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Hydrogen Bonding Selectivity in Molecular Assembly: A Novel 2:1 Molecular Complex of Caffeine and 4-Hydroxybenzoic Acid *via* C–H···O/O–H···O/ O–H···N Hydrogen Bond Coupling

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Caffeine (**1**) and 4-hydroxybenzoic acid (**2**) form a novel 2:1 molecular complex *via* C—H---O hydrogen bonding. Selectivity in the formation of hydrogen bonds in the X-ray structure of the complex is predicted by the relative acidity and basicity of the participating atoms in the groups. This is first time reported that caffeine is complexed with an aromatic hydroxy acid through two C—H---O hydrogen bonds involving N-CH_3 hydrogen and ring hydrogen of caffeine.

Key Words: Caffeine, 4-Hydroxybenzoic acid, Molecular recognition, Hydrogen bonds.

INTRODUCTION

Hydrogen bonds are used extensively as a tool to design the structure of molecular crystals, because of their strength as well as directional nature relative to other intermolecular non-covalent interaction. The understanding of the nature and selectivity of non-covalent intermolecular forces responsible for molecular recognition[1-3] has become a major focus in biological chemistry. One facet of this problem concerns plant polyphenols. Polyphenols of proanthocyanidins, ester of gallic acid, hydroxybenzoic acid and hexahydroxydiphenic acid are a distinctive group of higher plant secondary metabolities[4]. The complexes formed between CNS active caffeine with polyphenols and hydroxy acids are responsible for the taste and astringency of many beverages in tea.

Caffeine forms a large number of complexes of variable stoichiometry with polyphenols and hydroxy acid such as methylgallate[5], 3-nitrobenzoic acid[5], 5-chloro salicylic acid[6], pyrogallol[7], potassium chlorogenate[8], *etc*. But so far, no caffeine complex through C—H---O hydrogen bond is reported in literature.

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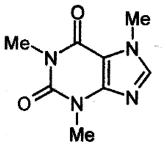
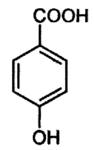
Here we report, the unprecedented C—H---O hydrogen bonding[9] mediated molecular complexation of caffeine (**1**) and 4-hydroxybenzoic acid (**2**). Caffeine has been crystallized[10] as 2:1 adduct (Fig. 1) with 4-hydroxybenzoic acid in water as solvent containing a few drops of ethanol and the complexes are subjected to X-ray crystallographic analysis[11].



(1)



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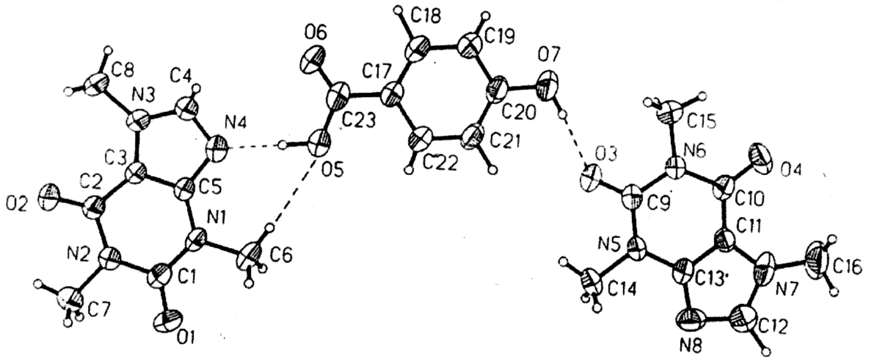

Fig. 1. ORTEP diagram of **1** and **2** (2:1 complex)

Two caffeine molecules are inclined at dihedral angles of 176.57° and 176.18° to 4-hydroxybenzoic acid and 179.15° to each other (of two caffeine molecules). The packing diagram (Fig. 2) shows that caffeine is encapsulated within the complex *via* C—H---O, O–H--N and O—H---O hydrogen bonds. All these three types of hydrogen bonds (Fig. 2) are observed between (i) the basic nitrogen (N-4) of caffeine and the carboxyl hydrogen of 4-hydroxybenzoic acid [O5H1---N4(1.737 Å)] and lone pair of O5 and one C–H of N1–CH3 group [C6H6B–O5 (2.590 Å)] resulting a seven membered ring. (ii) two novel C—H---O bonds in the complex: carboxycarbonyl of 4-hydroxybenzoic acid with C12-hydrogen of caffeine [C12HI2---O6 (2.215 Å)] and one hydrogen N-CH$_3$ group of caffeine with carboxyl oxygen of 4-hydroxy-benzoic acid with one of the keto amide group of caffeine [O7H1--O3 (1.871 Å)], (iii) phenolic hydrogen of 4-hydroxy benzoic acid [O7H and C9O3] of caffeine.

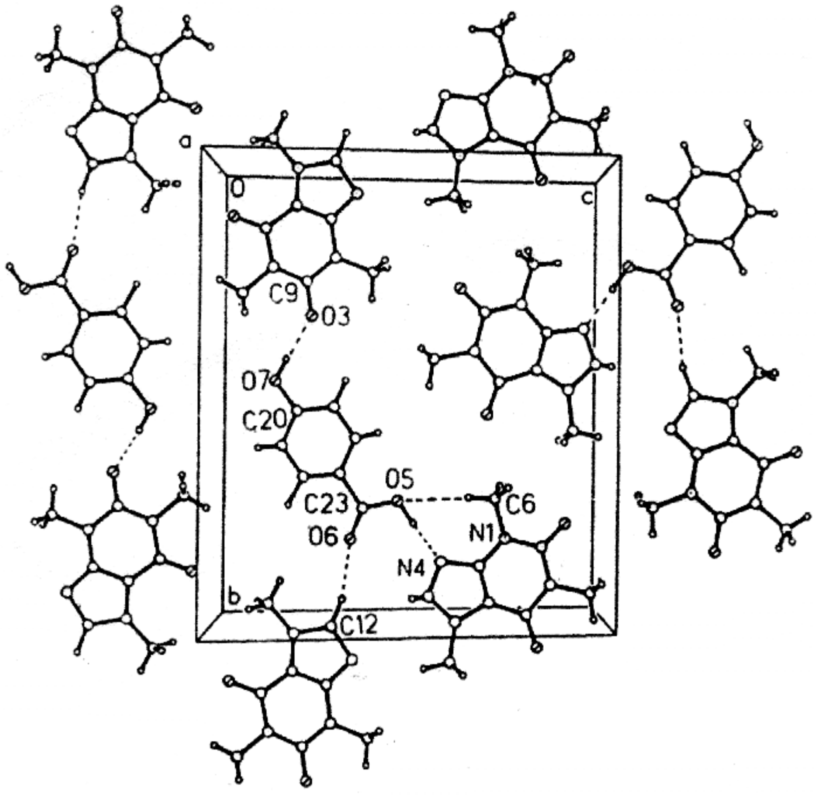

Fig. 2. Hydrogen bonding network of caffeine and 4-hydroxybenzoic acid 2:1 complex

An extensive in plane system of hydrogen bonding between the phenolic hydroxyl group and carboxyl hydrogen of 4-hydroxybenzoic acid (donors), carboxyl oxygen and carboxycarbonyl (C-H bond acceptors) and the keto amide groups and the basic N4 of caffeine (acceptors) ultimately makes specific contributions to the stabilization of the complex. Most interestingly, in the complex, both N-CH_3 [C(sp^3)-H] and ring hydrogen [C(sp^2)-H] of caffeine are found to be involved in the two unprecedented C—H---O hydrogen bonding with the carboxylic acid group of 4-hydroxybenzoic acid along with O–H--N and O—H---O hydrogen bonds. Thus the carboxyl group makes three hydrogen bonds with two different caffeine molecules. In the crystal structure of the complex, 4-hydroxy-benzoic acid molecule is stacked parallel between two caffeine molecules down the ‘b’ axis in layers. It is interesting to note the selectivity of hydrogen bonds in the complex (Fig. 2) where more acidic hydrogen of **2** makes hydrogen bond with the more basic N4 atom of **1** and less acidic phenolic hydrogen (compared to -CO_2 H) of **2** makes hydrogen bond with less basic oxygen of keto amide (C9O3) of **1**. However keto amide oxygen of (C9O3) in **1** is more basic compared to that of C10 O4 and thus it is preferred to make hydrogen bond with hydroxyl group of 4-hydroxybenzoic acid.

It is therefore significant to note that the hydrogen bonding and hydrophobic contribution is nevertheless probably the most important influencing factor for the complexation of caffeine (or proteins) with hydroxy acids in aqueous medium where water participation in hydrogen bonding is absent with either of the substrates or in the complex. The results have important practical implications in the fact that caffeine works as an analgesic adjuvancy with ibuprofen which has a -CO_2H group which is thus carried in the form of a complex in water, when it enters the body and stimulate the CNS. Thus our recognition model for caffeine and 4-hydroxybenzoic acid partially mimics the above biological event.

Supporting information: The crystallographic data for the complex has been deposited with the Cambridge Crystallographic Data Centre, CCDC 629181. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2, 1EZ, UK (Fax: +44-1223-336033; E-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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10. Colourless Block Crystal of 2:1 Complex (m.p. 138-139 ºC) were obtained from the 4-hydroxybenzoic acid (m.p. 215-217 ºC) and the caffeine (234.0-236.5 ºC) from water containg few drops of ethanol. ^{1}H NMR (200 MHz, $CDCl_3$) of the 2:1 co-crystal: δ 9.21 (phenolic -OH), 7.84 (d, 2H, $J = 8$ Hz *ortho* to -COOH), 7.48 (s, 1H, caffeine),

6.78 (d, 2H, J = 8 Hz, *ortho* to -OH), 3.92 (s, N-CH_3, caffeine), 3.52 (s, N-CH_3, caffeine), 3.33 (s, N-CH_3, caffeine).

11. Crystal data for 2:1 complex ($C_8H_{10}N_4O_2$:$C_7H_6O_3$), M = 526.52, monoclinic, space group $P2_1/n$, a = 10.225(0)Å, b = 16.766(10)Å, c = 14.959(10)Å, β = 100.45 (10)º, V = 25121.93 (2) $Å^3$, Z = 4, $\rho_{calcd.}$ = 1.387 Mg m^{-3} (293 K), μ (Mo-K_α) = 0.105 mm^{-1}, F(000) = 1104, λ = 0.71073 Å, R_{emerge} (I) = 0.0248, 4394 unique reflection out of 12993 with I > 2σ (I), R_1 = 0.0809, residual electron density, min/max -0.411/1.280 $eÅ^{-3}$. The data were collected on a SMART CCD area detector diffractometer using graphite monochromated with a detector distance of 4 cm and swing angle of -35º. The collected data were reduced by using the program SAINT [G.N. Sheldrick,; SAINT n4 software reference manual, Siemens Analytical X-ray systems, Inc., Madison, Wisconsin, USA (1996)]. The structure was solved by direct methods and refined by least-squares on F_{obs}^2 by using the SHELXTL [G.N. Sheldrick, SAINT v5 software reference manual, Siemens Analytical X-ray systems, Inc., Madison, Wisconsin, USA (1996)] software package.

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