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# Crystal Structures of Resorcin[4]arene and Tetramethylated Resorcin[4]arene Complexes Incorporating L-Carnitine through Cation–$\pi$ Interaction

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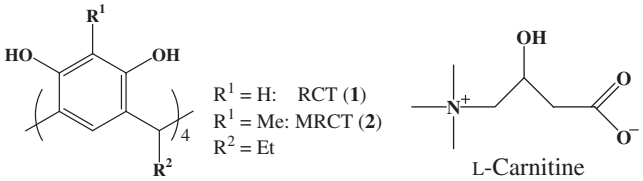
Resorcin[4]arene and tetramethylated resorcin[4]arene form complexes with L-carnitine, whose crystal structures were determined. Each complex contains two carnitine ligands in the asymmetric unit, each of which is incorporated into the cavity of the macrocyclic receptor through cation–$\pi$ interactions between the trimethylammonium moiety of the ligand and $\pi$–rings of the receptor.

It has now been well documented[1–4] that the cation–$\pi$ interaction plays a crucial role in a wide range of molecular recognition in chemistry and biology. Acetylcholine (ACh) and other choline and carnitine derivatives provide the best-documented examples of cation–$\pi$ interactions in ligand recognition. Crystal structures of ACh esterase,[5] ACh-binding proteins,[6,7] butylcholine esterase,[8] choline-binding protein,[9] choline kinase,[10] choline acetyltransferase,[11] phosphocholine-binding antibody,[12] carnitine acetyltransferases[13–17] (Figure S1 as Supporting Information), carnitine palmitoyltransferase,[18] carnitine octanoyltransferase,[19] or carnitine transporter[20] have revealed that the quaternary trimethylammonium motif of the ligand is bound to aromatic residues by cation–$\pi$ interaction. A variety of synthetic receptors for ACh and choline derivatives, constructed of aromatic walls, have also been available,[2,21] including cyclophane,[22,23] speleand,[24] polyphenolic,[25] catechol,[26] cryptophane,[27] calix[4]arene,[28–30] resorcinarene,[31–34] or pyrogallolarene[35] hosts as representatives, as well as those[32–35] for carnitine or its derivatives. However, for such artificial macrocyclic receptor systems, X-ray evidence for the presence of the cation–$\pi$ interaction is still rare: the only three examples, to our knowledge, are $8Na^+ \cdot (choline^+)_2 \cdot (p\text{-sulfonatocalix[4]arene}^{5-})_2$,[28] $ACh^+ \cdot$resorcin[4]arene$\cdot Cl^- \cdot H_2O$,[36] and (3-phenylpropionic acid choline ester$^+$)$_2 \cdot$(resorcin[4]arene)$_2 \cdot 2Cl^- \cdot 9H_2O$.[37]



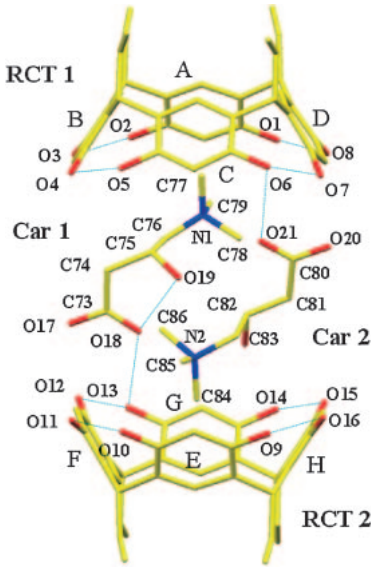




**Figure 1.** Molecular structure of the [**1**$\cdot$L-carnitine]$_2$ dimer. Distances (Å) from the carbon atoms of the trimethylammonium group of carnitine to the $\pi$–centroids of **1** (<4.1 Å): for Car1–RCT1, C77···ring C = 3.33, C77···ring D = 3.67, C77···ring B = 3.82, and C79···ring A = 3.54; for Car2–RCT2, C84···ring G = 3.41, C84···ring F = 3.63, C84···ring H = 3.78, and C85···ring E = 3.80. Hydrogen bonds distances (Å) from the carboxylate oxygen of carnitine to the phenolic oxygen of **1**: for Car1–RCT2, O18···O13 = 2.636(7) and for Car2–RCT1, O21···O6 = 2.631(7). Broken (blue) lines denote hydrogen bonds.

We report here crystal structures of two complexes formed between resorcin[4]arene (resorcinol cyclic tetramer; abbreviated as RCT (**1**)) and tetramethylated resorcin[4]arene (2-methylresorcinol cyclic tetramer; MRCT (**2**)) with L-carnitine (Chart 1), as a continuation of our X-ray studies[36–40] of cation–$\pi$ interactions between the quaternary alkylammonium moiety and the aromatic rings. L-Carnitine is a quaternary ammonium compound that is required for the transport of fatty acids from cytosol into the mitochondria for generating metabolic energy.[41]

Each of the RCT and MRCT complexes contains two crystallographically independent macrocyclic receptor molecules and two L-carnitine (Car1 and Car2) ligand molecules in the asymmetric unit, which form a dimeric structure constructed with two structurally equivalent receptor–ligand 1:1 substructures, as shown in Figures 1 and 2, respectively. Each carnitine ligand is located in such a way that its trimethylammonium end is incorporated into the cavity of a bowl-shaped receptor molecule, making close contacts with the aromatic rings of the receptor molecule through cation–$\pi$

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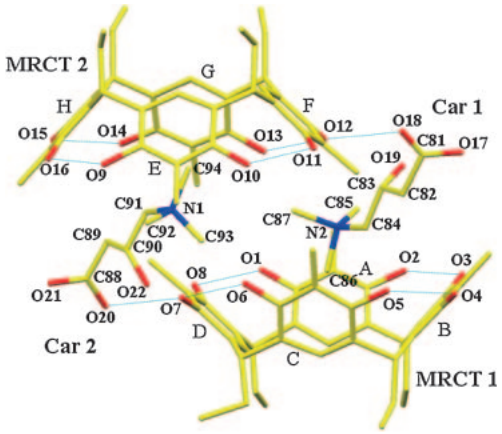


**Figure 2.** Molecular structure of the [**2**·L-carnitine]$_2$ dimer. Distances (Å) from the carbon atoms of the N group of carnitine to the $\pi$–centroids of **2** (<4.1 Å): for Car1–MRCT1, C86···ring A = 3.52, C86···ring C = 3.75, C86···ring B = 3.77, and C86···ring D = 4.05; for Car2–MRCT2, C94···ring E = 3.54, C94···ring G = 3.83, C94···ring F = 3.89, and C94···ring H = 4.06. Hydrogen bonds distances (Å) from the carboxylate oxygen of carnitine to the phenolic oxygen of **2**: for Car1–MRCT2, O18···O12 = 2.645(9) and for Car2–MRCT1, O20···O7 = 2.588(9). Broken (blue) lines denote hydrogen bonds.

interactions, and its carboxylate end forms a hydrogen bond with the phenolic oxygen of the pairing substructure.

The substitution at the 2-position on the aromatic rings does not disturb the formation of the monomeric [receptor–ligand] substructures through cation–$\pi$ interactions but affects their packings in the crystal lattice, which reflect in the architecture of the dimeric structures constructed with two substructures through O–H(phenolic)···O(carboxylate) hydrogen bonds: the hydrogen-bonded carboxylate oxygen of each carnitine is positioned above or below the hydrogen-bonded phenolic oxygen of the receptor in the RCT complex or side-by-side with the phenolic oxygen in the MRCT complex. All of the four L-carnitine molecules in the two complexes take a fully extended backbone (N–C–C–C–C) conformation except one (Car1) of the two in the RCT complex, which is partially folded (Table S4). In crystal structures of carnitine reported to date, the fully extended conformation is widely observed in DL-carnitine·HCl,[42] L-carnitine,[43] 2(L-carnitinium)·2[$AuCl_4$],[44] 2(L-carnitinium)·(L-tartrate),[45] and [$Cu_2$(L-carnitine)$_4$($H_2O$)$_2$]·($ClO_4$)$_4$·$H_2O$·$CH_2Cl_2$,[46] while the partially folded one occurs rarely in one of the two carnitine molecules in the $AuCl_4^-$ salt[44] and in one of the four carnitine molecules in the $Cu^{2+}$ complex.[46] On the other hand, in crystal structures of carnitine-containing protein structures,[13–20] a carnitine ligand is always bound in a partially folded conformation in acyltransferases,[13–19] while four carnitine ligands take various conformations including fully-extended and partially-folded in the carnitine-transporter.[20]

In conclusion, this study provides the first X-ray example that shows the existence of cation–$\pi$ interaction between the quaternary trimethylammonium moiety of the biologically important L-carnitine ligand and aromatic rings in the artificial receptor–ligand system that mimics the carnitine binding sites in acyltransfereses or a carnitine-transporter.

## Experimental

**Preparation of the RCT and MRCT Complexes with L-Carnitine.** RCT (**1**) and MRCT (**2**) host compounds were synthesized by an analogous method[47] for RCT. Each host solution and a L-carnitine solution were prepared by dissolving the host compound (700 mg) in ethanol (42 mL) and L-carnitine (1.0 g) in water (10 mL), respectively. Each host solution (0.1 mL), L-carnitine solution (2 mL), and water (0.4 mL) were mixed and allowed to stand at room temperature to give dark-orange crystals after 5 days. 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.** X-ray intensity data were measured on a Rigaku AFC-7R diffractometer (at the Instrument Center of the Institute for Molecular Science in Okazaki) with a rotating anode generator and a Mercury CCD camera, using graphite-monochromated Mo K$\alpha$ radiation ($\lambda$(Mo K$\alpha$) = 0.7169 Å) at 295 K. Data reduction, the cell refinement, and semiempirical absorption corrections were performed with the program CrystalClear.[48] The structures were solved by direct methods and refined by full-matrix least-squares techniques on $F_o^2$, minimizing $\Sigma w(|F_o| - |F_c|)^2$, with the programs SHELXS[49] and SHELXL,[49] respectively, on the platform and graphic software Yadokari-XG.[50] No attempt was made to locate H atoms. Crystal data for the **RCT** complex, 2(**1**)·2(L-carnitine)·EtOH·6$H_2O$: $C_{88}H_{126}N_2O_{29}$, fw = 1675.93, triclinic, space group $P1$, $a$ = 11.3793(11). $b$ = 13.4159(12), $c$ = 15.3572(15) Å, $\alpha$ = 81.207(6), $\beta$ = 84.103(7), $\gamma$ = 77.890(6)°, $V$ = 2259.3(4) Å$^3$, $Z$ = 1, $D_{calcd}$ = 1.172 g cm$^{-3}$, $\mu$(Mo K$\alpha$) = 0.140 cm$^{-1}$, $F(000)$ = 850. Solvent atoms (six water oxygen atoms and ethanol atoms) were refined with isotropic thermal parameters while the other non-H atoms with anisotropic parameters. Final $R$ = 0.117 and $R_w$ = 0.313 (for 11766 reflections with $I > 2\sigma(I)$ out of 13861 unique reflections in the range $3 < 2\theta < 55°$) and $GOF$ = 2.42. Crystal data for the **MRCT** complex, 2(**2**)·2(L-carnitine)·3EtOH: $C_{100}H_{142}N_2O_{25}$, fw = 1772.19, triclinic, space group $P1$, $a$ = 12.647(5). $b$ = 14.252(5), $c$ = 15.292(6) Å, $\alpha$ = 101.739(8), $\beta$ = 91.965(8), $\gamma$ = 114.603(7)°, $V$ = 2431.5(16) Å$^3$, $Z$ = 1, $D_{calcd}$ = 1.166 g cm$^{-3}$, $\mu$(Mo K$\alpha$) = 0.134 cm$^{-1}$, $F(000)$ = 914. Three ethanol molecules were refined under restraint with isotropic thermal parameters while the other non-H atoms were refined with anisotropic values. A carbon atom of an ethanol molecule was disordered at two positions. Final $R$ = 0.131 and $R_w$ = 0.307 (for 9461 reflections with $I > 2\sigma(I)$ out of 14742 unique reflections in the range $3 < 2\theta < 55°$) and $GOF$ = 1.72. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center as supplementary publication Nos. CCDC-810188 and CCDC-810187 for the RCT and MRCT complexes with L-carnitine, respectively. Copies of the data can be obtained free of charge from the Cambridge, CB2 1EZ, U.K.; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

## Supporting Information

Lists of crystal data and refinement details (Table S1), bond distances and angles of RCT, MRCT, and L-carnitine molecules

(Tables S2 and S3), conformations of L-carnitine molecules (Table S4), and hydrogen bond distances (Tables 5 and 6). A figure showing receptor–ligand cation–$\pi$ interaction in the crystal structure of an L-carnitine acetyltransferase (Figure S1). These materials are available free of charge on the web at http://www.csj.jp/journals/bcsj/.

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