Molecular recognition involving multiple cation–π interactions: the inclusion of the acetylcholine trimethylammonium moiety in resorcin[4]arene

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X-Ray analysis of the molecular complex formed between the neurotransmitter acetylcholine (ACh) and resorcin[4]-arene, ACh^+.resorcinarene.Cl^-.H_2O shows that the ACh molecule is captured by the macrocyclic resorcinol tetramer through multiple cation–π interactions between the quaternary trimethylammonium group of ACh and the four π-rings of the cavitand.

The cation–π interaction has attracted much attention because of its chemical,[1–3] biological[1] and theoretical[4] applications. It has been well documented that synthetic macrocyclic compounds comprised of aromatic rings exhibit a strong affinity for quaternary ammonium compounds including the neurotransmitter acetylcholine (ACh).[1a] Particular interest focuses on the origin of the strong molecular association: it has been proposed[1a] that the cationic ammonium group could bind to the π-faces of aromatic rings of its receptor through a cation–π interaction. Although a recent statistical analysis,[5] based on crystal structures from the Cambridge Structural Database, of the interactions between $R–N^+Me_3$ cations and phenyl rings demonstrates their preferable occurrence, X-ray evidence for such a cation–π interaction is still lacking† for artificial macrocyclic receptor systems,[1–3,6] involving synthetic ACh receptors.[1a,7] As the continuation of our X-ray investigations on the cation–π interaction,[8] we report here the crystal structure of the molecular complex formed between macrocyclic resorcin[4]arene **1**‡ and ACh, where the quaternary trimethylammonium group of ACh makes close contacts with the four π-rings of **1**. ^{1}H NMR spectroscopy confirms that the cation–π interaction also occurs in solution. The biological relevance of the multiple cation–π interactions for the interaction between ACh and acetylcholine esterase (AChE) is suggested.

The ACh–resorcin[4]arene molecular complex was prepared from $ACh^+.Cl^-$ (2 mmol) and **1**§ (0.2 mmol) dissolved in ethanol (5 ml)–water (3 ml). The mixture (pH 6) was allowed to stand at room temperature for three weeks after which colourless crystals (plates) formed.¶ 3,3-Dimethylbutyl acetate **2** was synthesized in 83% yield from acetyl chloride (50 mmol) and 3,3-dimethylbutan-1-ol (6 ml, 50 mmol).

Fig. 1 shows the molecular structure of the complex, ACh^+.**1**.Cl^-.H_2O, where **1** is neutral. The most interesting structural feature is the host–guest complexation between **1** and ACh through cation–π interactions, that is, between the quaternary trimethylammonium group of ACh and the multiple π-rings system of the macrocyclic resorcinol tetramer. The choline group makes close contacts through its two methyl groups with the four rings of the bowl-shaped cavitand. To our knowledge, this is the first crystal structure in which ACh shows the cation–π interaction between the trimethylammonium group and the π-electrons of the aromatic ring. The ACh molecule adopts a *gauche* conformation about the choline group due to an $N^+\cdots O$ electrostatic interaction [the torsion angle O(10)–C(39)–C(40)–N(1) = −77(5)°], usually observed[9] for the O–C–C–N^+ system, and *trans* about the C(38)–O(10) bond [C(37)–C(38)–O(10)–C(39) = −173(2)°]. Furthermore, in the crystal lattice this ACh is capped on its acetyl terminal group by the adjacent resorcinarene molecule (at $3/2 - x$, $1/2 + y$, $1/2 - z$), as shown in Fig. 2. Thus an ACh molecule is captured by two resorcinarene molecules in a head-to-tail arrangement. Interestingly, the polar carboxy oxygen O(9), rather than the apolar methyl group C(37), contacts with the aliphatic ethyl groups tethered to the tail of the cavitand [3.83(3) Å to C(29), 3.80(3) Å to C(31), 3.78(3) Å to C(33) and 3.68(3) Å to C(35)]. The chloride anion forms four hydrogen bonds with the hydroxy oxygen atoms O(1) [Cl···O(1) 3.04(1) Å], O(2) [3.12(1) Å] and O(7) [2.99(2) Å], each oxygen belonging to a different molecule, and a water oxygen atom O(11) [3.24(2) Å], but it does not contact with the cationic choline group of ACh.

The ^{1}H NMR spectrum (270 MHz, CD_3OD) of the ACh–resorcinarene **1** complex (30 mmol dm^{-3}) shows a singlet at δ 2.107 for the *N*-methyl protons of ACh, while the corresponding signal of ACh alone appears at δ 3.215. This upfield shift of 1.108 ppm for the complex is probably due to the aromatic ring-current effect, indicating that the quaternary trimethylammonium group associates preferentially with the π-rings of resorcinarene in solution, where the resorcinarene molecule

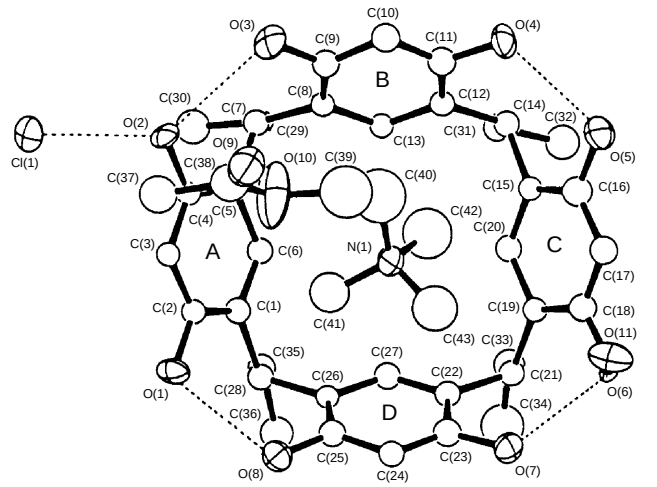
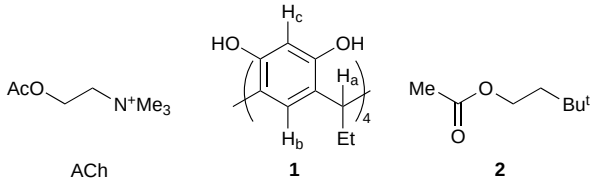


Fig. 1 Top view of the molecular structure of ACh^+.**1**.Cl^-.H_2O, showing the host–guest complexation between a cyclic resorcinol tetramer and an ACh molecule through cation–π multiple interactions; close contacts (< 3.6 Å): C(41)···C(2) [3.51(4)], C(41)···C(25) [3.56(4)], C(42)···C(12) [3.57(5)], C(42)···C(15) [3.43(5)], C(42)···C(16) [3.54(5)] and C(42)···C(20) [3.48(5) Å]; relevant methyl C···π-centroid distances: C(41)···ring A [3.60], C(41)···ring D [3.87], C(42)···ring B [3.64] and C(42)···ring C [3.36 Å]; relevant methyl C···ring–plane perpendicular distances: C(41)···ring A [3.48], C(41)···ring D [3.59], C(42)···ring B [3.52] and C(42)···ring C [3.31 Å]. Broken lines denote hydrogen bonds.



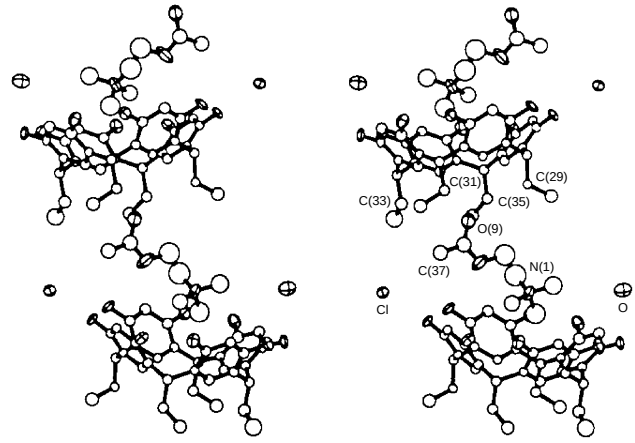


Fig. 2 Stereoview of a segment of the crystal structure of ACh^+.**1**.Cl^-.H_2O, showing the encapsulation of an ACh molecule between two resorcinarene molecules and close C–H···O contacts between the carboxyl oxygen of ACh and four CH_2 moieties tethered to the lower rim of the cavitand

retains the bowl-shaped conformation.‖ In addition, the ^1H NMR spectrum (270 MHz, CD_3OD) of the solution containing ACh (30 mmol dm^{-3}) and resorcinol monomer as noncyclic reference compound in a 1 : 4 molar ratio does not show an appreciable upfield shift of the *N*-methyl protons (δ 3.195) of ACh, showing the importance of the defined structure of **1** in its effective association with ACh, where the preorganized cavity of **1** makes cation–π multiple interactions possible and stabilizes them.

In order to examine more closely the significance of the quaternary trimethylammonium group in the cation–π interaction, a comparative study was undertaken using 3,3-dimethylbutyl acetate **2**, an uncharged compound isosteric to ACh, where the trimethylammonium nitrogen of ACh is replaced with a carbon atom. The ^1H NMR spectrum (270 MHz, CD_3OD) of the solution containing acetate **2** and resorcinarene **1** (30 mmol dm^{-3}; equimolar ratio) and that of **2** alone show only a small upfield shift of 0.052 ppm for the *tert*-butyl protons of **2** in the mixture (δ 0.895 and 0.947, respectively). This indicates that the intensity of interaction between the terminal *tert*-butyl group of **2** and the π-rings of **1** may be minor. Thus it appears again[1a,8] that the cationic nature of the quaternary choline group could be responsible for its preferable association with the π-ring, that is, through cation–π interaction.

In summary, (i) the ACh molecule contacts simultaneously with more than one aromatic ring through multiple cation–π interactions, thus mimicking the ACh binding to AChE. A recent X-ray study[10] has revealed that a total of 14 aromatic residues line the 'active site gorge' of AChE. A biological role of the multiple cation–π interactions might be that simultaneous contacts could promote the gain of total energy for molecular associations which are needed for rapid transport of ACh through the gorge ('aromatic guidance'[10]) and also for the ACh-fixing at the bottom of the gorge. In this regard, the trimethylammonium moiety of ACh, where one positive formal-charge is smeared out over the three methyl groups,[1a] seems to be an excellent device to achieve cation–π multiple interactions. (ii) This study clearly demonstrates that the aromatic system interacts strongly with the cationic choline moiety in preference to the neutral *tert*-butyl group. In order to provide further insights into the significance of the trimethylammonium group of ACh in the cation–π interaction, X-ray and solution studies, by exchanging the N^+Me_3 group with $N^+H_nMe_{3-n}$ (n = 1–3), are under way.

Footnotes

† There have been reported, to our knowledge, two crystal structures[3,11] of host–guest complexes between synthetic macrocycles of aromatic rings and quaternary ammonium compounds: however, in $4Na^+$.(trimethylanilinium$^+$).(*p*-sulfonatocalix[4]arene^{4-}).Cl^-;[3] the trimethylammonium group is located out of the cavity of the host, and in $(Et_3HN^+)_2$.(tetramethylresorcin[4]arene).SO_4^{2-}.4EtOH,[11] no mention is made on the cation–π interaction.

‡ 2,8,14,20-Tetraethyl-4,6,10,12,16,18,22,24-octahydroxycalix[4]arene.

§ Compound **1** was synthesized according to a literature procedure.[12]

¶ *Crystal data* for: ACh^+.**1**.Cl^-.H_2O.$C_{43}H_{58}ClNO_{11}$. M = 800.38, colourless plates, monoclinic, space group $P2_1/n$, a = 12.450(9), b = 21.598(7), c = 15.717(7) Å, β = 95.15(5)°, U = 4209(3) Å^3, Z = 4, D_m = 1.265 (measured by flotation in hexane–carbon tetrachloride), D_c = 1.263 g cm^{-3}, μ(Mo-Kα) = 1.50 cm^{-1}, T = 293 K, F(000) = 1712. A Rigaku AFC7R diffractometer with graphite-monochromated Mo-Kα (λ = 0.71069 Å) was used to collect 5847 unique data in the range $4 < 2\theta < 50°$, 1728 data with $I > 3\sigma(I)$ were used in the refinement. The diffraction pattern was in general quite weak and did not extend much beyond 2θ = 40°, mostly due to the small crystal size (0.08 × 0.30 × 0.30 mm) and some disorder of ACh molecules (as noted below). Residuals of R = 0.110 and R_w = 0.117 were obtained after 295 parameters had refined to convergence (TEXSAN), where only Cl, O and N atoms were treated anisotropically while all C atoms isotropically because of limited number of reflection data. The quality-of-fit index is 1.53, and the largest shift/esd = 0.18. High vibrational amplitudes [10–16 Å^2] for C(34), O(10), C(37), C(40), C(42) and C(43) of ACh might be due to disorder, that is, these atoms most likely occupy slightly different positions from molecule to molecule (attempts to find alternative chain conformations failed), causing the rather high R values. No attempt to locate the H atoms was made. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/317.

‖ In solution, resorcin[4]arene exists as mixtures of bowl-shaped (crown), saddle, boat and chair conformers.[13] In the ACh-1 system, the equivalency in the NMR spectra of four Ha protons (t, δ_H 4.175–4.233), four Hb (s, δ_H 6.248), and four Hc (s, δ_H 7.262) of **1** indicates that **1** has a symmetric macrocyclic skelton, suggesting **1** to have a bowl-shaped conformation.

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