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Supramolecular Assembly of Protonated Xanthine Alkaloids in Their Perchlorate Salts

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ABSTRACT: Single crystal X-ray structures of new perchlorate salts of a series of four xanthine alkaloids, for example, xanthine (xt), caffeine (cf), theophylline (tp), and theobromine (tb) are reported. The treatment of xanthine derivatives with 70% of HClO₄ afforded their salts Hxt·ClO₄·2(H₂O), **1**; Htp·ClO₄, **2**; Htb·ClO₄, **3**; and Hcf·ClO₄·H₂O, **4**. Xanthine form dimers via N(9)–H···O–C(6) hydrogen bond in the crystal structure. Of the two possible resonance structures of the protonated imidazoles, one of the structures was found to be major in xanthine, theobromine, and caffeine salts, while both structures are of equal contribution in theophylline salts. These observations also have been verified by using the structural information available in the Cambridge Structural Database. Interestingly, xanthine **1** is present as a dihydrate and **4** as a monohydrate, whereas **2** and **3** are crystallized without any water. Thus, proton transfer from the strong acid HClO₄ to the weakly basic imidazole ring of xanthines occurs which leads to the build up of H-bonded supramolecular networks.

Introduction

Caffeine, theophylline, and theobromine are methyl-substituted analogues of xanthine which are commonly used as mild stimulants and bronchodilators for treating the symptoms of asthma. Xanthine is known as dioxopurine which is a biologically important component of nucleic acids (DNA, RNA) and coenzymes. Caffeine, theobromine, and theophylline are key ingredients in coffee, chocolate, and tea leaves, respectively. The crystal structures of caffeine, theophylline, and theobromine hydrates and/or anhydrates, their transformations from hydrates to anhydrates, and polymorphism are well studied and still of continuing interest.¹ The interest in these studies can be attributed to requirement of crystalline forms of active drug molecules in the pharmaceutical industry.²⁻¹¹ The advantages of crystalline forms are their purity, stability, and clear understanding of their structures. Several cocrystals or salts of caffeine, theophylline, and theobromine with carboxylic acids were reported recently.¹²⁻²⁰ These cocrystals were shown to have better properties than the individual components. On the other hand, the structures of their inorganic acid salts (HClO₄, HCl, or H₂SO₄) were not explored to date. Unlike organic acids, inorganic acids are very strong, more selective, and directional, which make them ideal for geometry-based crystal design.²¹ In this paper, we would like to present the crystal structures of perchlorate slats of caffeine, theophylline, theobromine, and xanthine. Generally, perchlorates are also used as medicine for treating thyroid gland disorders as they can temporarily and reversibly inhibit the ability of the thyroid gland to absorb iodine from the bloodstream; thus, perchlorate is known as goitrogen. Second, perchlorate salts are more soluble in water, and most of them form good crystalline materials. Some of us

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recently reported the bridging of hydrogen bonded dimers of lumazine by $H_5O_2^+$ in its perchlorate salt.²²



The sp² nitrogen of imidazole ring has a higher affinity to react with acids due to its more basic nature in all four structures. The treatment of xanthine derivatives with 70% of HClO₄ resulted in their salts Hxt·ClO₄·2(H₂O), **1**; Htp·ClO₄, **2**; Htb·ClO₄, **3**; and Hcf·ClO₄·H₂O, **4** (xanthine (xt), caffeine (cf), theophylline (tp), and theobromine (tb)). The crystal structures of these salts were determined (Figure 1) and analyzed in terms of their hydrogen bonding associations. The crystallographic parameters are given in Table 1 and hydrogen bonding parameters are given in Table 2. We are interested in exploring the following aspects by studying the crystal structures of **1**–**4**.

- (1) How does the association of the cations differ from their neutral counterparts?
- (2) What is the role of ClO_4 ions in assembling the cations?
- (3) In principle, two resonance forms are possible for the protonated xanthine derivatives (Scheme 1). Which of these two forms appears in the crystal structures?



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Figure 1. ORTEP drawings with 50% probability: (a) Hxt in 1; (b) Htp in 2; (c) Htb in 3; (d) Hcf in 4.

Table 1.	Crystallographic Paramet	ters for the Crystal	Structures of 1-4
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compound	1	2	3	4
formula	C ₅ H ₉ ClN ₄ O ₈	C7H9ClN4O6	C7H9ClN4O6	C ₈ H ₁₃ ClN ₄ O ₇
M.W.	288.61	280.63	280.63	312.67
$T(\mathbf{K})$	293(2)	293(2)	293(2)	293(2)
system	triclinic	monoclinic	orthorhombic	monoclinic
space group	$P\overline{1}$	P2(1)/n	P2(1)2(1)2(1)	P2(1)/c
a (Å)	5.1625(10)	13.336(2)	8.311(3)	13.046(3)
$b(\mathbf{A})$	7.7449(15)	6.2492(10)	11.273(4)	6.5512(14)
$c(\dot{A})$	13.696(3)	14.659(2)	11.572(4)	16.945(4)
α (°)	100.214(5)	90.00	90.00	90.00
β (°)	91.591(5)	116.155(4)	90.00	112.255(5)
γ (°)	100.880(5)	90.00	90.00	90.00
$vol(Å^3)$	528.19(18)	1096.5(3)	1084.1(7)	1340.3(5)
Z	2	4	4	4
$D_{\rm calc} ({\rm Mg/m}^3)$	1.815	1.700	1.719	1.550
$R_1(I > 2\sigma(I))$	0.0343	0.0401	0.0565	0.0705
wR_2 (on F^2 , all data)	0.0989	0.1123	0.1634	0.2297

Results and Discussion

The xanthine perchlorate (1) is crystallized in triclinic space group $P\overline{1}$, and the asymmetric unit is constituted by one unit each of Hxt and ClO₄, and two molecules of water. The comparison of bond lengths N7–C8 (1.317 Å) and C8–N9 (1.340 Å) reveals that the contribution of the RF-II is the major one. The N7–C8 is the shortest C–N bond among all the C–N bonds in the ring, while the largest is the N1–C6 (1.386 Å). The Hxt molecules form a dimer through the amide-to-amide hydrogen bonds (Figure 2). Both N–H groups of imidazoles engage in N–H···O hydrogen bonds with water molecules. It is interesting to note here that both the water molecules donate two hydrogen bonds and receive one hydrogen bond. Water is different from "normal" molecular liquids. In H₂O, each molecule has two donor and two acceptor sites to form a tetrahedral network. Here one of the water molecules donates the protons to carbonyl groups such that the dimer stability is further enhanced by additional $O-H \cdots O$ hydrogen bonds and forms a one-dimensional chain. The second water molecule hydrogen bonds to two perchlorate ions such that there is an aggregate formation of two waters and two perchlorates. These aggregates further

Table 2. Hydrogen Bonding Parameters for the Crystal Structures of 1-4

-				
1	$N1-H1\cdots O2^{a}$	2.01	2.873(2)	180
	N3-H3···O102	2.03	2.867(2)	165
	$N7-H7\cdots O2W^{b}$	1.84	2.671(3)	162
	$N9-H9\cdots O1W^{c}$	1.81	2.656(2)	168
	$O1W-H1W1\cdots O103^d$	2.11	2.912(2)	174
	$O1W-H2W1\cdots O104^{e}$	2.24	3.020(3)	168
	O2W-H1W2O6 ^a	2.05	2.836(2)	174
	O2W-H2W2···O2	2.28	2.920(3)	143
	$C8-H8\cdots O104^{b}$	2.56	3.413(3)	153
2	$N(9) - H(9) \cdots O(2)^{f}$	1.91	2.764(4)	171
	$N(1) - H(1) \cdots O(103)^{g}$	2.14	2.900(7)	156
	$C(3N) - H(3B) \cdots O(101)$	2.42	3.257(7)	145
	$C(3N) - H(3C) \cdots O(2)^{f}$	2.56	3.465(4)	157
	$C(8) - H(8) \cdots O(104)^{h}$	2.40	3.320(6)	169
3	$N(7) - H(2) \cdots O(6)^{i}$	1.87	2.729(3)	173
	$N(9) - H(1) \cdots O(104)^{j}$	1.94	2.789(3)	169
	$C(8) - H(1A) \cdots O(103)^{i}$	2.43	3.143(3)	134
	$C(3N) - H(6A) \cdots O(101)^k$	2.45	3.290(4)	146
	$C(1N) - H(7A) \cdots O(103)$	2.55	3.489(3)	165
	$C(1N) - H(7C) \cdots O(2)^k$	2.54	3.066(3)	115
4	N9-H9···O1W	1.83	2.685(5)	173
	$C1N-H2N1\cdots O2^{l}$	2.43	3.356(4)	161
	$C3N-H3N3\cdots O2^{m}$	2.51	3.421(5)	158

 ${}^{a}-1-x, 1-y, 1-z, {}^{b}-1+x, 1+y, z, {}^{c}x, 1+y, z, {}^{d}x, -1+y, z, {}^{e}$ ${}^{e}1\text{-x}, 1\text{-y}, 2\text{-}z, {}^{f}3/2-x, 1-y, 1/2+z, {}^{g}1-x, -1/2+y, 1/2-z, {}^{h}1-x, {}^{-1/2}+y, 3/2-z, {}^{i}1-x, 1-y, -z, {}^{f}1/2+x, 1/2-y, -1/2+z, {}^{k}1/2-x, {}^{1}1/2+y, -1/2-z, {}^{l}1-x, 3-y, 1-z, {}^{m}1-x, 2-y, 1-z. {}^{}$



Figure 2. Illustrations for the crystal structure of 1: (a) assembling of Hxt dimers into two-dimensional layers via H_2O molecules and perchlorates; (b) packing of the layers.

link the one-dimensional chains into two- dimensional layers. The layers pack on each other such that the perchlorate ions are sandwiched by Hxt moieties. Similar molecular and supramolecular features were also found in the crystal structure of nitrate salt of xt.²³ In the literature, the crystal structure of only sodium salt of xanthine is known so far.²⁴ The sodium replaces the proton on N3. In this crystal structure, the deprotonated moieties form π -stacks which are further linked by hydrogen bonds with Na(H₂O)₆. The moieties of xanthine form dimers via N(9)–H···O–C(6) hydrogen bond in this crystal structure.

Theophylline perchlorate, **2**, crystallizes in P2(1)/n space group and the asymmetric unit contains one unit each of Htp and ClO₄ ions. The bond lengths of N7–C8 (1.320 Å) and N9–C8 (1.324 Å) are nearly equal indicating the equal



Figure 3. Illustrations for the crystal structure of **2**: assembling of Htp dimers into two-dimensional layers by perchlorate ions: (a) top view; (b) side view; (c) packing of the layers in the crystal lattice.



Figure 4. Illustrations for the crystal structure of 3: (a) one-dimensional chain; (b) packing of the chains in herringbone fashion.



Figure 5. Illustrations for the crystal structure of 4: (a) one-dimensional zigzag chain of Hcf moieties via $C-H\cdots O$ hydrogen bonds; (b) assembling of chains by perchlorate ions; (c) packing of the chains in crystal lattice.

contribution of both the resonance structures. This equalness in bond lenghts has been verified by analyzing the crystal structures of tp in CSD.²⁵ CSD contains 20 neutral structures of tp (*R*-factor < 8), in which the average bond lengths of N7–C8 and C8–N9 are found to be exactly equal (1.336 Å).

In 2, the Htp units engaged in dimer via $N-H\cdots O$ synthon through C6=O and imidazole N7-H groups (Figure 3). This synthon contains 10-atoms while the one observed in the crystal structure of 1 contains eight atoms. It is pertinent to note here that the similar dimeric synthon (10-membered ring) was also observed in the crystal structure of hydrate of theophylline.^{1m} The crystal structure of anhydrate of theophylline does not contain the type of dimers observed here but contains a one-dimensional chain of theophylline molecules.^{1k} Further in 2, the N9-H and C8-H binds to ClO₄ ion via $N-H\cdots O$ and $C-H\cdots O$ hydrogen bonds, respectively. The ClO_4 ion binds the dimers via $C-H\cdots O$ and anion $-\pi$ interactions (C4···OClO₃: 2.935 Å) to propagate crystal packing in three dimensions. The CSD analysis of the crystal structures of neutral tp indicates that out of 20 structure 9 structures were found to exhibit a similar dimer as in 2.

Theobromine perchlorate, **3**, crystallizes in orthorhombic and chiral space group $P2_12_12_1$. The N7–C8 (1.316 Å) and N9–C8 (1.354 Å) bond lengths indicate the contribution of resonance RF-II. CSD contains four crystals structures of neutral tb; out of these four, three structures contain nearly equal bond lengths of N7–C8 and N9–C8. The molecules in $\mathbf{3}$ have a chance to form amide-to-amide dimer which is observed in the crystal structure of Hxt and also in the crystal structure of theobromine itself. However, in 3, the Htb moieties are associated via one N-H···O (N9-H and C2=O) and $C-H\cdots O$ (MeC-H···C2=O) hydrogen bonds to form a zigzag one-dimensional chain (Figure 4). The perchlorates fit in between the Htb moieties and interact with N1-H via a N-H···O hydrogen bond. These one-dimensional chains pack in herringbone fashion via weak interactions such as C-H···O and anion··· π interactions (C4···OClO₃: 3.013) Å). In the crystal structure of theobromoine, two molecules form a dimer through a N-H···O hydrogen bond synthon similar to the one observed in the crystal structure of 1.^{1h}

Caffeine perchlorate, **4**, crystallized in monoclinic space group P2(1)/c as a monohydrate.²⁶ Here it is pertinent to note that caffeine itself crystallizes as hydrate which transforms at ambient conditions to an anhydrous phase, which in turn converts to a second anhydrous phase at higher temperature. Although the hydrate crystal structure was determined, the two anhydrate phases still defy a complete structural determination, because only powders and disordered crystals are

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obtained.^{1b,d} In the crystal structure of **4** the O-atoms of perchlorate ion exhibit disorder which was modeled and refined. The N7–C8 (1.316 Å) and N9–C8 (1.340 Å) bond lengths indicate the contribution of resonance RF-II. The longest C–N bond in **4** is N1–C2 with a distance of 1.396 Å. The CSD contains crystal structures of 19 neutral and two protonated cf (*R*-factor < 8). In the protonated structures the average bond lengths of N7–C8 (1.321 Å) and N9–C8 (1.343 Å) follow the same trend while they are nearly equal (1.338 and 1.339 Å) in neutral structures.

The Hcf moieties in 4 involve in a zigzag chain formation via $C-H\cdots O$ hydrogen bonds between N(1)-Me or N(3)-Me with the C(2)=O group. These chains are joined together by N-H···O and O-H···O hydrogen bonds between N9-H, two water molecules, and two perchlorate ions as shown in Figure 5. The hydrogen bonding pattern between perchlorates and water molecules is similar to the one observed in the crystal structure of 1. The CSD analysis of the structures (three) suggests that the protonated N-H always hydrogen bond to either anion or to H₂O, while the C-H···O zigzag chain observed here is not found in any of the 22 structures.

Conclusions

This is the first report of the single crystal X-ray structures and hydrogen bonded supramolecular assembly of a series of xanthine alkaloids mediated by proton transfer of HClO₄ which is a strong acid to weak base xanthines on imidazole ring. The analyses of crystal structures of perchlorate salts of xanthine, theophylline, theobromine, and caffeine indicate that the protonation of these derivatives makes the N7-C8 bond shorter than N9-C8 bond which is actually the shorter one in neutral molecules. This fact is supported further by our CSD analysis. In Htb and Hcf, the RF-II is stable due to the presence of the methyl group on electropositive nitrogen, whereas in the case of 1, the reasons are not clear about the greater contribution of RF-II than RF-I. The distance difference in 2 indicates the equal contribution of both forms in the crystal structure. In the crystal structures of 1 and 2, formation of dimeric synthons of Hxt (8-membered) and Htp (10membered) via N-H···O hydrogen bonding was observed. In 3, the Htb moieties are associated via one $N-H\cdots O$ and $C-H\cdots O$ hydrogen bond forming a seven-membered ring. In the crystal structure of 4, the Hcf moieties are exclusively joined together via $C-H\cdots O$ hydrogen bonds.

Experimental Section

A typical procedure for the synthesis of xanthine perchlorate salts: The purine derivatives such as xanthine (30 mg) were dissolved in 70% perchloric acid (0.5 mL) with gentle warming and the reaction mixture was kept at room temperature. After several days, colorless needle shaped crystals of compound (I) separated, which were collected and dried.

Single Crystal X-ray Determination. All the single crystal data were collected on a Bruker-APEX-II CCD X-ray diffractometer that uses graphite monochromated Mo K α radiation ($\mu = 0.71073$ Å) at room temperature (293 K) by the hemisphere method. The structures were solved by direct methods and refined by least-squares methods on F^2 using SHELX-97.²⁷ Non-hydrogen atoms were refined anisotropically and hydrogen atoms were fixed at calculated positions and refined using a riding model. The H-atoms attached to O-atom or N-atoms are located wherever possible and refined using the ridging model. The fractional coordinates, full list of bond lengths and angles, and the anisotropic displacement parameters have been deposited as Supporting Information. Pertinent

crystallographic details are given in Table 1 and hydrogen bond details are given Table 2. The disordered perchlorate ions in 4 were modeled and refined.

CSD Analysis. The structures are retrieved from CSD version 5.30 (November 2008 update).²⁵ The structures in which the transition metal atoms directly linked to xanthine moieties, containing higher factors than 8% are ignored. The hydrogen bonding patterns and bond lengths of individual structures are given in the Supporting Information.

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Supporting Information Available: Crystallographic tables for crystal structures 1–4, the hydrogen bonding patterns and bond lengths of individual structures of xanthines which are retrieved from CSD. This material is available free of charge via the Internet at http://pubs.acs.org.

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