Synthesis and structure of mono-bridged resorcinarene host: a ditopic receptor for ammonium guests†

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The synthesis and structural properties of tetramethoxy resorcinarene mono-crown-5 (**1**) are described. The binding characteristics of **1** toward acetylcholine and tetramethylammonium salts were investigated by ^{1}H NMR titration. It was observed that the cavity of **1** provides a better fit to acetylcholine compared to the smaller tetramethylammonium cation, as acetylcholine is able to interact with both the crown ether moiety and the free hydroxyl groups of receptor **1** simultaneously.

Introduction

The aromatic cavity of calixarenes has been found to offer an excellent model surrounding for the investigation of cation–π interactions, which are of great importance in chemical and biological systems.[1] The inclusion of quaternary ammonium cations in the cavity of calixarenes,[2] and resorcinarenes,[3] has been studied extensively over the years in the gas phase, in solution and in the solid state. The binding of acetylcholine in particular has gained a lot of interest due to its biological importance as a neurotransmitter and it has been shown, both in the liquid and in the solid state, that the cationic ammonium group of acetylcholine binds to the aromatic cavity of calixarenes through cation–π interactions.[4]

The use of ditopic receptors in ion-pair recognition has been an emerging field,[5] but it is also quite appealing to consider ditopic cavities as binding sites for biological molecules, which often possess cationic moieties as well as functional groups capable of forming hydrogen bonding interactions within the same molecule. Crown ethers and aromatic cavities have often been employed as the cation binding moieties, whereas, neutral amide, urea or thiourea functionalities have provided the hydrogen bonding sites.[5]

Our receptor design is based on a tetramethoxy resorcinarene[6] core, on which has been created additional cation binding sites by incorporation of crown ether moieties.[7] Thus, the four hydroxyl groups of tetramethoxy resorcinarene have been joined by a crown bridge, which results in two binding sites that can form cation–O and cation–π interactions with the guest through the oxygen atoms at the crown bridge and the aromatic walls of the resorcinarene core, respectively. However, depending on the reaction conditions, the mono-crown (**1**) derivative can be obtained in addition to the bis-crown (**2**) compound. Furthermore, the mono-bridged resorcinarene host has new binding properties due to the two distinctly different binding sites: crown pocket at one end and two hydroxyl groups at the other end of the resorcinarene cavity (Scheme 1).

Results and discussion

Synthesis

The bridging of tetramethoxy resorcinarene is accomplished by a nucleophilic substitution reaction with tetra(ethylene glycol) ditosylate in the presence of anhydrous Cs_2CO_3 base in DMF, as reported previously.[7] However, subsequent studies revealed that

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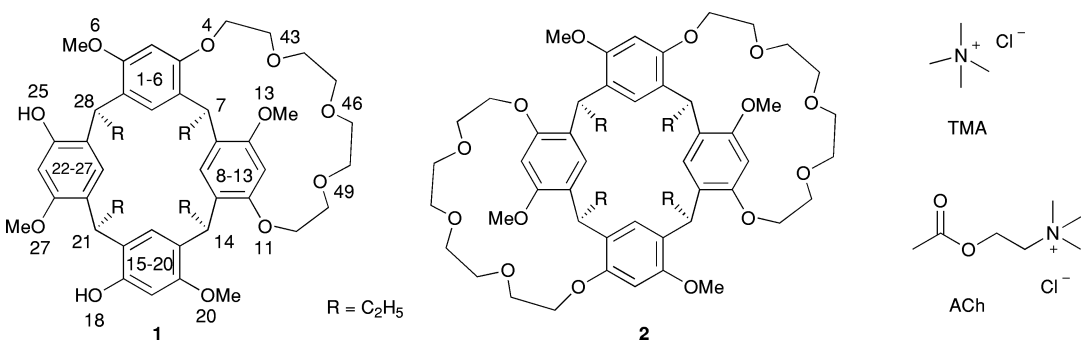
† Electronic supplementary information (ESI) available: Additional crystallographic details, titration data and NMR spectra of **1**. Crystallographic data in CIF format. CCDC reference numbers 735046–735048. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b911389d



Scheme 1 Structures of resorcinarene hosts **1** and **2**, and quaternary ammonium guests acetylcholine (ACh) and tetramethylammonium (TMA) cation. Crystallographic numbering for **1** is shown.

Table 1 Reaction conditions for the bridging reaction[a]

Entry	Deprotonation (min)	Reaction time (days)	Yield (%) 1	2
1	15	2	–	31
2	60	1	13	10
3	60	2	–	9
4	60[b]	1	–	18
5	30[b]	2	–	27

[a] The reactions were performed in anhydrous DMF under a N_2 atmosphere at 90 °C. Amounts of 4–8 equivalents of anhydrous Cs_2CO_3 and 1–2 equivalents of tetra(ethylene glycol) ditosylate were used. [b] With PTC (dibenzo-18-crown-6).

there are a few factors that affect the formation of mono-crown-5 (**1**) species in addition to the bis-crown-5 (**2**) derivative. The key step in the reaction seems to be the formation of a deprotonated resorcinarene nucleophile before the introduction of the crown reagent to the reaction, which then leads to either mono- or bis-bridged products (Table 1). If the parent resorcinarene is allowed to react with the Cs_2CO_3 base for 15 minutes before introducing the bridging reagent, only bis-crowned product is obtained (entry 1). If, on the other hand, the base is allowed to react with the parent resorcinarene alone for 60 minutes, both mono- and bis-crown products emerge (entry 2). The reason for this is proposed to be the role of the bridging reagent in the early stage of the reaction since it can act as a phase transfer catalyst (PTC), and as such, favor the complete deprotonation of the parent resorcinarene, and therefore, the formation of the bis-crown derivative. In fact, when a known PTC, dibenzo-18-crown-6, was added to the reaction mixture at the deprotonation step, only bis-crown products were obtained (entries 4–5). In addition, a longer reaction time (entry 3) will eventually lead to the formation of the bis-crown derivative, even when the optimal deprotonation conditions for the formation of the mono-crown species have been used, which also infers that the bridging reaction is quite slow. It was also noted that the amount of the bridging reagent (1–2 equivalents) or Cs_2CO_3 base (4–8 equivalents) had no substantial effect on the formation of the mono-crown product.

Structural properties

As the crown bridge is formed over adjacent aromatic rings of the resorcinarene core, the hydrogen bonding network on the upper rim is broken and the resorcinarene skeleton adopts a lower symmetry boat conformation instead of the existing crown conformation. Since **1** has no symmetry, all of the protons belonging to the resorcinarene core experience a different environment and, thus, give rise to individual resonances as seen in the ^{1}H NMR spectra of **1** (Fig. 1). Since each individual proton can be pinpointed in the spectra, the assessment of **1** as a host molecule has become more accessible in terms of identifying the binding site and interactions prevailing between the host and guest molecules.

Single crystals of **1** were grown from ethanol/water (I), methanol/chloroform (II) and acetonitrile/chloroform (III) solutions by slow evaporation. The crystals obtained are isostructural and both the left- and right-handed isomers are present in the unit cell (Table 2). In all of the structures the resorcinarene skeleton is found in a boat conformation, as expected, with an angle of 32.0° between the opposite upright aromatic rings and an angle of 152.1° between the aromatic rings in the horizontal plane (average values of the three structures). The respective opposite ring centroid distances are 5.74 and 7.91 Å (Fig. 2). The average cavity diameter[8] of the crown pocket is 6.26 Å, which is comparable to the one found previously with the respective bis-crown-5 (**2**) derivatives.[7] However, the entire cavity of **1** is more accessible, and therefore slightly bigger, compared to the bis-crown derivative due to the absence of the second crown bridge at the other end of the cavity.

Two solvent mediated hydrogen bonded pairs are formed between the left- and right-handed isomers of **1**. The first pair is formed in the vertical direction between two opposite facing

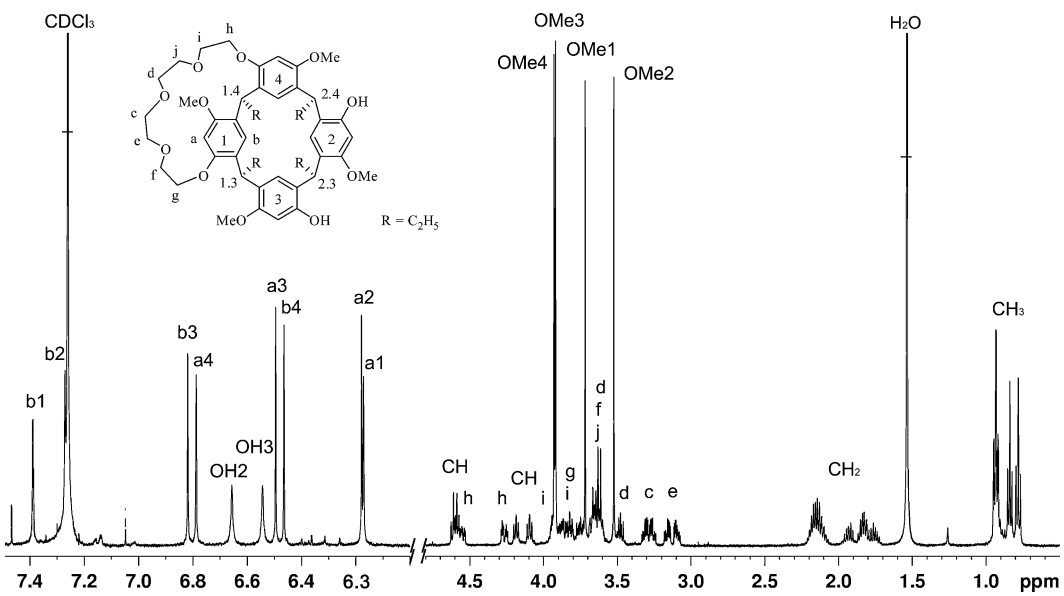


Fig. 1 ^{1}H NMR spectra of **1** in $CDCl_3$ at 30 °C with NMR assignments shown.

Table 2 Summary of crystallographic data

Structure	I	II	III
Composition	$C_{48}H_{62}O_{11}\cdot 2\ H_2O$	$C_{40}H_{62}O_{11}\cdot 2\ CH_3OH$	$C_{48}H_{62}O_{11}\cdot 4\ CH_3CN$
Formula weight	851.01	879.06	979.19
Crystal system	Triclinic	Triclinic	Triclinic
Space group	P-1	P-1	P-1
a/Å	10.7736(3)	10.8389(1)	10.8272(4)
b/Å	14.6309(4)	14.9945(1)	16.3070(5)
c/Å	16.0249(6)	16.0372(1)	17.0285(8)
α/°	68.959(1)	74.018(1)	72.658(2)
β/°	72.573(2)	70.853(1)	81.115(2)
γ/°	83.647(2)	86.719(1)	70.302(3)
V/Å^3	2249.3(1)	2365.50(3)	2697.1(2)
Z	2	2	2
Reflections	11384	12088	14021
Unique reflections	7760 [R(int) = 0.049]	8224 [R(int) = 0.033]	9311 [R(int) = 0.044]
Final R indices [$I>2\sigma(I)$], $R1$, w$R2$	0.0619, 0.1662	0.0461, 0.1197	0.0643, 0.1614
R indices (all data), $R1$, w$R2$	0.0845, 0.1856	0.0553, 0.1273	0.0924, 0.1804
CCDC deposition number	735046	735047	735048

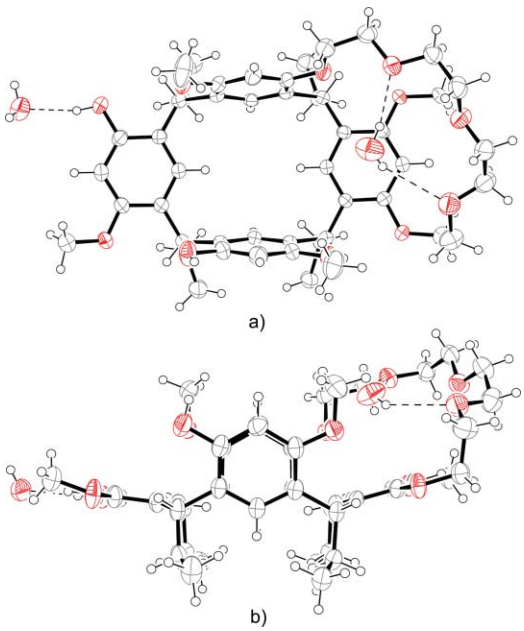


Fig. 2 Ortep plots (45% probability level) of structure I of **1**; a) top and b) front views. Structures II and III are isostructural with different coordinating solvent molecules, methanol and acetonitrile, respectively. Hydrogen bonds are shown by the dotted lines.

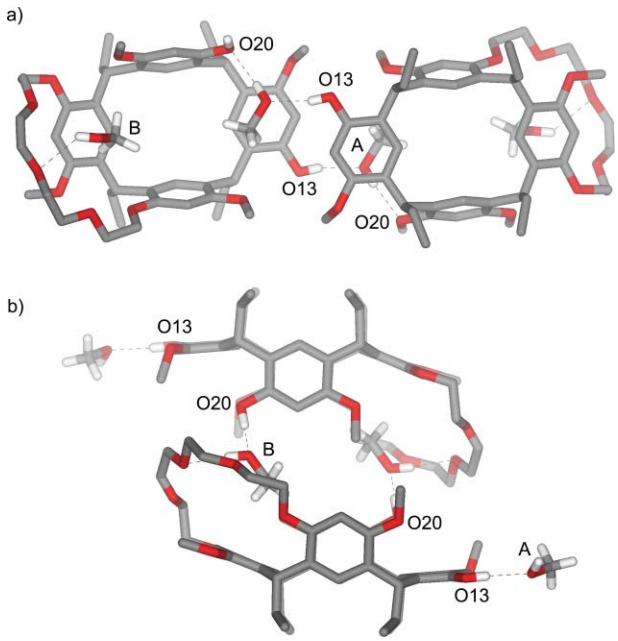


Fig. 3 a) The horizontal (top view) and b) the vertical (front view) pairs formed by solvent mediated hydrogen bonds between the left- and right-handed isomers of **1** (structure II). Non-hydrogen bonding hydrogen atoms of the parent resorcinarene molecule have been omitted for clarity. Dashed lines indicate hydrogen bonds.

resorcinarene molecules, which are connected to one another through two solvent mediated hydrogen bonds between the hydroxyl groups of the upright and horizontal aromatic rings of the neighboring molecules (O20 $\cdots$ solvent A $\cdots$ O13, 2.74–3.30 Å; Fig. 3a). The second pair forms in the vertical direction through a hydrogen bond formed between a second solvent molecule in the crown pocket and the hydroxyl group of the upright aromatic ring of the opposite facing resorcinarene molecule (solvent B $\cdots$ O20, 2.66–2.83 Å; Fig. 3b).

The difference between the structures I–III lies in the solvent molecules (water, methanol and acetonitrile, respectively) included in the crystal lattice and in the dimensions between the resorcinarene molecules due to the different size of the coordinating solvent molecules (Fig. 4). The distance between the planes formed by the methine bridges (C7–C14–C21–C28) of the two resorcinarene molecules in the horizontal pair increases with increasing size of the coordinating solvent molecule: 4.03, 4.69 and 7.34 Å (structures I, II and III, respectively). Furthermore, depending on the size of the coordinating solvent molecule, the resorcinarene molecules are either pulled closer or away from one another, which can be indicated by the contact angle‡ (ϕ) between

‡ The contact angle is determined as the angle between horizontal aromatic rings of the facing neighboring resorcinarene molecules: C9A-C12A-C12B or C9A-C12A-C13B.

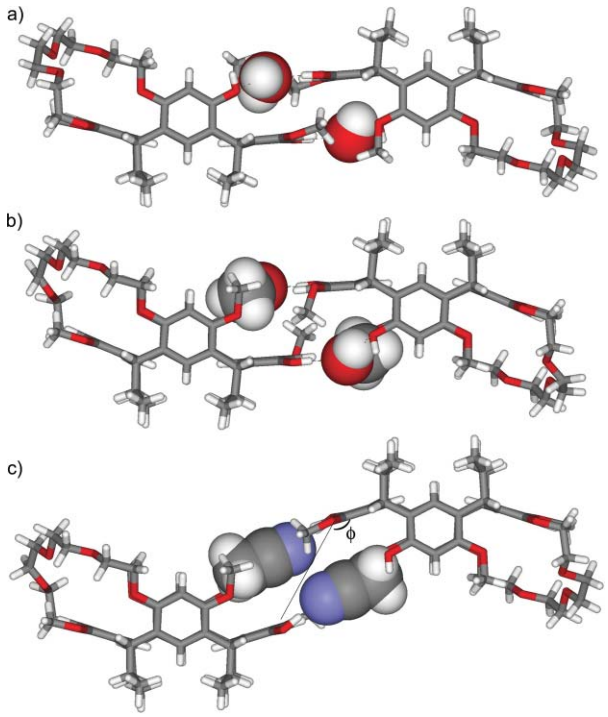


Fig. 4 The varying dimensionality of the structures a) I, b) II and c) III induced by the coordinating solvent molecules (shown as VDW model). The contact angle (ϕ) between two resorcinarene molecules in a horizontal pair is shown for structure III.

the two resorcinarene molecules, and the angles are 125.7°, 119.5° and 135.5° for structures I, II and III, respectively. Thus, the crystal packing of **1** changes depending on the different size of the guest molecule included in the cavity, although, the binding motif remains the same.

Binding studies

The binding abilities of **1** toward alkali metal cations were investigated by a picrate extraction experiment. No extraction of alkali metal picrates was observed by **1**, however, which was quite surprising since our previous studies had shown the analagous bis-crown derivative **2** to extract K^+, Rb^+ and Cs^+ cations.[7] One reason for this disparity could be the wider cavity of **1** compared to the cavity of **2** as was noted in the crystal structure analysis. Not defeated by this result, we started to consider the ditopic nature of **1**, which in addition to the crown binding site would be able to offer hydrogen bonding interactions as well. This prompted us to investigate acetylcholine (ACh) as a suitable guest, which has both a cationic choline moiety to interact with the crown pocket and an acetate group capable of forming hydrogen bonding interactions with the hydroxyl groups.

The binding of acetylcholine to **1** was investigated by a ^{1}H NMR titration technique in $CDCl_3$. The addition of acetylcholine, as a chloride salt, induced considerable changes in the ^{1}H NMR spectrum of **1** even at small guest concentration (Fig. 5). The resonances belonging to the aromatic H_a and methoxy protons in the crown pocket and the protons in the crown bridge were affected the most, as well as the two hydroxyl protons, which would broaden and finally disappear in the course of the titration experiment.

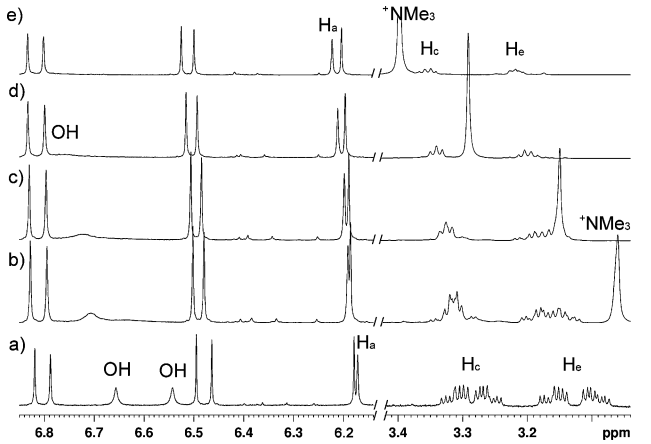


Fig. 5 ^{1}H NMR spectra of **1** with increasing amounts of ACh in $CDCl_3$ at 30 °C. a) Free **1** and b) 0.3, c) 0.5, d) 1 and e) 2 equivalents of ACh (added as chloride salt).

The H_c and H_e protons of the crown bridge could easily be monitored as there were no other overlapping resonances. With an increasing amount of acetylcholine added, the resonances of the H_c and H_e protons became simpler, which is an indication that the crown bridge loses some of its flexibility upon guest binding. In addition, the *N*-methyl protons of acetylcholine had a maximum upfield shift of 0.38 ppm from the corresponding signal of the free acetylcholine, yet, the methyl protons of the acetate group had barely been affected. These observations suggest that the methyl ammonium group of acetylcholine interacts with the crown ether oxygens and the aromatic walls of the crown pocket of **1**, while the acetate part points to the hydroxyl groups at the other end of the cavity.

The binding stoichiometry was determined by modified Job plot analysis,[9] which gave a maximum corresponding to 1:1 host–guest complex formation. EQNMR[10] analysis of the titration data provided the stability constant of 150 M^{-1} §, which is 10–10^3 orders smaller compared to the values found with acetylcholine complexes of resorcinarenes,[4d] pyrogallarenes[4a] or deep-cavitands.[4e,f] This is probably due to the aromatic ring current effect induced by the four aromatic rings of the resorcinarene cavity in the crown conformation, which was found to be one of the key interactions of the bound acetylcholine in these complexes.[4] In receptor **1**, however, the aromatic ring current effect is not as pronounced due to the boat conformation of the resorcinarene skeleton, which results in weaker binding.

As a reference, the binding of **1** was also investigated with a smaller tetramethylammonium (TMA) cation. Due to the low solubility of TMA chloride in $CDCl_3$, the ^{1}H NMR titration experiment was conducted in a 1:1 mixture of $CDCl_3$–CD_3OD. However, a 1:1 mixture of **1** with TMA chloride in $CDCl_3$ could be made (saturated with the salt), which enabled a direct comparison, with respect to acetylcholine, of the changes induced in the ^{1}H NMR spectrum of **1** by TMA cations upon binding (Fig. 6). In fact, the changes in the chemical shifts observed for **1** belonged to the aromatic and methoxy protons in the crown pocket and to the crown ether protons, although the changes

§ Error was <10% for both of the determined binding constants of **1**.

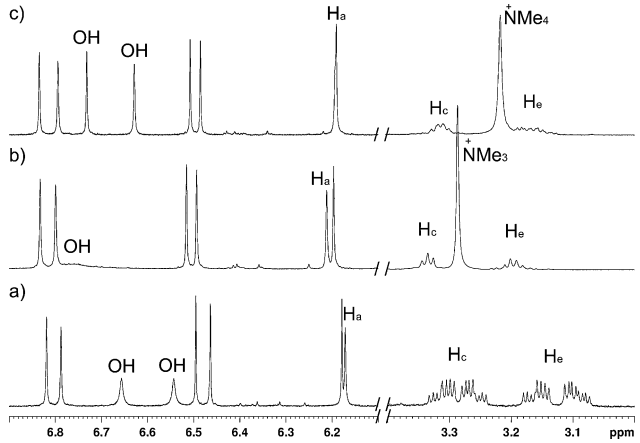


Fig. 6 ^{1}H NMR spectra of a) **1**, and 1:1 complexes of **1** with b) ACh and c) TMA (as chloride salts) in $CDCl_3$.

were more subtle compared to the changes with acetylcholine. Furthermore, the *N*-methyl protons of TMA had a similar upfield shift of 0.33 ppm, which indicated that the TMA cation was bound to the receptor **1** in a similar fashion. The hydroxyl groups, on the other hand, behaved quite differently compared to the spectra with acetylcholine, and although there was a considerable downfield shift of 0.081 ppm, the resonances remained sharp and did not disappear into the baseline. This might be an indication of the counter anion forming hydrogen bonding interactions with the hydroxyl groups at the opposite end of the cavity.[2a] The titration data was fitted to a 1:1 binding model by EQNMR[10] analysis, which gave a binding constant of 30 M^{-1}§. Based on these results the cavity of **1** seems slightly too big for the spherical TMA cation alone but offers a better fit for the elongated acetylcholine molecule with two distinctly different binding sites at either end of the cavity to offer hydrogen bonding interactions with the acetate group, and, cation–O and cation–π interactions with the quaternary trimethylammonium group of acetylcholine, which is illustrated in Fig. 7 (Spartan ST 2004). Unfortunately, all attempts to obtain good quality crystals for crystal structure analysis have so far failed.

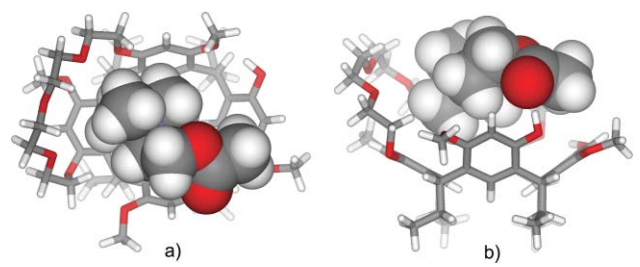


Fig. 7 A schematic drawing of the complex of **1** with ACh cation; a) top and b) front views. (Spartan ST 2004).

In the case of the smaller TMA cation, the cavity of **1** could function as a ditopic binding site for the ion-pair, with the anion binding site on the hydroxyl group end of the cavity. This however, would require more investigations on the nature of the possible counter anions and their effect on the binding, which is not in the scope of this study.

Conclusions and outlook

In conclusion, the synthesis and structural properties of a mono-bridged resorcinarene host **1** are reported. Depending on the reaction conditions used, the bridging reaction of the parent resorcinarene can also produce mono-crown species in addition to the bis-crown products, which gives rise to a ditopic receptor molecule with two distinctly different binding sites. The dual nature of the cavity formed between the crown bridge at the one end and the two hydroxyl groups at the other offers an optimal fit for acetylcholine as a guest molecule: the quaternary trimethylammonium group interacts with the crown moiety through cation–O and cation–π interactions, whereas, hydrogen bonding interactions prevail between the acetate group and the hydroxyl part of the cavity.

In light of the results obtained, the ditopic cavity of **1** makes it a potential receptor for biological molecules with various functionalities by means of providing multiple binding sites, and therefore, selectivity induced by complementarity. In our future studies we plan to improve and investigate the selectivity and binding properties of receptor **1** toward acetylcholine related guest molecules in more detail.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX 500 spectrometer and chemical shifts were calibrated to the residual proton and carbon resonance of the solvent. ESI mass spectra were measured with a Micromass LCT ESI-TOF instrument. Elemental analyses were determined with a Vario EL III instrument. Melting points were measured in open capillaries with a Stuart Scientific SMP3 melting point apparatus and are uncorrected. Tetramethoxy resorcinarene[6] and tetra(ethylene glycol) ditosylate[11] were prepared according to literature procedures. All other reagents used were commercial unless otherwise noted. DMF was distilled over 4 Å molecular sieves prior to use and stored under a N_2 atmosphere.

Preparation of mono-bridged resorcinarene 1

A mixture of tetramethoxy resorcinarene (1.03 g, 1.57 mmol) and anhydrous Cs_2CO_3 (4.14 g, 12.7 mmol) was suspended in dry DMF (50 mL) under a N_2 atmosphere and the reaction mixture was stirred vigorously at 90 °C for 60 minutes before the dropwise addition of tetra(ethylene glycol) ditosylate (0.86 g, 1.82 mmol) in DMF (10 mL). The brown reaction mixture was allowed to stir at 90 °C for 1 day. After cooling to room temperature the reaction mixture was filtered by suction through a pad of Hyflo Super® and solvent was removed under vacuum. The residue was dissolved in chloroform and washed two times with brine, dried over $MgSO_4$ and evaporated to dryness under vacuum. Purification was done in two steps by flash chromatography using neutral alumina and chloroform as the eluent in the first purification. The second purification was done on silica using isocratic acetone–chloroform (2:8) mixture as the eluent. Recrystallization from methanol afforded the product (0.17 g, 13%) as a white crystalline solid; mp 124-126 °C; δ_H ($CDCl_3$, 500 MHz) 7.39 (s, 1H; 1/H_b), 7.27 (s, 1H; 2/H_b), 6.82 (s, 1H; 3/H_b), 6.79 (s, 1H; 4/H_a), 6.66 (s, 1H; 2/O*H*), 6.55 (s, 1H; 3/O*H*), 6.50 (s, 1H; 3/H_a), 6.46 (s, 1H; 4/H_b), 6.18 (s, 1H; 2/H_a), 6.17 (s, 1H; 1/H_a), 4.62–4.53

(overlapping t's and m, 3H; 2.4/C*H*, 1.4/C*H* and H_h), 4.28–4.25 (m, 1H, H_h), 4.19 (t, $J = 6.9$ Hz, 1H; 2.3/C*H*), 4.10 (t, $J = 6.9$ Hz, 1H; 1.3/C*H*), 3.95–3.93 (overlapping m and s, 4H; H_i and 4/OCH_3), 3.92 (s, 3H; 3/OCH_3), 3.90–3.86 (m, 1H; H_g), 3.82 (m, 1H; H_i), 3.76 (m, 1H; H_g), 3.72 (s, 3H; 1/OCH_3), 3.68–3.59 (m, 5H; H_j, H_f and H_d), 3.52 (s, 3H; 2/OCH_3), 3.48 (m, 1H; H_d), 3.33–3.24 (m, 2H; H_c), 3.18–3.07 (m, 2H; H_e), 2.21–2.07 (m, 4H; CH_2), 1.96–1.72 (m, 4H; CH_2), 0.93 (td, $J = 1.0$ and $J = 6.1$ Hz, 6H; 1, 2/CH_3), 0.83 (t, $J = 7.2$, 3H; 1/CH_3), 0.78 (t, $J = 7.3$, 3H; 2/CH_3); δ_C ($CDCl_3$, 500 MHz) 156.7 (2/Ar*C*), 155.6 (1/Ar*C*), 155.0 (4/Ar*C*), 154.7 (4/Ar*C*), 154.4 (1/Ar*C*), 153.3 (3/Ar*C*), 152.9 (2/Ar*C*), 152.1 (3/Ar*C*), 127.03 (4/Ar*C*), 126.97 (4/Ar*C*), 126.5 (3/C_b), 125.8 (3/Ar*C*), 125.5 (1/Ar*C*), 125.4 (4/C_b), 125.1 (3/Ar*C*), 124.19 (1/C_b), 124.17 (2/C_b), 124.1 (2/Ar*C*), 123.5 (1/Ar*C*), 121.3 (2/Ar*C*), 100.1 (3/C_a), 99.1 (2/C_a), 97.8 (4/C_a), 96.5 (1/C_a), 71.7 (C_i), 71.4 (C_j), 70.6 (C_c), 70.4 (C_d), 70.3 (C_e), 69.3 (C_f), 68.9 (C_g), 68.5 (C_h), 56.0 (3/O*C*H$_3$), 55.63 (1/O*C*H$_3$), 55.57 (4/O*C*H$_3$), 55.4 (2/O*C*H$_3$), 36.1 (1.3/*C*H), 35.3 (1.4/*C*H), 35.14 (2.3/*C*H), 35.12 (2.4/*C*H), 30.3 (2.4/*C*H$_2$), 29.5 (1.4/*C*H$_2$), 27.1 (1.3/*C*H$_2$), 27.0 (2.3/*C*H$_2$), 12.43 (*C*H$_3$), 12.40 (*C*H$_3$), 12.2 (*C*H$_3$); MS (ESI-TOF): *m/z* 853.42 (M + K^+, 100%), required 853.39; Anal. Found: C, 66.98; H, 7.48. Calcd for $C_{48}H_{62}O_{11}\cdot 2.5H_2O$: C, 67.03; H, 7.85.

Picrate extraction experiments

The alkali metal (Na^+, K^+, Rb^+ and Cs^+) picrate extraction experiments were performed by using 2.5 mM solutions of **1** in chloroform and picrate salts in deionized water according to the procedure described earlier.[7a] The absorption of the extracted picrate was measured from the aqueous layer at 375 nm and compared against a blank solution (no host in chloroform) of the appropriate picrate salt. Three separate measurements were made.

NMR titration experiments

^{1}H NMR titrations were performed by adding subsequently increasing aliquots of the salt (AChCl or TMACl) in deuterated solvent into the solution of **1** ($CDCl_3$ and 1:1 $CDCl_3$–CD_3OD, respectively) and recording the spectra after each addition at 30 °C. The titration data was analyzed by the computer program EQNMR.[10] Job plot samples were prepared with 0.3, 0.5, 1, 2 and 3 equivalents of the salt while keeping the sum of **1** and guest concentration equal.

X-Ray crystallography

Data were recorded on a Nonius Kappa CCD diffractometer with Apex II detector using graphite monochromatized CuK_α [$\lambda(CuK_\alpha) = 1.54178$ Å] radiation at a temperature of 173.0 K. The data were processed with Denzo-SMN v0.97.638.[12] The structures were solved by direct methods (SHELXS-97[13]) and refinements based on F^2 were made by full-matrix least-squares techniques (SHELXL-97[14]). The hydrogen atoms were calculated to their idealized positions with isotropic temperature factors (1.2 or 1.5 times the C temperature factor) and refined as riding atoms except for the water and hydroxyl hydrogens, which were located from the difference Fourier map. Absorption correction[15] was made to all structures. Mercury,[16] ViewerLite[17] and Ortep[18] were used to prepare the figures. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication nos. CCDC 735046–735048.† Copies of the data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif.

In structure I, DFIX was used to restrain the –OH bond distances (0.84 Å) and DANG was used to restrain the HOH bond angle of the two water molecules closer to the ideal 105°. In structure II, the crown bridge –C47-**C48**-**O49**-C50– and solvent methanol were disordered (same FVAR) over two positions with site occupancy of 0.80:0.20. The bond distances were restrained to be equal (SADI). The temperature factor of the disordered methanol oxygen, O20B, was fixed (EADP) with the anisotropic displacement parameter of its counter part and DFIX was used to restrain the–OH bond distance (0.84). In structure III, one crown bridge oxygen atom, –C48-**O49**-C50–, was disordered over two positions with site occupancy of 0.76:0.24. The bond distances were restrained to be equal (SADI) and the temperature factors were fixed (EADP) with the anisotropic displacement parameter of O46.

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