Multiple Cation-π Interactions between the Trimethylammonium Moiety and the Aromatic Rings within a Molecular Complex Formed between 3-Phenylpropionic Acid Choline Ester and Resorcin[4]arene

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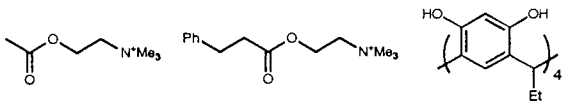
X-ray analysis of the molecular complex formed between 3-phenylpropionic acid choline ester (**1**) and tetraethylresorcin[4]-arene (**2**) has shown that the choline ester **1** is captured by the bowl-shaped **2** through multiple cation–π interactions between the quaternary trimethylammonium group of **1** and the aromatic rings of **2** and that **1** itself forms a folded structure to make close contacts between its trimethylammonium moiety and the phenyl ring through cation-π interactions.

There has been increasing interest in cation–π interaction between cations and the π-face of an aromatic ring because of its chemical and biological significance.[1] It has been well documented[1a,2-5] that synthetic macrocyclic compounds comprised of aromatic rings exhibit a strong affinity for quaternary ammonium compounds. However, X-ray evidence for the presence of the cation–π interaction is still limited for such artificial macrocyclic systems, involving synthetic receptors[1a,5] for the neurotransmitter acetylcholine (ACh): the only one X-ray example,[6] to our knowledge, is ACh–resorcin[4]arene molecular complex.[7-14] We report here the crystal structure of the molecular complex formed between 3-phenylpropionic acid choline ester in the form of its chloride **1** and macrocyclic tetraethylresorcin[4]arene **2**, where the quaternary trimethyl-ammonium group of **1** makes close contacts with the π-rings of **2**. The choline ester **1**, which is itself designed so as to examine whether intramolecular cation–π interactions between its head and tail terminals could occur, adopts a folded structure in which its trimethylammonium moiety is, indeed, close to its phenyl ring.



ACh **1** **2**

The choline ester **1** was synthesized by the DCC method[15] in 55% yield from 3-phenylpropionic acid (10 mmol) and choline chloride (10 mmol) in acetonitrile. The choline ester–resorcin[4]arene molecular complex was prepared from **1** (2 mmol) and **2**[16] (0.2 mmol) dissolved in ethanol (10 ml)–water (4 ml). The mixture (pH 6) was allowed to stand at room temperature to give colorless crystals (plates) after a month in the yield of 48%.[17]

Figure 1 shows the crystal structure of the molecular complex with the composition of $2(\mathbf{1}^{+}\cdot\mathbf{2})\cdot 2Cl^{-}\cdot 9H_2O$, where **2** is neutral. The most interesting structural feature of the complex is the host–guest complexation between the choline ester **1** and macrocyclic resorcinol tetramer **2**: there are two crystallographically independent **2**–**1** host-guest molecular units, I and II, whose structures are essentially equivalent. In each of the I and II units,

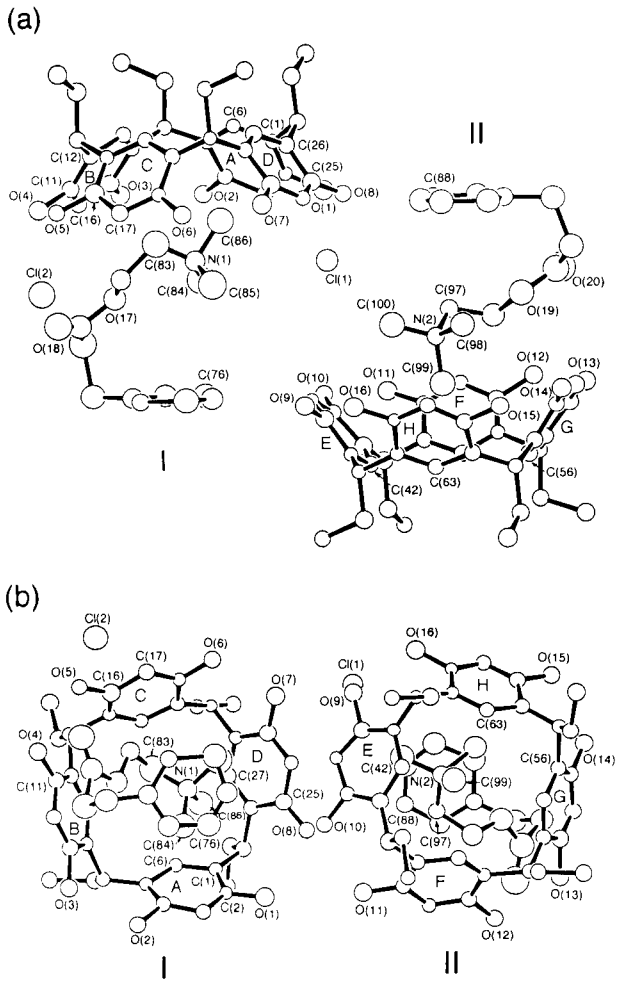


Figure 1. (a) ORTEP drawing of the molecular complex, $2(\mathbf{1}^{+}\cdot\mathbf{2})\cdot 2Cl^{-}\cdot 9H_2O$, with the numbering scheme. There are two crystallographically independent **2**-**1**$^{+}$ host–guest molecular units, I and II. Close contacts (< 3.7 Å): C(83)···C(11) 3.49(6), C(83)···C(12) 3.63(6), C(83)···C(16) 3.48(7), C(83)···C(17) 3.69(7), C(86)···C(1) 3.46(7), C(86)-C(2) 3.54(6), C(86)···C(6) 3.60(6), C(86)···C(25) 3.49(6), C(86)···C(26) 3.40(6), C(86)···C(27) 3.47(6), C(97)···C(88) 3.69(5), C(99)···C(42) 3.62(6), C(99)···C(56) 3.62(6), C(99)···C(63) 3.58(6) Å; methyl C···ring-plane perpendicular distances: C(83)···ring B 3.48, C(83)···ring C 3.47, C(86)···ring A 3.36, C(86)···ring D 3.60, C(99)···ring E 3.60, C(99)···ring F 3.77, C(99)···ring G 3.76, C(99)···ring H 3.54, C(84)···phenyl (choline ester I) 3.76, C(97)···phenyl (choline ester II) 3.67 Å. (b) Top view of the molecular complex. In (a) and (b), crystallization waters are omitted for clarity. Thermal ellipsoids scaled at 30% probability level.

the choline ester **1** makes close contacts between its quaternary trimethylammonium group and the π-rings of **2** through multiple cation–π interactions. A minor difference between the I and II

molecular units exists in the arrangement of the ammonium group of **1** in the cavity of **2**: two carbon atoms [C(83) methylene and C(86) methyl] are incorporated in I while one carbon atom [C(99) methyl] in II. Close contacts of 3.40(6)–3.69(7) Å are comparable to those of 3.43(5)–3.57(5) Å observed in the ACh-**2** complex.[6] Interestingly, the choline ester **1** itself forms the folded structure in which the phenyl ring head group is close to the quaternary trimethylammonium tail group: the closest contact of 3.76(7) Å between C(76) and C(84) for I and that of 3.69(5) Å between C(88) and C(97) for II. These values are in good agreement with 3.699(5)–3.764(4) Å between the trimethyl moiety and the indole ring observed in indole-3-acetic acid choline ester,[18] a compound analogous to **1**. The choline moiety adopts the *gauche* conformation about the C(82)–C(83) bond [torsion angle O(17)–C(82)–C(83)–N(1) = –65(5)°] for I and the C(96)–C(97) [O(19)–C(96)–C(97)–N(2) = –79(4)°] for II, due to an $N^+\cdots O$ electrostatic interaction, as usually observed[19] for the O–C–C–N^+ system. Despite the conformational rigidity in the O–C–C–N^+ chain, the occurrence of the folded structure for **1** might be quite significant because **1** could be highly flexible from the steric point of view, indicating the major importance of the cation-π interaction. Two chloride anions form hydrogen bonds with hydroxyl groups of **2** and with waters (not shown in Figure 1) but do not contact with the cationic choline group of **1**: $Cl(1)\cdots O(7)$ = 2.99(3), $Cl(2)\cdots O(5)$ = 3.04(3) Å.

The ^1H NMR spectrum (270 MHz, CD_3OD) of **1** alone (3 mmol dm^{-3}) gives a singlet at δ 3.107 for the *N*-methyl protons, while the corresponding signal for ACh appears at δ 3.215. The corresponding signal for the **1**–**2** complex (3 mmol dm^{-3}) shows a singlet at δ 2.682. This larger upfield shift for the complex is probably due to the aromatic current effect between the *N*-methyl protons and the π-rings of **2**, in addition to the ring-current effect in **1** itself. This observation indicates that the quaternary trimethylammonium group associates preferentially with the π-rings of resorcinarene also in dilute solution.

In summary, this is the second X-ray example that provides apparent evidence for the cation-π interaction between the quaternary ammonium derivative and the aromatic ring of a macrocyclic *neutral* receptor. The four-times occurrence of the cation–π interaction in the asymmetric unit of a crystal, two times within **1** itself and the other two times between **1** and **2**, indicates the preferable nature of such a cation-π interaction. Multiple cation–π interactions observed here could mimic the ACh binding to its esterase (AChE), since a total of 14 aromatic residues line the 'active site gorge' of AChE from *Torpedo california*.[20]

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7 There have been reported, to our knowledge, eight other crystal structures[3,8-14] of host-guest complexes between synthetic macrocycles comprised of aromatic rings and quaternary ammonium compounds: however, in $4Na^+.$(trimethylanilinium$^+$).(*p*-sulfonatocalix[4]arene^{4-}).-Cl^-,[3] ($H_4N^+)_6.$(*p*-sulfonatocalix[4]arene^{5-}).($MeSO_4^-$),[8] and in $(Et_3HN^+)_2.$(calix[6]arene^{2-}),[9] the trimethylammonium group,[3] ammonium[8] or triethylammonium[9] ions are located out of the cavity of the host. In $8Na^+.$(choline$^+)_2.$(*p*-sulfonatocalix[4]arene$^{5-})_2$,[10] $(Me_4N^+)_2.$(*p*-*tert*-butylcalix[6]arene^{2-}),[11] $(Me_4N^+)_5.$(*p*-sulfonatocalix[4]-arene^{5-}),[12] and in $(Et_4N^+).$(dihomooxa-*p*-*tert*-butylcalix[4]arene$^-$).-CH_3CN,[13] although the trimethylammonium group[10] of choline or the tetramethyl-[11,12] or tetraethylammonium[13] ions locate in the cavity of the macrocycle, the significance of the cation–π interaction is difficult to evaluate because the host molecules[10-13] are negatively charged. In $(Et_3HN^+)_2.$(tetramethylresorcin[4]arene).$SO_4^{2-}.3EtOH$,[14] no mention is made on the cation–π interaction.

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16 2,8,14,20-Tetraethyl-4,6,10,12,16,18,22,24-octahydroxy-calix[4]arene **2** was synthesized according to a literature procedure (Y. Aoyama, Y. Tanaka, and S. Sugahara, *J. Am. Chem. Soc.*, **111**, 5397 (1989)).

17 Crystal data: $C_{100}H_{146}O_{29}N_2Cl_2$, monoclinic, space group $P2_1/c$, a = 13.367(6), b = 19.53(1), c = 39.95(2) Å, β = 96.65(4)°, V = 10359(8) Å^3, Z = 4, D_c = 1.225 g cm^{-3}, μ (Mo Kα) = 1.38 cm^{-1}. A crystal (0.1 × 0.6 × 0.6 mm) was sealed in a glass capillary with a drop of mother liquor. The intensity data ($2\theta < 45°$) were collected on a Rigaku AFC7R diffractometer with graphite-monochromated Mo-Kα (λ = 0.71069 Å) and the structure was solved by direct methods (SAPI90). The final cycle of refinement was based on 3233 observed reflections ($I > 3\sigma(I)$) and 533 variables and converged to R = 15.8% and R_w = 17.0%, where all non-H atoms were treated isotropically because of limited number of reflection data. Both of the two independent choline esters and nine crystallization waters in the asymmetric unit are loosely packed in the crystal lattice, reflecting in their high vibrational amplitudes [9-17 Å^2], causing the rather high R values. No attempt was made to locate H atoms.

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