_{20}P_4$ required 1089.3), 1111.5 ($[M + Na]^+$, 100).

5,17-Bis(dimethoxyphosphoryl)-25,26,27,28-tetrakis-(2-methoxyethoxy)calix[4]arene **14**. Yield (86%); m.p. 170–175°C; R_f ($CHCl_3/CH_3OH$, 25:1) 0.30; IR (KBr) $\nu = 1451$, 1270, 1019, 765, 824 cm^{-1}; ^{1}H NMR ($CDCl_3$) $\delta = 3.22$ (d, $J = 13.4$ Hz, 4H, ArC$\underline{H}_2$Ar), 3.37 (s, 6H, $CH_2OC\underline{H}_3$), 3.44 (s, 6H, $CH_2OC\underline{H}_3$), 3.80–3.74 (m, 16H, P-O$C\underline{H}_3$ and $OCH_2C\underline{H}_2OCH_3$), 3.84 (t, $J = 5.4$ Hz, 4H, $OCH_2C\underline{H}_2OCH_3$), 4.00 (t, $J = 5.9$ Hz, 4H, $OC\underline{H}_2CH_2OCH_3$), 4.32 (t, $J = 5.4$ Hz, 4H, $OC\underline{H}_2$-CH_2OCH_3), 4.52 (d, $J = 13.4$ Hz, 4H, ArC$\underline{H}_2$Ar), 6.25 (d, $J = 7.3$ Hz, 4H, Ar), 6.34 (t, $J = 7.3$ Hz, 2H, Ar), 7.47 (d, $J = 13.2$ Hz, 4H, Ar); ^{13}C NMR ($CDCl_3$) $\delta = 30.6$ (ArC$\underline{H}_2$Ar), 52.6 (d, $J = 5.3$ Hz, PO$\underline{C}H_3$), 58.5, 58.7 ($OCH_2CH_2O\underline{C}H_3$), 71.7, 71.8 ($OCH_2\underline{C}H_2OCH_3$), 73.0, 73.6 ($O\underline{C}H_2CH_2OCH_3$), 119.5 (d, $J = 191.5$), 122.8, 128.0, 132.5 (d, $J = 10.7$ Hz), 132.9, 136.8 (d, $J = 16.0$ Hz), 154.8, 161.6 (d, $J = 3.9$ Hz). ^{31}P NMR ($CDCl_3$) $\delta = 24.01$; HR-ESI-MS $m/z = 873.3418$ ($[M + H]^+$, $C_{44}H_{59}O_{14}P_2$ required 873.3380).

General Procedure for Synthesis of **1** *and* **3**

The compound **11** or **12** (1.0 mmol) was dissolved in 2 ml of trimethylsilyl bromide and stirred overnight at room temperature under argon. The trimethylsilyl bromide was removed under vacuum and residue was dissolved in CH_3OH (2 ml) and stirred overnight at room temperature. The solvent was evaporated to yield product **1** or **3** as white, fluffy powder respectively.

5,11,17,23-Tetrakis(dihydroxyphosphoryl)-25,26,27,28-tetrapropoxycalix[4]arene **1**. Yield (100%); m.p. 231–235°C; IR (KBr) $\nu = 3400$–3600, 2250–2350, 1461, 1127, 1002 cm^{-1}; ^{1}H NMR (D_2O) $\delta = 0.60$ (t, $J = 7.3$ Hz, 12H, $OCH_2CH_2C\underline{H}_3$), 1.64 (m, 8H, $OCH_2C\underline{H}_2CH_3$), 3.26 (d, $J = 12.2$ Hz, 4H, ArC$\underline{H}_2$Ar), 3.83 (t, $J = 7.8$ Hz, 8H, $OC\underline{H}_2CH_2CH_3$), 4.13 (d, $J = 12.2$ Hz, 4H, ArC$\underline{H}_2$Ar), 7.26 (d, $J = 11.7$ Hz, 8H, Ar); ^{13}C NMR (D_2O) $\delta = 9.0$ ($OCH_2CH_2\underline{C}H_3$), 22.4 ($OCH_2\underline{C}H_2CH_3$), 30.0 (Ar$\underline{C}H_2$Ar), 79.2 ($O\underline{C}H_2CH_2CH_3$), 130.9, 134.6 (d, $J = 12.6$ Hz), 137.9 (d, $J = 167.1$ Hz), 152.6; ^{31}P NMR (D_2O) $\delta = 11.72$; LR-ESI-MS $m/z = 911.6$ ($[M\text{-}H]^-$, 7%, $C_{40}H_{51}O_{16}P_4$ required 911.2), 455.4 ($[M - 2H]^{2-}$, 64), 303.4 ($[M - 3H]^{3-}$, 100).

5,17-Bis(dihydroxyphosphoryl)-25,26,27,28-tetrapropoxycalix[4]arene **3**. Yield (100%); m.p. 237–240°C; IR (KBr) $\nu = 3400$–3600, 2350–2250, 1460, 1209, 1003, 967 cm^{-1}; ^{1}H NMR ($CDCl_3$) $\delta = 0.88$ (t, $J = 7.3$ Hz, 6H, $OCH_2CH_2C\underline{H}_3$), 1.11 (t, $J = 7.3$ Hz, 6H, $OCH_2CH_2C\underline{H}_3$), 1.85–1.93 (m, 4H, $OCH_2C\underline{H}_2CH_3$), 1.93–2.05 (m, 4H, $OCH_2C\underline{H}_2CH_3$), 3.17 (d, $J = 13.3$ Hz, 4H, ArC$\underline{H}_2$Ar), 3.68 (t, $J = 7.0$ Hz, 4H, $OC\underline{H}_2CH_2CH_3$), 4.02 (t, $J = 8.2$ Hz, 4H, $OC\underline{H}_2CH_2CH_3$), 4.45 (d, $J = 13.3$ Hz, 4H, ArC$\underline{H}_2$Ar), 4.40–4.60 (bs, OH), 6.62 (d, $J = 14.2$ Hz, 4H, Ar), 6.93 (t, $J = 7.3$ Hz, 2H, Ar), 7.14 (d, $J = 7.3$ Hz, 4H, Ar); ^{13}C NMR (D_2O) $\delta = 12.6$, 12.9 ($OCH_2CH_2\underline{C}H_3$), 25.7, 25.8 ($OCH_2\underline{C}H_2CH_3$), 33.2 (Ar$\underline{C}H_2$Ar), 79.4, 79.6 ($O\underline{C}H_2CH_2CH_3$), 125.9, 131.4, 133.9, 137.0, 137.2 (d, $J = 12.2$ Hz), 138.0 (d, $J = 166.1$ Hz), 158.2, 159.6; ^{31}P NMR (D_2O) $\delta = 12.56$; HR-ESI-MS $m/z = 751.2819$ ($[M - H]^-$, $C_{40}H_{49}O_{10}P_2$ required 751.2801).

General Procedure for the Preparation of Lithium Salts of Calix[4]arenes **2** *and* **4–6**

Dimethyl ester **11–14** (1 mmol) in dry acetonitrile (2 ml) was added to a solution of lithium bromide (44 mmol for a **11, 13**; 22 mmol for a **12, 14**) in dry acetonitrile 60 ml and 30 ml, respectively. The reaction mixture was refluxed for 48 h. The precipitate was filtered off, washed with dry acetonitrile, and dried, to yield the product (74–98%).

5,11,17,23-Tetrakis-(hydroxymethoxyphosphoryl)-25,26,27,28-tetrapropoxycalix[4]arene Tetralithium Salt **2**. Yield (98%); m.p. >300°C; IR (KBr) $\nu = 3000$–3700, 1600–1700, 1464, 1191, 1080, 1040, 777 cm^{-1}; ^{1}H NMR (D_2O) $\delta = 0.86$ (t, $J = 7.1$ Hz, 12H, $OCH_2CH_2C\underline{H}_3$), 1.85–1.93 (m, 8H, $OCH_2C\underline{H}_2CH_3$), 2.87 (d, $J = 10.7$ Hz, 12H, $OC\underline{H}_3$), 3.23 (d, $J = 12.8$ Hz, 4H, ArC$\underline{H}_2$Ar), 3.82 (t, $J = 7.69$ Hz, 8H, $OC\underline{H}_2CH_2CH_3$), 4.40 (d, $J = 12.8$ Hz, 4H, ArC$\underline{H}_2$Ar), 7.08 (d, $J = 12.4$ Hz, 8H, Ar); ^{13}C NMR (D_2O) $\delta = 10.2$ ($OCH_2CH_2\underline{C}H_3$), 23.3 ($OCH_2\underline{C}H_2CH_3$), 30.3 (Ar$\underline{C}H_2$Ar), 51.8 (d, $J = 4.6$ Hz, PO$\underline{C}H_3$), 77.1 ($O\underline{C}H_2CH_2CH_3$), 126.3 (d, $J = 178.8$ Hz), 132.1 (d, $J = 10.7$ Hz), 134.6 (d, $J = 14.7$ Hz), 158.2; ^{31}P NMR (D_2O) $\delta = 18.12$; LR-ESI-MS $m/z = 489.1$ ($[M - 2Li]^{2-}$, 100%, $C_{44}H_{56}Li_2O_{16}P_4$ required 489.1).

5,17-Bis-(hydroxymethoxyphosphoryl)-25,26,27,28-tetrapropoxycalix[4]arene Dilithium Salt **4**. Yield

(88%); m.p. >300°C; IR (KBr) $\nu = 3200–3700, 1600–1700, 1461, 1196, 1082, 1044, 775\ cm^{-1}$; ^1H NMR (CD_3OD) $\delta = 0.93$ (t, $J = 7.3$ Hz, 6H, $OCH_2CH_2C\underline{H}_3$), 1.16 (t, $J = 7.8$ Hz, 6H, $OCH_2CH_2C\underline{H}_3$), 1.88–1.94 (m, 4H, $OCH_2C\underline{H}_2CH_3$), 1.99–2.05 (m, 4H, $OCH_2C\underline{H}_2CH_3$), 3.21 (d, $J = 13.4$ Hz, 4H, $ArC\underline{H}_2Ar$), 3.53 (d, $J = 11.2$ Hz, 6H, $OC\underline{H}_3$), 3.68 (t, $J = 6.86$ Hz, 4H, $OC\underline{H}_2CH_2CH_3$), 4.12 (t, $J = 8.3$ Hz, 4H, $OC\underline{H}_2CH_2CH_3$), 4.50 (d, $J = 13.4$ Hz, 4H, $ArC\underline{H}_2Ar$), 6.10–6.18 (m, 6H, Ar), 7.58 (d, $J = 12.2$ Hz, 4H, Ar); ^{13}C NMR (CD_3OD) $\delta = 9.1$, 10.3 ($OCH_2CH_2\underline{C}H_3$), 23.1, 23.6 ($OCH_2\underline{C}H_2CH_3$), 30.7 ($Ar\underline{C}H_2Ar$), 50.8 (d, $J = 5.0$ Hz, $PO\underline{C}H_3$), 76.6, 77.0 ($O\underline{C}H_2CH_2CH_3$), 121.9, 127.3 (d, $J = 179.6$ Hz), 127.6, 132.5 (d, $J = 9.6$ Hz), 132.8, 136.6 (d, $J = 14.7$ Hz), 155.2, 160.0; ^{31}P NMR (CD_3OD) $\delta = 17.70$; HR-ESI-MS $m/z = 799.3492$ ($[M + Li]^+$, $C_{42}H_{52}Li_3O_{10}P_2$ required 799.3516).

5,11,17,23-Tetrakis-(hydroxymethoxyphosphoryl)-25,26,27,28-tetrakis(2-methoxyethoxy)calix[4]arene Tetralithium Salt **5**. Yield (98%); m.p. >300°C; IR (KBr) $\nu = 3200–3700, 1600–1700, 1467, 1194, 1082, 1036, 789\ cm^{-1}$; ^1H NMR (D_2O) $\delta = 2.88$ (d, $J = 10.7$ Hz, 12H, $POC\underline{H}_3$), 3.29 (d, $J = 12.7$ Hz, 4H, $ArC\underline{H}_2Ar$), 3.30 (s, 12H, $OCH_2CH_2OC\underline{H}_3$), 3.85 (t, $J = 4.9$ Hz, 8H, $OCH_2C\underline{H}_2OCH_3$), 4.11 (t, $J = 4.9$ Hz, 8H, $OC\underline{H}_2CH_2OCH_3$), 4.37 (d, $J = 12.7$, 4H, $ArC\underline{H}_2Ar$), 7.10 (d, $J = 12.7$ Hz, 8H, Ar); ^{13}C NMR (D_2O) $\delta = 30.3$ ($Ar\underline{C}H_2Ar$), 51.9 (d, $J = 4.6$ Hz, $PO\underline{C}H_3$), 58.1 ($OCH_2CH_2O\underline{C}H_3$), 72.1 ($OCH_2\underline{C}H_2OCH_3$), 73.0 ($O\underline{C}H_2CH_2OCH_3$), 126.3 (d, $J = 179.2$ Hz), 131.9 (d, $J = 10.5$ Hz), 134.8 (d, $J = 14.7$ Hz), 158.2; ^{31}P NMR (D_2O) $\delta = 18.10$; LR-ESI-MS $m/z = 1049.6$ ($[M\text{-}Li]^-$, 7%, $C_{44}H_{56}Li_3O_{20}P_4$ required 1049.3), 521.4 ($[M\text{-}2Li]^{2-}$, 100), 345.3 ($[M\text{-}3Li]^{3-}$, 82), 257.1 ($[M - 4Li]^{4-}$, 50).

5,17-Bis-(hydroxymethoxyphosphoryl)-25,26,27,28-tetrakis(2-methoxyethoxy)calix[4]arene Dilithium Salt **6**. Yield (74%); m.p. >300°C; IR (KBr) $\nu = 3200–3700, 1600–1700, 1467, 1198, 1082, 1048, 782\ cm^{-1}$; ^1H NMR (D_2O) $\delta = 3.21$ (d, $J = 13.2$ Hz, 4H, $ArC\underline{H}_2Ar$), 3.23 (s, 6H, $OCH_2CH_2OC\underline{H}_3$), 3.31 (d, $J = 10.7$ Hz, 6H, $POC\underline{H}_3$), 3.32 (s, 6H, $OCH_2CH_2OC\underline{H}_3$), 3.68–3.72 (m, 4H, $OCH_2C\underline{H}_2OCH_3$), 3.82–3.86 (m, 4H, $OC\underline{H}_2CH_2OCH_3$), 3.88 (t, $J = 5.4$ Hz, 4H, $OCH_2C\underline{H}_2OCH_3$), 4.26 (t, $J = 5.37$ Hz, 4H, $OC\underline{H}_2CH_2OCH_3$), 4.33 (d, $J = 13.2$ Hz, 4H, $ArC\underline{H}_2Ar$), 6.23 (s, 6H, Ar), 7.37 (d, $J = 12.7$ Hz, 4H, Ar); ^{13}C NMR (D_2O) $\delta = 30.4$ ($Ar\underline{C}H_2Ar$), 51.8 (d, $J = 4.6$ Hz, $PO\underline{C}H_3$), 58.0, 58.1 ($OCH_2CH_2O\underline{C}H_3$), 71.8, 72.3 ($OCH_2\underline{C}H_2OCH_3$), 72.5, 73.5 ($O\underline{C}H_2CH_2OCH_3$), 123.1, 125.8 (d, $J = 179.3$ Hz), 128.0, 132.3 (d, $J = 9.9$ Hz), 133.6, 136.6 (d, $J = 15.2$ Hz), 154.8, 160.2; ^{31}P NMR (D_2O) $\delta = 18.96$; HR-ESI-MS $m/z = 863.3351$ ($[M + Li]^+$, $C_{42}H_{52}Li_3O_{14}P_2$ required 863.3312).

RESULTS AND DISCUSSION

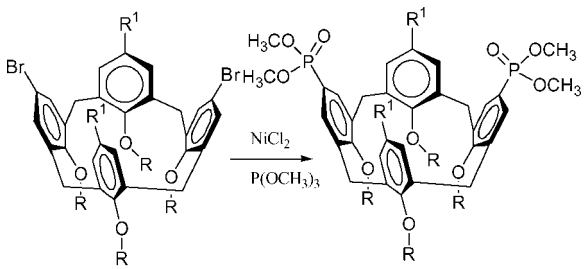
The compounds **1–6** were readily prepared in two steps from the known *cone* bromo calix[4]arenes **7–10** [13]. Appropriate dimethyl esters were obtained by means of Arbuzov reaction of trimethyl phosphite with **7–10** in the presence of anhydrous $NiCl_2$ [10,14]. The described procedures were modified. Diphenyl ether and trimethyl phosphite were used instead of benzonitrile and triethyl phosphite respectively. In this way the yields were improved up to 85% (Scheme 1).

The dimethyl esters **11** and **12** were treated with excess of bromotrimethylsilane at room temperature to yield phosphonic acids **1** and **3** respectively. The reaction of dimethyl esters **11–14** with excess of LiBr in refluxed acetonitrile afforded **2** and **4–6** (Scheme 2).

The solubility of host molecules **1–6** in distilled water and 0.2 M phosphate buffer at pH 7.0 was examined (Table 1).

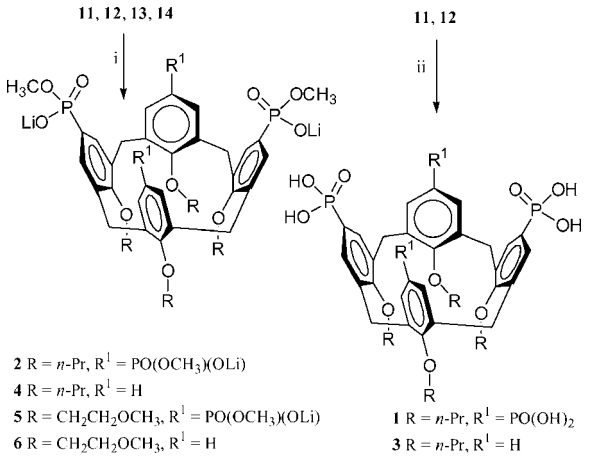
As one can see from the data collected in Table 1, the solubility strongly depends on the structure. The presence of four phosphonic groups at upper rim or methoxyethoxy substituents at lower rim improved the solubility of the final host. The observed results are the consequence of the hydrophilic character of these groups.

The compounds **1** and **2** were selected for preliminary study of host-guest properties in the phosphate buffer pD 7.3 at 25°C. It would be of great value for biochemists as well as pharmacologists to gain access to a small defined model of the adrenergic receptor that imitates the natural receptor-ligand



7 R = *n*-Pr, R^1 = Br
8 R = *n*-Pr, R^1 = H
9 R = $CH_2CH_2OCH_3$, R^1 = Br
10 R = $CH_2CH_2OCH_3$, R^1 = H
11 R = *n*-Pr, R^1 = $PO(OCH_3)_2$
12 R = *n*-Pr, R^1 = H
13 R = $CH_2CH_2OCH_3$, R^1 = $PO(OCH_3)_2$
14 R = $CH_2CH_2OCH_3$, R^1 = H

SCHEME 1 The synthesis of calix[4]arenes bis- and tetrakis-dimethylphosphonates.



SCHEME 2 Reagents and conditions: (i), excess of LiBr, acetonitrile, reflux; (ii), excess $(CH_3)_3SiBr$, RT.

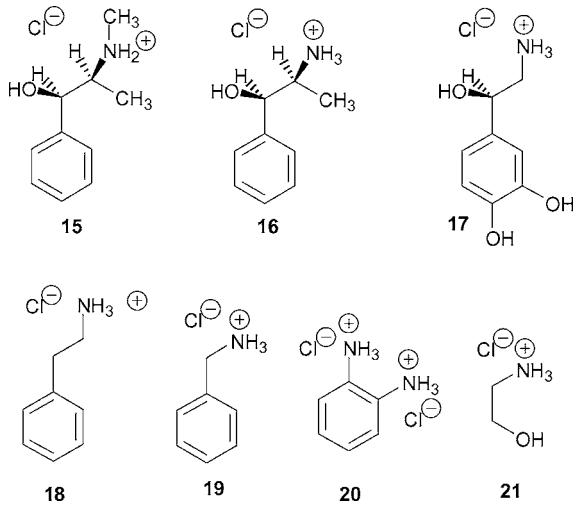


FIGURE 1 The structures of examined guests.

interactions. Therefore, the following guests were examined to verify the scope and limitation of the complex formation: (1*R*,2*S*)-(−)-ephedrine hydrochloride **15**, (1*R*,2*S*)-(−)-norephedrine hydrochloride **16**, (R)-(−)-noradrenaline hydrochloride **17**, 2-phenylethylamine hydrochloride **18**, benzylamine hydrochloride **19**, 1,2-phenylenediamine dihydrochloride **20**, ethanolamine hydrochloride **21** (Fig. 1).

We performed dilution experiments to investigate the complex formation between host **1, 2**, and ammonium guests [15]. In these experiments, ^{1}H NMR spectra were obtained at a series of concentrations **1** or **2** and fixed guest concentration (1 mM). The changes that occurred in the chemical shifts of the guest protons were monitored. The shifts in the ^{1}H NMR resonances were then fitted to the theoretical equation governing 1:1 fast exchange complex formation [15]. Additionally, self-association of the host **1** and **2** was excluded. The ^{1}H NMR spectrum of the host was not changed up to 40 mM. The dilution experiments were performed four times for each host and the experimental error for K was evaluated. Table 2 summarizes the results of our study.

Job's method of continuous variations confirms the postulated 1:1 stoichiometry for all guests [15]. Maxima for mol fraction 0.5 were observed (Job plot for ephedrine **15** is presented in Fig. 2).

Only in the case of noradrenaline **17** with hosts **1** and **2** maxima were detected in the range 0.4–0.45 of mol fraction, nevertheless the shifts in the ^{1}H NMR resonances fitted very well to the theoretical equation governing 1:1 fast exchange complex formation. Upon inclusion, all guests protons experience an upfield shift. Evaluation of each of these different protons gave similar values of binding constant. The changes of $\Delta\delta$ for (1*R*,2*S*)-(−)-ephedrine hydrochloride **15** versus host **1** concentration are presented in Fig. 3.

Based on the values of K and $\Delta\delta$ observed for ephedrine protons we are able to draw the following conclusions. The chemical induced shift (CIS) is observed for all protons of guest but C—CH_3 protons showed the highest CIS. It means that the phenyl ring of ephedrine upon complexation is not introduced into the calixarene cavity exclusively. In this case the aromatic protons should show the largest CIS in the

TABLE 1 The Solubility of **1–6** (mM) in 1 l of the Solvent at Room Temperature

	Water (mM)	*Buffer (mM)*[a]
1	<1	50
2	>300	200
3	<1	<1
4	8	<1
5	>300	25
6	>250	50

[a]Phosphate buffer 200 mM, pH 7.0.

TABLE 2 Association Constants ($K_{1:1}$) (M^{-1}) from NMR Titrations in 200 mM Phosphate Buffered D_2O (pD 7.3) at 25°C[a]

	Guest	**15**	**16**	**17**	**18**	**19**	**20**	**21**
Host	**1**	85	102	114	145	72	NB[b]	11
Host	**2**	45	58	45	70	ND[b]	NB[b]	ND[b]

[a]Errors in K_a were estimated for four independent runs and were smaller then 20%.
[b]NB = no binding, ND = not determined.

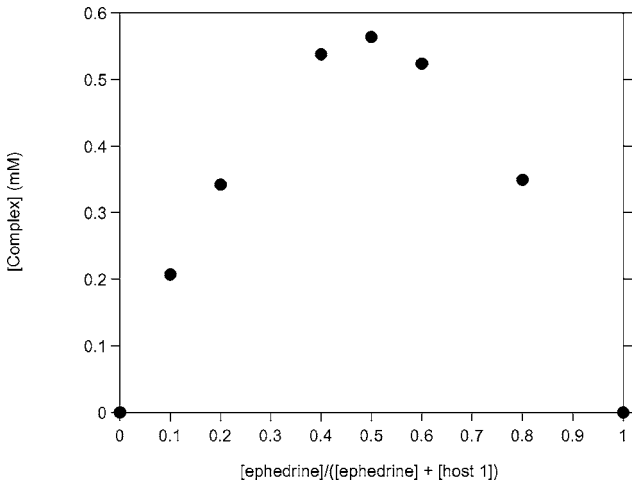


FIGURE 2 The Job plot for complex formation of (1*R*,2*S*)-ephedrine hydrochloride **15** with host **1**.

order $H_{para} > H_{meta} > H_{ortho}$. If phenyl ring upon complex formation was outside cavity, the chemical induced shift for aromatic protons would not be observed. All guest protons shift to higher magnetic fields (Fig. 3) which indicates equilibrium between the two inclusion modes of the guest as depicted in Fig. 4.

The exact structure for these two modes is unknown. Figure 4 represents only our expectation of these modes. This type of behavior is characteristic for guests **15–19**. Even for the noradrenaline **17** the partial inclusion of phenyl ring bearing two hydroxyl groups was observed. The analysis of association constants from Table 2, from the guest structure point of view, demonstrated that better complex formation is supported by the possessing of phenyl ring and ammonium cation separated by two-carbon chain in the guest structure. There is weak or no binding when the guest does not possess phenyl ring (ethanolamine **21**) or when the ammonium cations are too close to the phenyl ring (1,2-phenylenediamine **20**). The collected data suggests that in the binding process consisted of the ion interaction between guest ammonium cation and host phosphonates anions, and hydrophobic interaction of guest phenyl ring and calixarene cavity. It seems that in the case of aqueous solution the ion interaction has to be supported by hydrophobic effect of host for effective binding. From this point of view the highest association constant observed for 2-phenylethylammonium cation **18** is simple to explain. Any changes in the structure of guest, which decreased ionic or hydrophobic interaction with host, should be reflected in the lower binding constant. These changes are exactly observed. The contribution of hydrophobic interaction can be decreased by shorter distance between ammonium cation and phenyl ring (**18** versus **19** and **20**), and steric hindrance substituents from phenyl ring (**18** versus **17**), or absence of phenyl ring (**18** versus **21**). The contribution of ionic interaction was decreased when some steric hindrance at the ammonium cation (**18** versus **15**) or neighbourhood (**18** versus **16**) was present.

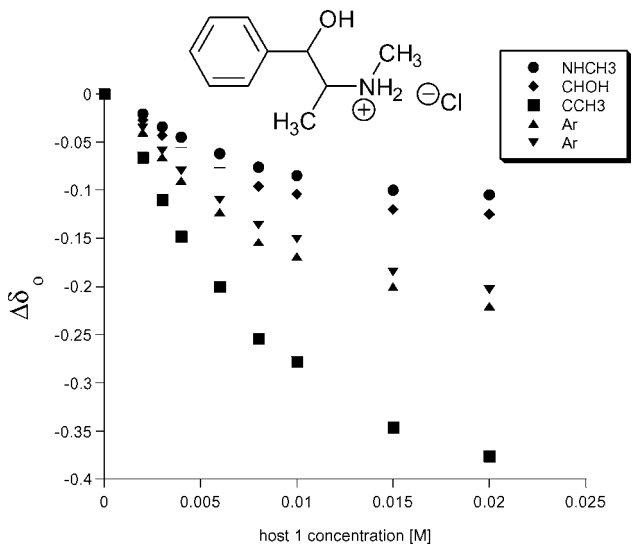


FIGURE 3 Plots of $\Delta\delta_{obs}$ (ppm) versus host **1** concentration, in 200 mM phosphate buffered D_2O (pD 7.3) at 25°C. The concentration of (1*R*,2*S*)-ephedrine hydrochloride **15** was 1 mM.

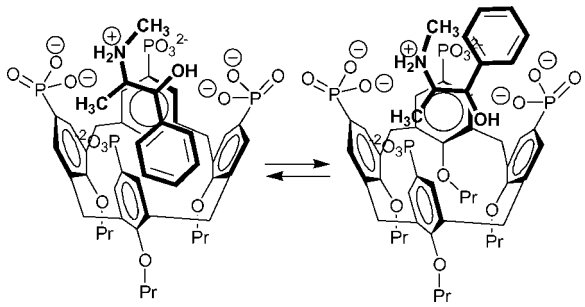


FIGURE 4 The proposed inclusion modes of (1*R*,2*S*)-ephedrine hydrochloride **15** into host **1**.

The comparison of binding ability of hosts **1** and **2** indicates that for ammonium type guest stronger interaction is observed when phosphonic acids groups are attached at upper rim of calix[4]-arene instead of lithium methyl phosphonate groups.

The examined hosts **1** and **2** were fixed in the cone conformation to form hydrophobic cavity with hydrophilic groups at the upper rim. The synthesis of more flexible and rigid structures is in progress.

We hope that some of them can show better complexation of the ammonium type guests in aqueous solution.

CONCLUSION

We have shown that derivatives of calix[4]arenes bearing phosphonic acids or lithium methyl phosphonate groups at the upper rim can be used for the study of host-guest complex formation in the water solution. The participation of the calixarene hydrophobic cavity and structural requirements for guests in the binding process were demonstrated. The preliminary results indicated the ability of these hosts **1** and **2** for formation of the complexes with ammonium type guests with K up to 145 (M^{-1}). Ongoing investigations are directed towards the design and synthesis of compounds that can interact stronger with ammonium type guests in aqueous solution.

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