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Tetramethylated Resorcin[4]arene-Based Molecular Capsules Incorporating a Tetraethylammonium Ion through Cation–π Interactions

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Tetramethylated resorcin[4]arene self-assembles to form molecular capsules incorporating a tetraethylammonium ion within the cavity through cation–π interactions. Two “head-to-head” arranged substructures are staggered with each other so as to participate in methyl–hydroxy van der Waals interactions between pairing substructures. The tetraethylammonium ion is oriented in a vertical or horizontal fashion.

Acetylcholine, a neurotransmitter, could bind to acetylcholine esterase through cation–π interactions between the quaternary cationic trimethylammonium group and the π system of aromatic amino acid residues of the enzyme.[1] We[2–4] and Rissanen and co-workers[5–7] have demonstrated the occurrence of such a cation–π interaction in molecular complexes formed between resorcin[4]arenes (resorcinol cyclic tetramer: RCT; **1** where Y = Et in Chart 1) and acetylcholine,[2] a choline ester,[3] alkylammonium cations,[4–6] or diquats cations.[7] Interestingly, when small spherical cations[4–7] were used in complex formation, resorcin[4]arenes self-assembled to form molecular capsules held by water bridges,[4,5] alcohol and water-mixed[7] bridges, or alcohol and halide ion-mixed[6,7] bridges, encapsulating a cation molecule within the cavity through cation–π interactions.[4–7] In a previous report,[4] we presented a guest-driven capsule-formation mechanism in which a tetraethylammonium guest cation might lead to the formation of a “head-to-head” arranged resorcinarene dimer through cation–π interactions. We have now extended this study to the tetramethylated resorcin[4]arene (2-methylresorcinol cyclic tetramer: MRCT; **2** where Y = Et) system in order not only to further address the capsule-formation mechanism for quaternary alkylammonium ions, but also to examine whether methyl substituents on resorcinol rings might exert any effect on the molecular architecture of the capsular structure. We report here on two crystal structures of MRCT complexes with tetraethylammonium ion, where capsule formation is achieved by cation–π interactions and, in addition, by methyl–hydroxy van der Waals interactions between substructures. Two substructures are staggered with each other, and an incorporated tetraethylammonium ion is oriented in a vertical or horizontal fashion with reference to the facing plane of pairing substructures.

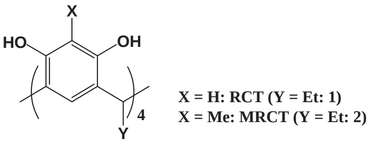

Chart 1.

MRCT complexes with tetraethylammonium ion, $\mathrm{Et_4N^+ \cdot 2(\mathbf{2}) \cdot Cl^- \cdot H_2O \cdot 2EtOH}$ and $\mathrm{Et_4N^+ \cdot (\mathbf{2} \cdot \mathbf{2}^-) \cdot 8H_2O}$, were prepared from tetraethylammonium chloride and MRCT **2** dissolved in EtOH or MeOH, respectively. The crystal structures of these compounds were determined by X-ray diffraction. Figure 1 shows the molecular structure of $\mathrm{Et_4N^+ \cdot 2(\mathbf{2}) \cdot Cl^- \cdot H_2O \cdot 2EtOH}$, where two bowl-shaped MRCT molecules form a “head-to-head” arranged MRCT dimer, incorporating a tetraethylammonium cation within the cavity through cation–π interactions, as is the case for $\mathrm{Et_4N^+ \cdot (\mathbf{1} \cdot \mathbf{1}^-) \cdot 8H_2O \cdot 2EtOH}$,[4] as expected. Half of the capsule molecule is crystallographically independent with a two-fold axis passing through both the central nitrogen atom and the terminal carbon atom C(42) of the $\mathrm{Et_4N^+}$ guest molecule. Two facing MRCT molecules are staggered with each other such that the methyl substituents, C(29) and C(30), of the MRCT rings are pincered by hydroxy

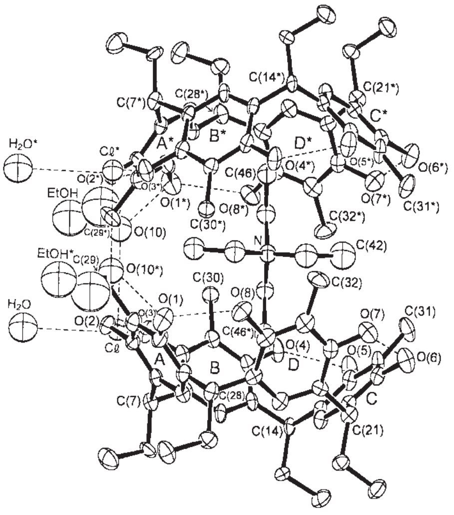

Fig. 1. Molecular structure of $\mathrm{Et_4N^+ \cdot 2(\mathbf{2}) \cdot Cl^- \cdot H_2O \cdot 2EtOH}$. $\mathrm{Et_4N^+}$ molecule is disordered over two positions related by symmetry of a two-fold axis, which passes through the N and C(42) atoms (only one orientation is shown for clarity). Atoms designated by asterisk (*) are related to their parent atoms by a two-fold symmetry. Broken lines denote hydrogen bonds. Two substructures are staggered with each other with close contacts (Å): O(1)···C(30*) = 3.77(2), C(30*)···O(8) = 3.47(2), O(2)···C(29*) = 3.96(2), C(29*)···O(3) = 3.82(2), and O(4)···C(32*) = 4.10(2). Perpendicular distances from C(46) to the ring planes are: 3.59, 3.44, 3.37, and 3.43 Å to rings A*, B*, C*, and D*, respectively. Hydrogen-bond distances (Å): O(1)···O(8) = 2.77(2), O(2)···O(3) = 2.72(1), O(4)···O(5) = 2.61(1), O(6)···O(7) = 2.74(1), O(3)···Cl = 3.17(1), Cl···O(10) = 3.18(1), O(10)···O(1*) = 2.66(2), and O($\mathrm{H_2O}$)···Cl = 3.18(2).

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groups belonging to the pairing substructure through van der Waals contacts, $\mathrm{O(1)\cdots C(30^{*})\cdots O(8)}$ and $\mathrm{O(2)\cdots C(29^{*})\cdots O(3)}$ and their two-fold symmetry-related $\mathrm{O(1^{*})\cdots C(30)\cdots O(8^{*})}$ and $\mathrm{O(2^{*})\cdots C(29)\cdots O(3^{*})}$. The capsule structure is further stabilized by a pair of two-atom bridged hydrogen bonds between substructures, $\mathrm{O(3)\cdots Cl\cdots O(10)\cdots O(1^{*})}$ and $\mathrm{O(3^{*})\cdots Cl^{*}\cdots O(10^{*})\cdots O(1)}$. These hydrogen bonds are formed at one side on the spherical capsule, while the opposite side is rather opened; this reflects in a mutual inclination of pairing substructures with a dihedral angle of 9.2° between two planes, each of which is defined by four bridging methylene atoms. The perpendicular distances from C(7*), C(14*), C(21*), and C(28*) to the plane through C(7), C(14), C(21), and C(28) atoms are 9.22, 10.00, 10.31, and 9.59 Å, respectively. The ethyl terminal carbon atom, C(46) [or C(46*)], of the $\mathrm{Et_4N^+}$ guest molecule is embedded in a bowl-shaped cavity of a substructure with $\mathrm{C{-}H\cdots\pi}$ close contacts, and thus the $\mathrm{Et_4N^+}$ molecule is oriented in a vertical fashion with respect to the facing plane of two substructures.

Figure 2 shows the molecular structure of $\mathrm{Et_4N^+}\cdot(\mathbf{2}\cdot\mathbf{2}^-)\cdot 8\mathrm{H_2O}$, which forms a "head-to-head" arranged molecular capsule encapsulating an $\mathrm{Et_4N^+}$ ion. A quarter of the capsule molecule is crystallographically independent; the MRCT **2** molecule is related to itself within the molecule by a two-fold axis and, in addition, two MRCT substructures are related to each other by another two-fold axis passing through both the central nitrogen atom and the terminal carbon atom, C(24), of the $\mathrm{Et_4N^+}$ molecule, where these two-fold axes orthogonally intersect at the $\mathrm{Et_4N^+}$ nitrogen atom. The operation of the latter two-fold symmetry creates a staggered arrangement between two substructures, where methyl substituents of the MRCT rings are pincered by hydroxy groups through van der Waals contacts, $\mathrm{O(2)\cdots C(15^{**})\cdots O(3)}$ and $\mathrm{O(1)\cdots C(16^{**})\cdots O(4^{*})}$, and their symmetry-related $\mathrm{O(2^{*})\cdots C(15^{***})\cdots O(3^{*})}$ and $\mathrm{O(1^{*})\cdots C(16^{***})\cdots O(4)}$. The capsule structure is further stabilized by a pair of two-water bridged hydrogen bonds between substructures, $\mathrm{O(2)\cdots O(5)\cdots O(5^{**})\cdots O(2^{**})}$ and $\mathrm{O(2^{*})\cdots O(5^{*})\cdots O(5^{***})\cdots O(2^{***})}$. The separation between two parallel planes, each formed by four methylene atoms, is 9.53 Å, while the corresponding one is 9.14 Å in a RCT dimer capsule, $\mathrm{Et_4N^+}\cdot(\mathbf{1}\cdot\mathbf{1}^-)\cdot 8\mathrm{H_2O}\cdot 2\mathrm{EtOH}$,[4] where two substructures are exactly eclipsed and stabilized by sixteen hydrogen bonds through eight water bridges. The $\mathrm{Et_4N^+}$ molecule is oriented in a horizontal fashion, as is the case of $\mathrm{Et_4N^+}\cdot(\mathbf{1}\cdot\mathbf{1}^-)\cdot 8\mathrm{H_2O}\cdot 2\mathrm{EtOH}$.[4]

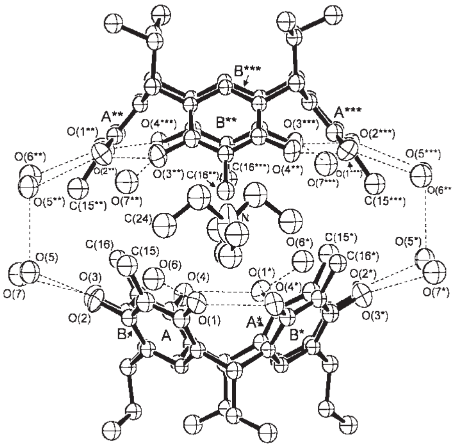

Fig. 2. Molecular structure of $\mathrm{Et_4N^+}\cdot(\mathbf{2}\cdot\mathbf{2}^-)\cdot 8\mathrm{H_2O}$. $\mathrm{Et_4N^+}$ molecule is disordered over two positions related by a two-fold symmetry (only one orientation is shown with the thermal ellipsoids at arbitrary scale for clarity). Atoms designated by asterisks (*, **, or ***) are related to their parent atoms by two-fold symmetries. Broken lines denote hydrogen bonds. Two substructures are staggered with each other with close contacts (Å): $\mathrm{O(1)\cdots C(16^{**})} = 3.97(2)$, $\mathrm{C(16^{**})\cdots O(4^{*})} = 4.24(2)$, $\mathrm{O(2)\cdots C(15^{**})} = 4.13(2)$, and $\mathrm{C(15^{**})\cdots O(3)} = 3.92(2)$. Hydrogen-bond distances (Å): $\mathrm{O(1)\cdots O(4^{*})} = 2.77(2)$, $\mathrm{O(2)\cdots O(3)} = 2.73(2)$, $\mathrm{O(1)\cdots O(6)} = 2.72(3)$, $\mathrm{O(2)\cdots O(5)} = 2.84(1)$, $\mathrm{O(3)\cdots O(7)} = 2.79(3)$, and $\mathrm{O(5)\cdots O(5^{**})} = 2.91(4)$.

Methyl substitution on the resorcinarene rings affects the architecture of the capsule structures: facing substructures are staggered with each other in the present MRCT capsules, whereas those in dimeric capsules for *unsubstituted* resorcinarenes are usually eclipsed[4–8] or in minor cases staggered.[6,7] The formation of the staggered structure of MRCT capsules is explicable from a steric point of view; under a condition that the same separation between two substructures is kept as that, for example, in the present $\mathrm{Et_4N^+}\cdot(\mathbf{2}\cdot\mathbf{2}^-)\cdot 8\mathrm{H_2O}$, the eclipsed arrangement might cause a steric crash between two neighboring methyl groups, each from pairing substructures, and then, in order to avoid this steric hindrance, substructures rotate mutually by about 45° to adopt a staggered arrangement. The encapsulated $\mathrm{Et_4N^+}$ molecule takes a vertical or horizontal orientation with reference to the facing plane of pairing substructures; the factor that determines the orientation of an incorporated $\mathrm{Et_4N^+}$ is unknown at this stage. There have been reported three other MRCT compounds: $2(\mathbf{2})\cdot 2\mathrm{MeOH}\cdot 4\mathrm{H_2O}$,[9] $2(\mathbf{2})\cdot 2\mathrm{EtOH}\cdot(\mathrm{EtOH})_{0.7}\cdot(\mathrm{H_2O})_{0.3}$,[9] and $2(\mathbf{2})\cdot 2(\mathrm{imidazole})\cdot 3\mathrm{H_2O}$.[9] In each compound, two MRCT **2** molecules that are related by a crystallographic center of symmetry form a "head-to-head" arranged molecular capsule, which captures a pair of neutral substrates within the cavity. Each MeOH or EtOH ligand is oriented in such a way that its hydroxy and alkyl groups locate near the phenyl rings of a MRCT molecule through $\mathrm{O{-}H\cdots\pi}$ and $\mathrm{C{-}H\cdots\pi}$ interactions. Additionally, its hydroxy head forms an $\mathrm{O{-}H\cdots O}$(alcohol) hydrogen bond with the hydroxy group of the pairing substructure; similarly, the imidazole ligand locates in the vicinity of the phenyl rings of a MRCT molecule through $\mathrm{N{-}H\cdots\pi}$ and $\mathrm{C{-}H\cdots\pi}$ interactions, and the remaining ring-nitrogen atom forms an $\mathrm{O{-}H\cdots N}$ hydrogen bond with the hydroxy group of the pairing substructure. A methyl–methyl clash is avoided by shifting two substructures in a parallel fashion and the resulting capsule structures are irregular in shape; the separation between the two parallel planes, each defined by four methylene carbon atoms in each of MeOH-, EtOH-, and imidazole-containing capsules, is 8.6, 8.9, and 9.2 Å, respectively. Methyl–methyl hydrophobic interactions between the facing substructures contribute to self-assembled "head-to-head" arranged dimer formation.

In summary, the capsule formation incorporating a tetraethylammonium ion through cation–π interactions has been substantiated for MRCT, as was for RCT,[4] this being consistent with a guest-driven capsule formation mechanism. A structural characteristic of MRCT capsules is their staggered arrangement, which could be stabilized by intra-capsular methyl–hydroxy van der Waals interactions.

Experimental

Preparation of $\mathbf{Et_4N^+ \cdot 2(2) \cdot Cl^- \cdot H_2O \cdot 2EtOH}$ and $\mathbf{Et_4N^+ \cdot (2 \cdot 2^-) \cdot 8H_2O}$. Tetramethylated tetraethylresorcin[4]arene[10] (MRCT, **2**) was synthesized, by an analogous method[11] for tetraethylresorcin[4]arene (RCT, **1**), from 2-methylresorcinol and propionaldehyde. MRCT **2** (0.1 mmol) dissolved in EtOH (10 mL) was added to an aqueous solution (2 mL) of tetraethylammonium chloride (1 mmol), and the mixture (pH 5) was allowed to stand at room temperature to give dark-orange crystals, $Et_4N^+ \cdot 2(\mathbf{2}) \cdot Cl^- \cdot H_2O \cdot 2EtOH$, after one month with a yield of 40%. The use of tetraethylammonium bromide or iodide gave dark-orange microcrystals, which were too small to be subjected to single-crystal X-ray analysis. The same procedure by using MRCT **2** (0.1 mmol) dissolved in MeOH (10 mL) and tetraethylammonium chloride (1 mmol) in water (2 mL) yielded dark-orange crystals, $Et_4N^+ \cdot (\mathbf{2} \cdot \mathbf{2}^-) \cdot 8H_2O$, after one month in a yield of 41%. This compound was also obtained when tetraethylammonium bromide or iodide was used; the best X-ray data in quality were obtained when tetraethylammonium chloride was used, and thus they were adopted here. Molecular formulae were determined by X-ray analyses, since elemental microanalyses of these compounds were not possible due to their rapid decomposition out of solution.

X-ray Crystallography. Each crystal was sealed in a glass capillary, and intensity data were measured on a Rigaku AFC7R diffractometer with an 18 kW rotating anode generator, using graphite-monochromated Mo Kα radiation ($\lambda(\mathrm{Mo\,K}\alpha) = 0.7107$ Å) at 293 K. The structures were solved by direct methods and refined by full-matrix least-squares techniques. All calculations were carried out using the teXsan crystallographic software package.[12] No attempt was made to locate H atoms. Crystal data for $(Et_4N^+)_{0.5} \cdot \mathbf{2} \cdot (Cl^-)_{0.5} \cdot (H_2O)_{0.5} \cdot EtOH$: $C_{46}H_{65}Cl_{0.5}N_{0.5}O_{9.5}$, fw = 794.74, monoclinic, space group $P2/n$, $a = 12.347(7)$, $b = 12.569(3)$, $c = 28.777(12)$ Å, $\beta = 98.58(4)^\circ$, $V = 4416(3)$ Å^3, $Z = 4$, $D_{\mathrm{calcd}} = 1.195$ g cm^{-3}, $\mu(\mathrm{Mo\,K}\alpha) = 1.11$ cm^{-1}, $F(000) = 1716$, $R = 0.099$ and $R_w = 0.109$ (for 2415 reflections with $I > 3\sigma(I)$ out of 7989 unique in the range $4 < 2\theta < 50^\circ$), and GOF = 1.40. Only MRCT atoms were treated anisotropically, while all other atoms were treated isotropically due to a limited number of reflections. Chloride ion and water molecule ride on the same two-fold axis. Crystal data for $(Et_4N^+)_{0.25} \cdot (\mathbf{2} \cdot \mathbf{2}^-)_{0.25} \cdot 2H_2O$: $C_{22}H_{31.75}N_{0.25}O_{5.5}$, fw = 387.74, orthorhombic, space group $Pnnn$, $a = 15.048(4)$, $b = 23.773(6)$, $c = 12.692(4)$ Å, $V = 4540(1)$ Å^3, $Z = 8$, $D_{\mathrm{calcd}} = 1.134$ g cm^{-3}, $\mu(\mathrm{Mo\,K}\alpha) = 0.80$ cm^{-1}, $F(000) = 1676$, $R = 0.149$ and $R_w = 0.158$ (for 1088 reflections with $I > 3\sigma(I)$ out of 3688 unique in the range $4 < 2\theta < 50^\circ$), and GOF = 3.19. Owing to a limited number of reflections, only nitrogen and oxygen atoms, except for half-occupied water molecules, O(6) and O(7), were treated anisotropically in least-squares refinements. High R values are caused, at least in part, by an extensive disordering of Et_4N^+; ethyl carbon atoms C(21), C(22), C(23), and C(24) of Et_4N^+ are so highly disordered that resulting atomic coordinates in original least-squares refinements gave unreasonable molecular dimensions and geometry, and thus they were fixed in the final refinements, except for their isotropic thermal parameters. Water molecule O(5) rides on a two-fold axis. Any one of sixteen hydroxy substituents belonging to two MRCT molecules constituting the capsule could be deprotonated, as is the case for $Et_4N^+ \cdot (\mathbf{1} \cdot \mathbf{1}^-) \cdot 8H_2O \cdot 2EtOH$.[4] Crystallographic data have been deposited with the Cambridge Crystallographic Data Center as supplementary publication Nos. CCDC-218355 and -273830. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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