Thiamine as a Cationic Host in Anion Coordination Chemistry. Crystal Structures of Five Anion Salts of Thiamine Monophosphate

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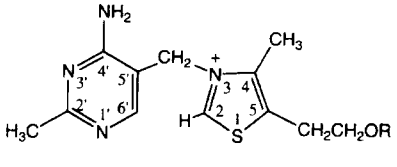
Five anion salts of thiamine monophosphate {(TMP), $TMP^+ \cdot Cl^- \cdot 2H_2O$ (**1**), $TMP^+ \cdot NO_3^- \cdot 2H_2O$ (**2**), $TMP^+ \cdot ClO_4^- \cdot 2H_2O$ (**3**), $TMP^+ \cdot ClO_4^- \cdot H_2O$ (**4**), and $TMP^{2+} \cdot 2CF_3SO_3^-$ (**5**)} have been prepared and structurally characterized by X-ray diffraction in order to examine the host–guest-like anion binding in TMP compounds. In each salt, the TMP molecule adopts the usually observed *F* conformation and, as a cationic host, captures anionic or electronegative guests (= A) through three kinds of anion-bridging interactions: C2–H···A···pyrimidinium-ring, N4′1–H···A···thiazolium-ring, and C6′–H···A···thiazolium-ring. Compared with the thiamine system, the TMP system displays more varieties of self-assembled and higher-ordered structures, due to an additional involvement of the phosphate group: a dimeric structure is formed through both 'head-to-tail' and 'tail-to-tail' hydrogen bonds in **1**, where 'head' and 'tail' refer to the pyrimidinium ring and the phosphate group, respectively; a 'head-to-head' hydrogen-bonded dimer forms in **2**; each TMP molecule being linked to two other TMP molecules to form a 'head-to-tail' cyclic dimer for each neighbor, thus creating an infinite columnar structure in **3**; each TMP molecule is linked to two neighbors, to one in the 'head-to-head' fashion and to the other in the 'tail-to-tail' fashion, producing an infinite chain structure in **4**; and an anion-bridged 'head-to-tail' macrocycle, $[TMP–A–]_2$, is formed and linked to two neighboring macrocycles in the 'tail-to-tail' fashion to generate an infinite columnar structure in **5**.

Anion coordination chemistry has received much attention not only because, in contrast to conventional cation coordination chemistry, it has been developed relatively recently,[1] but because it is now building up an active research area,[2] and also because anions play essential roles in biological processes.[2e] Thiamine (vitamin B_1; **I** in Chart 1) is a cofactor, as its diphosphate ester (TDP), for a number of metabolic enzymes that catalyze the decarboxylation of α-keto acids and the transfer of aldehyde or acyl groups.[3] It is well established[4] that a substrate anion, such as pyruvate, directly reacts with TPP at the C2 site of the thiazolium moiety to form a reaction intermediate 1-hydroxyethyl thiamine diphosphate. Thiamine acts as a monovalent cation because of the quaternary nitrogen N3 of the thiazolium ring or as a divalent one (H-thiamine) with the additional protonation at the N1′ of the pyrimidine ring. At present, more than thirty crystal structures of thiamine salts have been reported.[5] We have noticed[6] that there are two kinds of well-defined 'anion holes' around a thiamine molecule: the 'anion hole I' is occupied by an anion molecule, which bridges between the pyrimidine and the thiazolium rings through a C2–H···anion···pyrimidine interaction ('anion-bridge I'), and the 'anion hole II' is occupied by an anion, which bridges between the two rings through an N4′–H···anion···thiazolium interaction ('anion-bridge II'). The occurrence of these 'anion holes' depends on the conformation of thiamine;[6] that is, the 'anion hole I' exists only when thiamine adopts the *F* conformation (φT = C5′–C3,5′–N3–C2 is approximately 0° and φP = N3–C3,5′–C5′–C4′ is approximately ±90°, defined by Pletcher and Sax et al.[7]), while the 'anion hole II' occurs for thiamine with either the *F*- or the *S*-form (φT is approximately ±100° and φP is approximately ±150°[7]). For the *V*-form (φT is approximately ±90 and φP is approximately ∓90°[7]), neither of them is possible. Thus, the interaction of thiamine with anions is of great interest not only from a biological point of view, that it would serve as a model for interactions of the coenzyme with substrate anions, apoenzymes, or thiamine-binding proteins, but also from the viewpoint of anion coordination chemistry.

Thiamine monophosphate (TMP) is a precursor of TDP and presents an additional phosphate group at the C(5)-substituted side chain. A limited number of crystal structures of TMP or C2-substituted TMP so far reported, $TMP^+ \cdot HPO_4^- \cdot 3H_2O$,[8] $[Rh_2(acetato)_4(TMP)_2] \cdot 1.5H_2O$,[9] $TMP^+ \cdot PF_6^- \cdot 2H_2O$,[10] $HBTMP^+ \cdot Cl^- \cdot 3H_2O$[11] (HBTMP = 2-($\alpha$-hyroxybenzyl)thiamine monophosphate) and $[Hg(HBTMP)_2Cl_2]$,[11] has led us to further systematically examine whether this host–guest-like anion coordination could



R = H	thiamine (I)
HPO_3^-	TMP
$H_2P_2O_6^-$	TDP

Chart 1.

occur for TMP, thereby ascertaining its general significance in a thiamine-anion interaction. We report here on the crystal structures of five TMP salts involving anions with different sizes and shapes: $TMP^+ \cdot Cl^- \cdot 2H_2O$ (**1**), $TMP^+ \cdot NO_3^- \cdot 2H_2O$ (**2**), $TMP^+ \cdot ClO_4^- \cdot 2H_2O$ (**3**), $TMP^+ \cdot ClO_4^- \cdot H_2O$ (**4**), and $TMP^{2+} \cdot 2CF_3SO_3^-$ (**5**). We found an additional anion hole 'III' that affects the conformation of thiamine, where an anion forms a hydrogen bond with the pyrimidinium ring C6′–H, and further makes an electrostatic close contact with the thiazolium ring. The significance of TMP as a building block of a variety of suplamolecules is emphasized.

Experimental

Preparation of Crystals of the TMP Salts 1—5. Crystals of the Cl^- salt **1** were obtained by recrystallization of TMP·Cl (Sigma) dissolved in an aqueous solution (pH about 3.5). Crystals of **2—5** were obtained from an aqueous methanolic solution (5 ml water and 5 ml MeOH) dissolving TMP·Cl (0.1 mmol) and sodium nitrate (0.5 mmol) for **2** (pH about 4), sodium perchlorate (0.2 mmol) for **3** (pH about 4), sodium perchlorate (0.5 mmol) for **4** (pH about 4), or trifluoromethanesulfonic acid (two drops) for **5** (pH about 1), respectively. Colorless crystals formed after a few weeks by allowing the solution to stand at room temperature.

Crystal Structure Determination. A crystal was mounted on a glass fiber for each of **1—5**. Reflection data were collected on a Rigaku AFC7R diffractometer with graphite-monochromated Mo $K\alpha$ radiation (λ = 0.71069 Å) using a 18 kW rotating-anode generator. The ω–2θ scan technique was used for data collection. Three standard reflections were measured every 150 reflections and showed no significant variation through the data collection. Intensity data were corrected for Lorentz and polarization effects, but not for absorption. Crystal data and data collection are given in Table 1, together with refinement details.

The structures were solved by direct methods using the SHELXS-86 program[12] and refined by full-matrix least-squares on F^2 using SHELXL-93 program.[13] One of two water molecules in **2** and perchlorate oxygens in **3** and **4** were disordered, in two positions for each atom, with the occupancy factors estimated from their electron densities. The hydrogen atoms bonded to the phosphate group and to water molecules were located in difference Fourier maps, except those attached to the disordered water in **2**. The other hydrogen atoms were added at their ideal positions. All non-hydrogen atoms were refined anisotropically and the hydrogen atoms were included

Table 1. Crystal Data and Details of Structure Refinements for **1—5**

Compound	**1**	**2**	**3**	**4**	**5**
Empirical formula	$C_{12}H_{22}ClN_4O_6PS$	$C_{12}H_{22}N_5O_9PS$	$C_{12}H_{22}ClN_4O_{10}PS$	$C_{12}H_{20}ClN_4O_9PS$	$C_{14}H_{19}F_6N_4O_{10}PS_3$
Formula weight	416.82	443.38	480.82	462.80	644.48
Space group	$P\bar{1}$	$C2/c$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
a/Å	9.550(1)	25.472(6)	10.990(1)	10.959(2)	11.942(4)
b/Å	11.552(2)	10.491(2)	11.720(1)	12.047(2)	15.343(3)
c/Å	8.7078(7)	15.033(2)	8.3764(7)	8.084(1)	7.661(3)
α/°	99.537(9)		97.290(8)	93.83(1)	103.29(2)
β/°	100.578(9)	110.97(1)	101.439(8)	107.61(1)	103.94(3)
γ/°	102.28(1)		75.897(8)	73.10(1)	71.28(2)
V/Å^3	901.5(2)	3751(1)	1022.1(2)	973.1(3)	1272.4(7)
Z	2	8	2	2	2
$F(000)$	436	1856	500	480	656
D_{calc}/g cm^{-3}	1.54	1.57	1.56	1.58	1.68
Crystal size/mm	0.55 × 0.3 × 0.22	0.4 × 0.3 × 0.25	0.5 × 0.35 × 0.25	0.53 × 0.48 × 0.22	0.5 × 0.4 × 0.1
T/K	293	293	293	293	293
μ (Mo $K\alpha$)/cm^{-1}	4.54	3.17	4.26	4.40	4.54
Scan technique	ω–2θ	ω–2θ	ω–2θ	ω–2θ	ω–2θ
Scan rate/°/min^{-1} in ω	8	8	8	8	8
Scan width/°	1.21 + 0.30 tanθ	1.21 + 0.30 tanθ	1.26 + 0.30 tanθ	1.42 + 0.30 tanθ	1.37+ 0.30 tanθ
2θ Range/°	3.0—55.0	3.0—55.0	3.0—55.0	3.0—55.0	3.0—55.0
Reflections measured	4653	4025	5075	4836	6248
Unique reflections used ($I > 2\sigma(I)$) (M)	4168	3842	4722	4494	5834
Variables (N)	228	260	300	271	345
Weighting scheme, w[a]					
a	0.079	0.091	0.082	0.108	0.092
b	0.341	5.695	0.956	0.852	0.478
R[b]	0.034	0.053	0.055	0.061	0.066
R_w[c]	0.103	0.146	0.147	0.179	0.156
S[d]	0.912	0.969	1.023	1.080	0.983
Max. shift/error in final cycle	0.02	0.17	0.16	0.18	0.12
Max. residual/e Å^{-3}	0.32	0.66	0.59	0.60	0.50

a) $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP)]$, where $P = (F_o^2 + 2F_c^2)/3$. b) $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. c) $R_w = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$. d) $S = [\Sigma w(F_o^2 - F_c^2)^2/(M-N)]^{1/2}$.

in the refinements, but fixed with their isotropic displacement parameters of the same as U_{eq}'s of the corresponding bonded atom. The final atomic coordinates are listed in Tables S1, S2, S3, S4, and S5 and anisotropic thermal parameters in Tables S6, S7, S8, S9, and S10 (supplementary material).[14] Crystallographic data have benn deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition numbers 139648-139652.

Results and Discussion

Molecular Structures. The molecular structures of **1**—**5** are shown in Figs. 1, 2, 3, 4, and 5, respectively. The bond lengths and angles of TMP in **1**—**5** are listed in Table S11 and those of anions in **2**—**5** in Table S12 (supplementary material).[14] The molecular dimensions of the TMP molecule agree well among the five structures except for those of the phosphate group, for which ionization causes some differences, that is, protonated phosphate oxygen atoms are involved in longer bond lengths. In **1**—**4** the phosphate group is monoprotonated, while it is fully protonated in **5**. The approximately equal bond lengths of P5d–O5d1 (1.528(2) Å) and P5d–O5d2 (1.531(1) Å) in **1**, which are slightly shorter than the protonated ones (1.534(4) and 1.540(5) Å) in **5**, imply that a proton is disordered in such a way that it is shared by O5d1 and O5d2. In each compound, the TMP molecule is protonated at N1′, with the C2′–N1′–C6′ bond angle (120.0(2) for **3**—121.7(5)° for **5**) being typical of the N1′-protonated pyrimidine ring and larger than that of the free base by about 5°.[15] Thus, the TMP molecule is a mono-

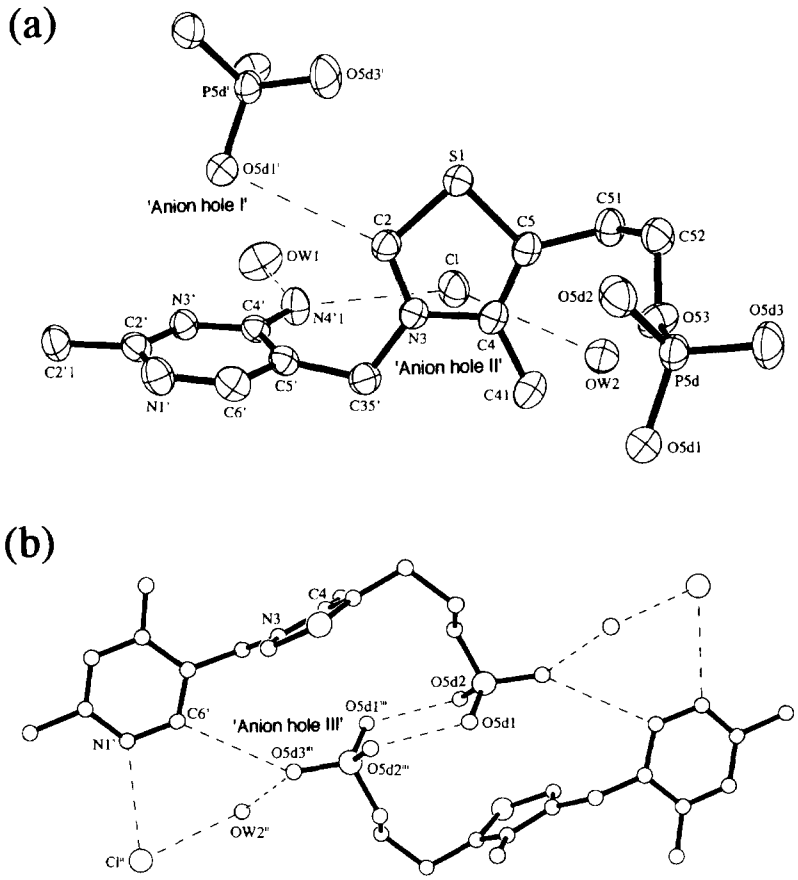


Fig. 1. (a) Molecular structure of $TMP^+ \cdot Cl^- \cdot 2H_2O$ (**1**) with the numbering scheme, showing a phosphate group of a neighboring TMP molecule at the 'anion hole I' and a chloride ion at the 'anion hole II'. (b) The 'tail-to-tail' dimeric structure formed by a pair of O5d1–H···O5d2 hydrogen bonds across a center of symmetry in **1**. The C6′–H···phosphate···thiazolium-ring bridge at the 'anion hole III' is also shown. Broken lines denote hydrogen bonds. Hydrogen atoms are omitted for clarity.

Table 2. Torsion Angles (°) of TMP in **1**—**5**[a)]

Compound	**1**	**2**	**3**	**4**	**5**
φT = C5′–C35′–N3–C2	10.1(2)	5.0(5)	11.6(4)	4.8(4)	0.0(7)
φP = N3–C35′–C5′–C4′	82.9(2)	75.2(4)	76.4(3)	70.6(4)	−85.9(6)
$\varphi 5\alpha$ = S1–C5–C51–C52	88.4(2)	−74.4(4)	66.6(4)	−81.2(3)	39.5(7)
$\varphi 5\beta$ = C5–C51–C52–O53	63.2(2)	−67.2(4)	−56.7(5)	−66.2(4)	−69.2(6)
$\varphi 5\gamma$ = C51–C52–O53–P5d	−155.8(1)	168.9(2)	−122.1(4)	147.7(2)	176.5(4)

a) The conformational terms, φT etc., are defined by Pletcher and Sax et al.[7,16]

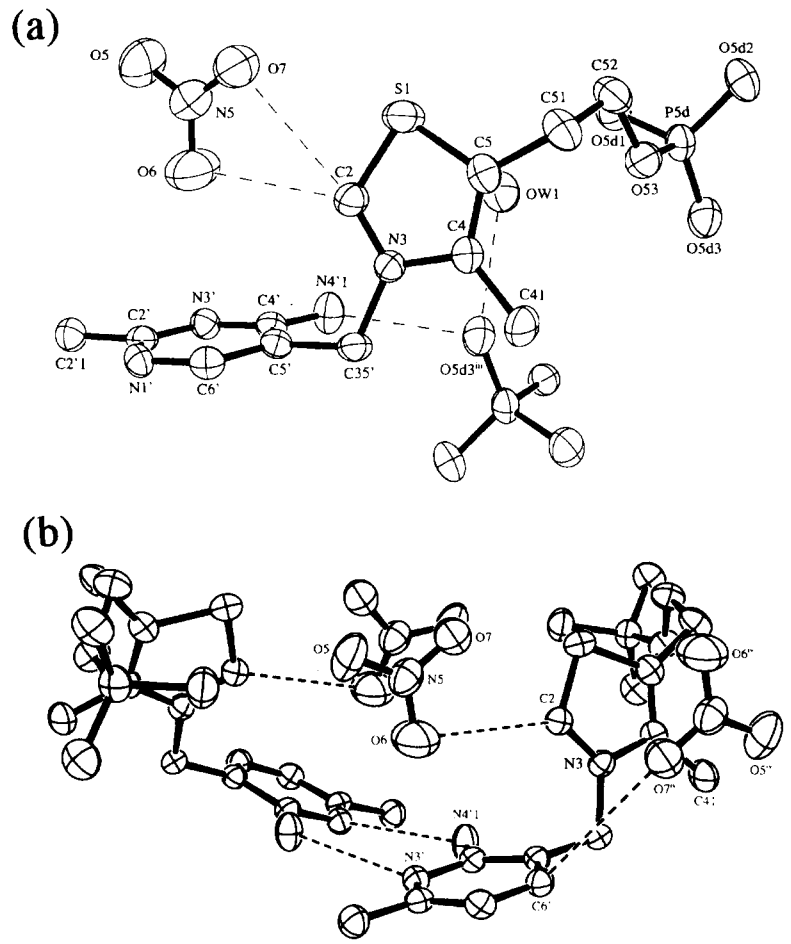


Fig. 2. (a) Molecular structure of $TMP^{+}\cdot NO_3^{-}\cdot 2H_2O$ (**2**), showing a nitrate ion at the 'anion hole I' and a phosphate group at the 'anion hole II'. Disordered OW2 is not shown. (b) The 'head-to-head' dimer formed by a pair of N4′1–H···N3′ hydrogen bonds across a center of symmetry in **2**. The C6′–H···nitrate···thiazolium-ring bridge at the 'anion hole III' is also shown. Broken lines denote hydrogen bonds. Hydrogen atoms are omitted for clarity.

valent cation in **1**—**4**, while a divalent cation in **5**. As shown in Table 2, a common feature of these five compounds is that TMP adopts the usually observed *F* conformation, where the hydrogen atom attached to C2 of the thiazolium ring locates over the pyrimidine ring. The C5 2-phosphatoethyl side chain is folded back towards the thiazolium ring to make a close contact between the electronegative O53 atom and the electropositive[7] S1 atom in **3** and **5** (O53···S1 = 2.883(3) and 2.939(4) Å, respectively), while it is extended away from the S1 atom in **1**, **2**, and **4**, showing the conformational flexibility of the C5 side chain, a common feature observed in thiamine structures:[5] Conformational parameters of the C5 side chain are given in terms of the torsion angles $\varphi 5\alpha$, $\varphi 5\beta$, and $\varphi 5\gamma$[16] in Table 2.

Host–Guest Interactions. The hydrogen bonds and close contacts in **1**—**5** are given in Tables 3, 4, 5, 6, and 7, respectively. Figure 1a shows the interactions between a TMP molecule and anion guests in **1**. A chloride ion is held by a TMP molecule through an N4′1–H···Cl^{-} hydrogen bond (N4′1···Cl = 3.151(2) Å) and a Cl^{-}···thiazolium-ring close contact (the closest contact of 3.529(2) Å with C4), that is, it locates at the 'anion hole II', where an electrostatic force of attraction would occur between the anion and

Table 3. Hydrogen Bonds and Other Short Contacts in **1**[a)]

Hydrogen bonds Donor-H	Acceptor	D···A/Å	H···A/Å	D–H···A/°
C2–H2	O5d1^{i}	3.172(2)	2.27	163
N1′–H1′	Cl^{ii}	3.111(2)	2.29	158
N4′1–H4′1	OW1	2.831(2)	1.99	164
N4′1–H4′2	Cl	3.151(2)	2.35	156
C6′–H6′	O5d3^{iii}	3.177(2)	2.35	147
O5d1–H5d1[b)]	O5d2^{iii}	2.532(2)	1.66	174
O5d2–H5d2[b)]	O5d1^{iii}	2.532(2)	1.50	171
OW1–HW1a	OW2^{i}	2.808(2)	1.98	176
OW1–HW1b	OW2^{iv}	2.882(3)	2.03	175
OW2–HW2a	Cl	3.148(2)	2.22	176
OW2–HW2b	O5d3^{v}	2.663(2)	1.77	169

Other short contacts/Å					
S1	O5d3^{i}	2.938(2)	C4	O5d2^{iii}	3.497(2)
N3	Cl	3.611(2)	C4′	O5d1^{i}	3.658(2)
N3	O5d3^{iii}	3.540(2)	C5′	O5d1^{i}	3.666(2)
C4	Cl	3.529(2)	C6′	O5d1^{i}	3.691(2)

a) Symmetry code: (none) x, y, z; (i) $x, y, z-1$; (ii) $1+x, y, z$; (iii) $1-x, -y, 2-z$; (iv) $-x, 1-y, 1-z$; (v) $-x, -y, 2-z$;
b) Disordered hydrogen atom with the occupancy factor of 0.5.

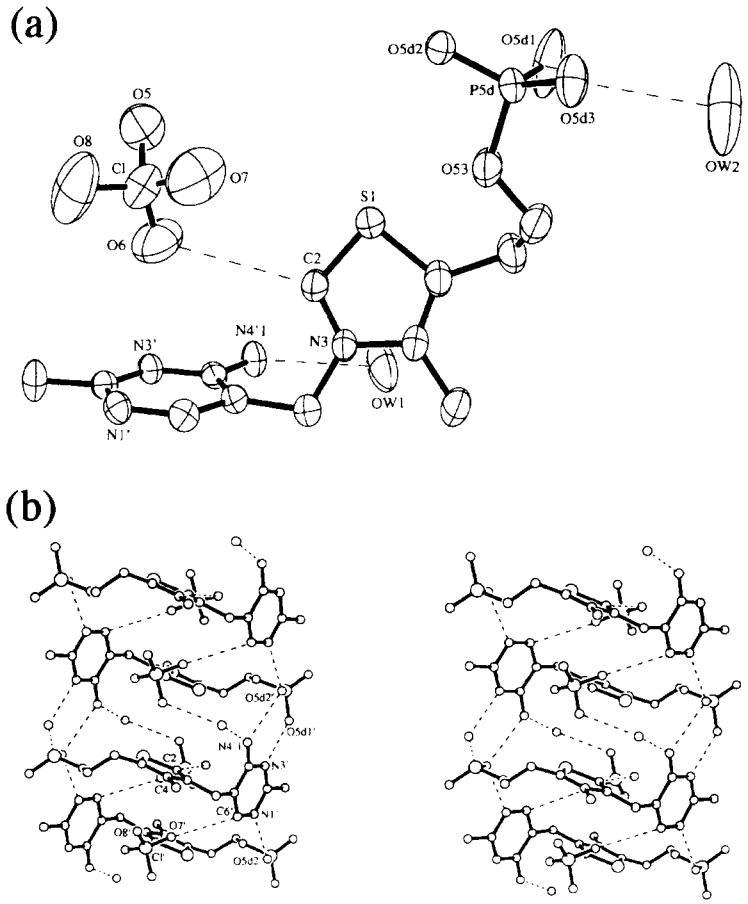


Fig. 3. (a) Molecular structure of $TMP^{+}\cdot ClO_4^{-}\cdot 2H_2O$ (**3**), showing the 'anion holes I and II' occupied by a perchlorate ion and a water molecule, respectively. (b) Stereoscopic view of the molecular column in **3**. The C6′–H···perchlorate···thiazolium-ring bridge at the 'anion hole III' is also shown. Note the formation of two kinds of hydrogen-bonded cyclic dimers in the 'head-to-tail' fashion, one through an N1′–H···O5d2 hydrogen bond, and the other through N4′1–H···O5d2 and O5d1–H···N3′ hydrogen bonds. Broken lines denote hydrogen bonds. Hydrogen atoms are omitted for clarity.

Table 4. Hydrogen Bonds and Other Short Contacts in **2**[a)]

Hydrogen bonds Donor-H	Acceptor	D···A/Å	H···A/Å	D–H···A/°
C2–H2[b)]	O6	3.215(5)	2.30	168
C2–H2[b)]	O7	3.061(5)	2.53	117
N1′–H1′	O5d2^{i}	2.638(4)	1.78	175
N4′1–H4′1	N3′^{ii}	2.982(4)	2.15	164
N4′1–H4′2	O5d3^{iii}	2.771(4)	1.94	162
C6′–H6′	O7^{iv}	3.393(5)	2.84	119
O5d1–H5d1	OW1	2.564(4)	1.61	174
OW1–HW1a	O5d3^{iii}	2.793(4)	1.92	161
OW1–HW1b	O5^{ii}	2.853(5)	1.92	161
Other short contacts/Å				
S1	O5^{ii}	3.189(4)	C4	O5d3^{iii} 3.489(5)
S1	O7	3.128(3)	C2′	O6 3.151(5)
C2	O7^{iv}	3.173(5)	N3′	O6 2.960(5)
N3	O5d3^{iii}	3.264(4)	C4′	O6 3.131(5)
N3	O7^{iv}	3.042(5)	C5′	O6 3.493(5)

a) Symmetry code: (none) x, y, z; (i) $x-0.5, y-0.5, z$; (ii) $-x, y, 0.5-z$; (iii) $0.5-x, 0.5-y, 1-z$; (iv) $-x, 1-y, 1-z$.
b) Bifurcated hydrogen bond.

the positively charged thiazolium moiety due to the quaternary nitrogen N(3).[17] The phosphate group of the neighboring TMP molecule occupies the 'anion hole I', and thus the O5d1 forms a hydrogen bond with C2–H (C2···O5d1 = 3.172(2) Å) and, interestingly in this case, O5d3 makes an electrostatic close contact with S1 (2.938(2) Å), but the contact with the pyrimidine ring is loose (the closest distance of 3.658(2) Å with C4′). Loose contact with the pyrimidine ring has also been observed in (H–thiamine)(thiamine)$[Hg_2I_7]\cdot 2H_2O$[18] and $[Mn(thiamine)Cl_2(H_2O)]_2(thiamine)_2Cl_4\cdot 2H_2O$,[19] possibly due to a crystal-packing influence.

Figure 2a depicts interactions between a TMP molecule and anion guests in **2**. A nitrate ion forms a bifurcated hydrogen bond with C2–H of the thiazolium moiety through O6 (3.215(5) Å) and O7 (3.061(5) Å), and O7 at the same time makes a close contact with S1 (3.128(3) Å), and in addition this nitrate ion locates over the pyrimidinium ring (the closest contact of 3.131(5) Å with C4′), thus occupying the 'anion hole I', where the anion would make an electrostatic interaction with the positively charged pyrimidinium mioety due to the protonation at the nitrogen N(1′).[17] A phosphate group of the neighboring TMP molecule is at the 'anion hole II', where O5d3 participates in N4′1–H···O5d3···thiazolium-ring inter-

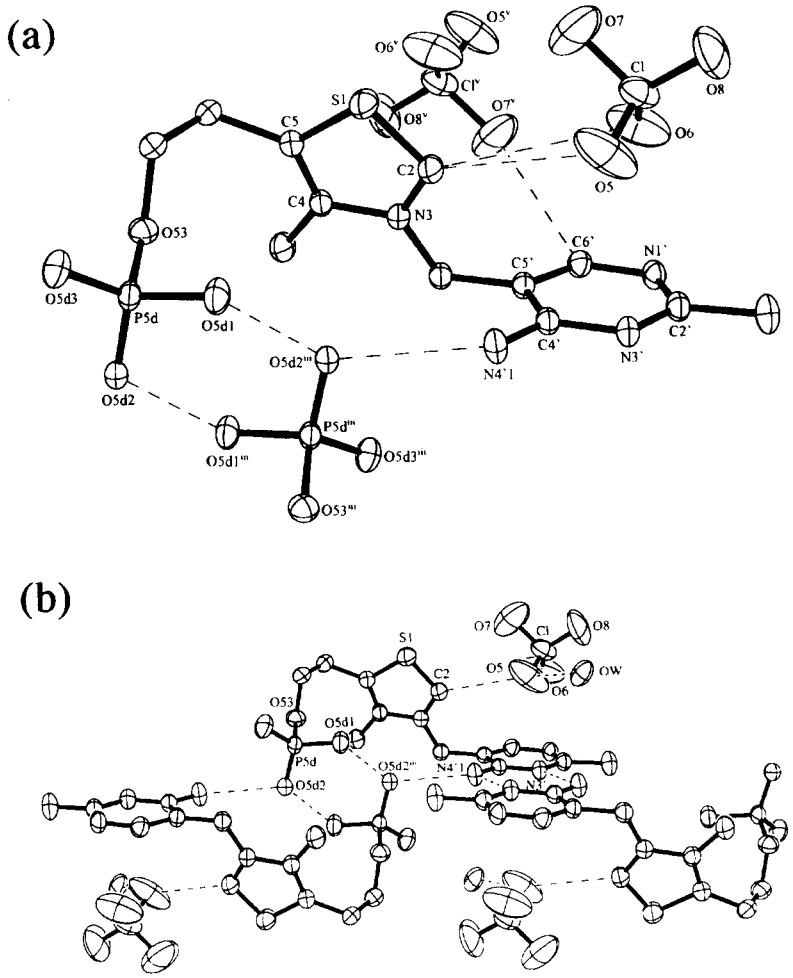


Fig. 4. (a) Molecular structure of $TMP^+ \cdot ClO_4^- \cdot H_2O$ (**4**), showing the 'anion holes I and II' occupied by a perchlorate ion and the phosphate group of a neighboring TMP molecule, respectively. The C6′–H···perchlorate···thiazolium-ring bridge at the 'anion hole III' is also shown. (b) Molecular chain linked in the 'head-to-head' and 'tail-to-tail' fashions in **4**. Broken lines denote hydrogen bonds. Hydrogen atoms are omitted for clarity.

action (N4′1···O5d3 = 2.771(4) and O5d3···N3 = 3.264(4) Å).

As shown in Figs. 3a and 4a, a TMP molecule captures a perchlorate ion at the 'anion hole I', by forming a C2–H···ClO_4^-···pyrimidinium-ring bridge in both **3** and **4** (C2···O6 = 3.257(6) and O6···N3′ = 3.159(5) Å in **3**; bifurcated hydrogen bond of C2···O5 = 3.45(1) and C2···O6 = 3.521(9) Å, and O6···N1′ = 3.068(6) Å in **4**). A water molecule in **3** (Fig. 3a) or a phosphate group of the neighboring molecule in **4** (Fig. 4a) acts as the second bridge between N4′1 and the thiazolium ring at the 'anion hole II' (N4′1···OW1 = 2.800(4) and OW1···N3 = 3.252(4) Å in **3**; N4′···O5d2 = 2.756(3) and O5d2···N3 = 3.149(3) Å in **4**). The involvement of a water molecule in the 'anion hole II' has often been observed in hydrated thiamine structures with the *F*-form.[20,21]

Figure 5a shows that the 'anion holes I and II' are occupied by two crystallographically independent $CF_3SO_3^-$ ions in **5**, through C2–H···O10···pyrimidinium-ring and N4′1–H···O7···thiazolium-ring interactions, respectively (C2···O10 = 3.120(8) and O10···C4′ = 2.954(7) Å; N4′1···O7 = 2.913(7) and O7···N3 = 3.033(6) Å).

Besides the two types of anion-bridges described above, we notice here an additional anion-bridging interaction of the form C6′–H···anion···thiazolium-ring; we call this bridge the 'anion-bridge III' and this location as the 'anion hole III', where the anion would make an electrostatic interaction with the electropositive thiazolium moiety.[17] In **1**, for example, O5d3 of the neighboring phosphate group accepts a hydrogen bond from C6′–H (3.177(2) Å) and, at the same time, O5d3 and O5d2 contact closely with the thiazolium ring of the same molecule (O5d3···N3 = 3.540(2) and O5d2···C4 = 3.497(2) Å; see also Fig. 1b). This anion-bridge forms through O7 in **2** (C6′···O7 = 3.393(5) and O7···N3 = 3.042(5) Å; Fig. 2b), O7–Cl–O8 in **3** (C6′···O7 = 3.241(6) and O7···C2 = 3.252(7) and O8···C4 = 3.253(7) Å; Fig. 3b), O7–Cl–O6 in **4** (C6′···O7 = 3.139(6) and O7···N3 = 3.427(9) and O6···C2 = 3.178(7) Å; Fig. 4a), and O5d3 in **5** (C6′···O5d3 = 3.251(6) and O5d3···C2 = 3.163(7) Å; Fig. 5b). The H···O distances in these C6′–H···O contacts (2.35, 2.84, 2.70, 2.45, and 2.64 Å for **1**—**5**, respectively), are close to or shorter than the sum of the van der Waals

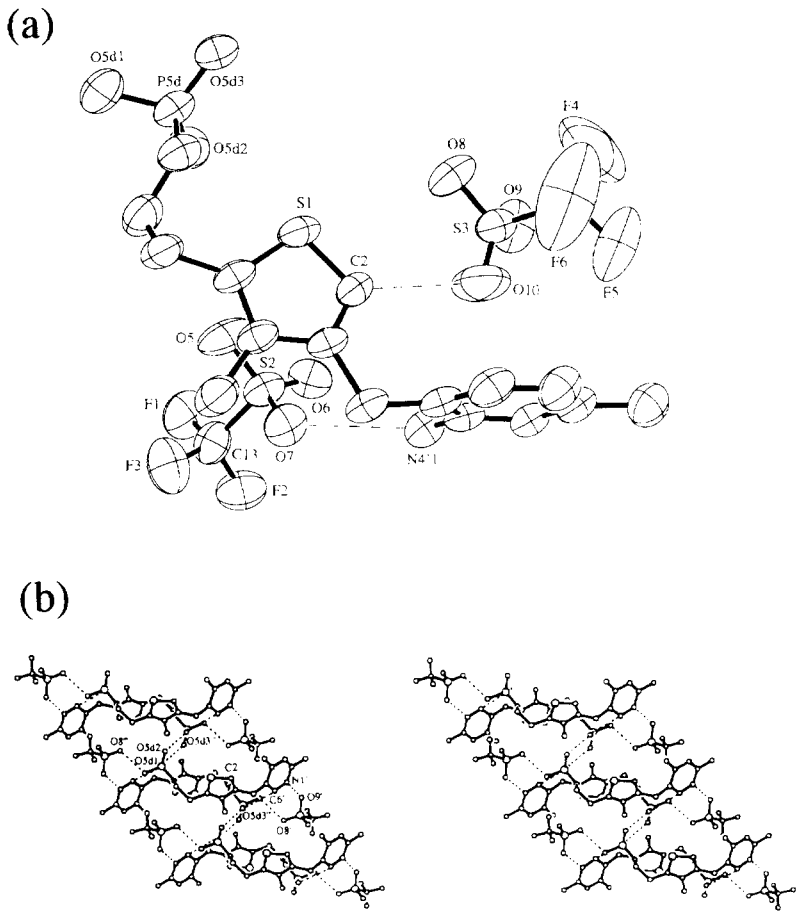


Fig. 5. (a) Molecular structure of $TMP^{2+}\cdot 2CF_3SO_3^-$ (**5**), showing the 'anion holes I and II' occupied by $CF_3SO_3^-$ ions. (b) Stereoscopic view of the molecular column in **5**. The C6′–H···phosphate···thiazolium-ring bridge at the 'anion hole III' is also shown. Note the formation of hydrogen-bonded macrocyclic unit $[TMP{-}CF_3SO_3^-{-}]_2$ across a center of symmetry. Broken lines denote hydrogen bonds. Hydrogen atoms are omitted for clarity.

Table 5. Hydrogen Bonds and Other Short Contacts in **3**[a)]

Hydrogen bonds Donor-H	Acceptor	D···A/Å	H···A/Å	D–H···A/°
C2–H2	O6	3.257(6)	2.34	168
N1′–H1′	O5d2^{i}	2.708(3)	1.86	167
N4′1–H4′1	O5d2^{ii}	2.999(3)	2.14	176
N4′1–H4′2	OW1	2.800(4)	1.98	159
C6′–H6′	O7^{i}	3.241(6)	2.70	118
O5d1–H5d1	N3′^{ii}	2.687(4)	1.73	169
OW1–HW1a	OW2^{iii}	2.733(4)	1.80	160
OW1–HW1b	O5^{ii}	2.809(5)	1.81	174
OW2–HW2a	O5d3^{iv}	2.719(4)	1.75	164
OW2–HW2b	O5d3	2.805(4)	1.94	151

Other short contacts/Å					
S1	O53	2.883(3)	C4	O8^{i}	3.253(7)
S1	O8^{i}	3.380(5)	C5	C5^{ii}	3.081(5)
C2	O7^{i}	3.252(7)	C5	O8^{i}	3.279(6)
C2	O8^{i}	3.310(7)	N1′	O6	0.352(6)
N3	OW1	3.352(4)	C2′	O6	3.191(5)
N3	O8^{i}	3.270(8)	N3′	O6	3.159(5)
C4	OW1	3.396(5)	C4′	O6	3.309(5)
C4	O5^{ii}	3.373(5)	C5′	O6	3.495(5)

a) Symmetry code: (none) x, y, z; (i) $-x, -y, 1-z$; (ii) $-x, -y, -z$; (iii) $1-x, -y, z$; (iv) $1-x, 1-y, 1-z$.

Table 6. Hydrogen Bonds and Other Short Contacts in **4**[a)]

Hydrogen bonds Donor-H	Acceptor	D···A/Å	H···A/Å	D–H···A/°
C2–H2[b)]	O5	3.446(11)	2.63	147
C2–H2[b)]	O6	3.521(9)	2.66	154
N1′–H1′	OW^{i}	2.633(3)	1.77	176
N4′1–H4′1	N3′^{ii}	3.012(4)	2.16	171
N4′1–H4′2	O5d2^{iii}	2.756(3)	1.93	161
C6′–H6′	O7^{v}	3.139(6)	2.45	131
O5d1–H5d1	O5d2^{iii}	2.583(3)	1.77	172
OW–HWa	O5d3^{iv}	2.596(3)	1.75	164
OW–HWb	O5	2.882(9)	2.01	153

Other short contacts/Å					
S1	O6^{v}	3.369(5)	N1′	O6	3.068(6)
C2	O6^{v}	3.178(7)	C2′	O6	3.173(7)
N3	O5d2^{iii}	3.149(3)	N3′	O5	3.379(11)
N3	O6^{v}	3.356(6)	N3′	O6	3.465(7)
N3	O7^{v}	3.427(9)	C4′	O5	3.490(10)
C4	O5d2^{iii}	3.250(4)	C6′	O6	3.229(6)

a) Symmetry code: (none) x, y, z; (i) $x, y, z-1$; (ii) $1-x, 1-y, 1-z$; (iii) $1-x, -y, 1-z$; (iv) $x, 1+y, z$; (v) $-x, 1-y, -z$.
b) Bifurcated hydrogen bond.

Table 7. Hydrogen Bonds and Other Short Contacts in **5**[a)]

Hydrogen bonds Donor-H	Acceptor	D···A/Å	H···A/Å	D–H···A/°
C2–H2	O10	3.120(8)	2.24	157
N1′–H1′	O9^{i}	2.818(7)	1.96	178
N4′1–H4′1	O6^{ii}	2.981(6)	2.13	171
N4′1–H4′2	O7	2.913(7)	2.06	170
C6′–H6′	O5d3^{iv}	3.251(6)	2.64	124
O5d1–H5d1	O8^{iii}	2.664(6)	1.67	168
O5d2–H5d2	O5d3^{iii}	2.528(6)	1.31	168

Other short contacts/Å					
S1	O53	2.939(4)	C5	O5	3.314(6)
C2	O5d3^{iv}	3.163(7)	C2′	O10	3.491(9)
N3	O7	3.033(6)	N3′	O10	3.071(7)
N3	O5d3^{iv}	3.226(6)	C4′	O10	2.954(7)
C4	O7	3.207(6)	C5′	O10	3.428(8)

a) Symmetry code: (none) x, y, z; (i) $x, y, z-1$; (ii) $1-x, -y, 1-z$; (iii) $1-x, 1-y, 2-z$; (iv) $1-x, 1-y, 1-z$.

radii (2.72 Å[22]), indicating an attractive interaction between C6′–H and anion.

Correlation of the Anion Complexation with the Molecular Conformations. There exist three main conformations (*F*, *S*, and *V*) for thiamine and its derivatives. As far as thiamine molecule, itself, is concerned, energy calculations based on molecular mechanics have shown[23] that the energy difference between the three conformers is small, suggesting that the molecular conformation is susceptible to intermolecular forces. Indeed, as noted in introductory discussion, the conformation of thiamine is closely related to its interactions with co-existing anions or anionic groups. There seems a correlation between the conformation and the size of anion: Thiamine in the *F*-form is able to accommodate a wide range of anion guests to be bound at the 'anion holes I and/or II', from small inorganic anions such as Cl^-,[16,19,24] Br^-,[25] I^-,[26] SCN^-,[20,27] NO_3^-,[28] BF_4^-,[20] ClO_4^-,[10,29] phosphate,[9,30] sulfonate,[31] PF_6^-,[10] to large metallate anions like $CuCl_4^{2-}$,[32] $PtCl_4^{2-}$,[33] $PtCl_6^{2-}$,[6] $Pt(SCN)_4^{2-}$,[21] $Pt(SCN)_6^{2-}$,[21] $[SnMe_2(H_2O)Cl_3]^-$,[34] and $[Hg_2I_7]^{3-}$,[18] while thiamine in the *S*-form accepts large anions, like $CdCl_4^{2-}$,[35] $CoCl_4^{2-}$,[36] and $HgCl_4^{2-}$,[37] in the 'anion hole II'. The present work shows that there exists another anion-bridge at the 'anion hole III', that is, a C6′–H···anion···thiazolium-ring bridge ('anion-bridge III'). This finding led us to survey whether such an interaction also exists in the crystal structures of thiamine and thiamine derivatives. As Table S13 (supplementary material)[14] shows, the 'anion-bridge III' indeed occurs, though less frequently compared to the 'anion-bridges I and II', not only for *F*-form thiamine[6,10,18,20,24a,25a,28c,28d,29,32–34] but also for *S*-form thiamine.[35,36] Thus the 'anion-bridge III' is an important structural feature that affects the conformation of thiamine. It now appears that the *F*-form accompanies the 'anion holes I, II, and III', while the *S*-form does the 'anion holes II and III', suggesting that more anion interactions favor the *F*-form. Thus, it can be expected that TMP prefers the *F*-form, since the phosphate group of TMP acts as an additional anion, and thus favors to form more hydrogen bonds and electrostatic interactions with TMP itself. Indeed, among the eight known TMP structures, where each TMP molecule adopts the *F*-form, majority of which (all five TMP structures reported here and $TMP^+ \cdot PF_6^-$[10]) contain the 'anion holes I, II, and III', and in minor cases ($TMP^+ \cdot HPO_4^-$[8] and $[Rh_2(acetato)_4(TMP)_2]$[9]) the 'anion hole III' is missing. On the other hand, the C2-substituted TMP molecule in $HBTMP^+ \cdot Cl^-$[11] and $[Hg(HBTMP)_2Cl_2]$[11] is forced to take the *S*-form due to the steric hindrance between the C2-substituent and the pyrimidine moiety, as observed in all of the known C2-substituted thiamine derivatives.[5]

None of these 'anion-bridges I, II, and III' has been observed in the crystal structures of thiamine-dependent enzymes, such as transketolase,[38] pyruvate oxidase,[39] and pyruvate decarboxylase,[40] since the thiamine diphosphate coenzyme takes the *V*-form in these enzymes. However, because of a widespread occurrence of these host–guest-like interactions for thiamine that adopts the *F*-form, we can expect that anionic or electronegative groups of amino acid residues take part in these interactions with thiamine in the *F*-form, for example, in thiamine-binding proteins.[41]

Thiamine as a Building Block of Supramolecules. Thiamine acts as not only a naturally occurring cationic host that forms host–guest-like complexes with anions, but also a building block of higher-ordered structures, supramolecules.[21] This is also the case for the present TMP structures. As shown in Fig. 1b, a dimeric structure is formed through two kinds of intermolecular hydrogen bonds in **1**, one in the 'head-to-tail' fashion through a pair of C6′–H···O5d3 hydrogen bonds and the other in the 'tail-to-tail' fashion through a couple of O5d1–H···O5d2 hydrogen bonds, where 'head' and 'tail' refer to the pyrimidinium ring and the phosphate group, respectively. For thiamine, on the other hand, though its 2-hydroxyethyl tail group is able to act, in principle, as both hydrogen-bonding donor and acceptor, self-association of the hydroxy groups has never been observed. Thus, the 'tail-to-tail' arrangement is peculiar to TMP.

In **2**, as Fig. 2b shows, a 'head-to-head' dimer is formed by a pair of interbase N4′1–H···N3′ hydrogen bonds. This type of structure is usually observed in thiamine structures, for example, in thiamine·NO_3^-.[28c]

In **3**, as shown in Fig. 3b, each TMP molecule is linked to two neighbors to form two kinds of 'head-to-tail' cyclic dimer structures, one through a pair of N1′–H···O5d2 hydrogen bonds, and the other through a pair of double N4′1–H···O5d2 and O5d1–H···N3′ hydrogen bonds, thus generating an infinite molecular column. Two ClO_4^- ions are sandwiched between two adjacent dimers in the column. The latter type of 'head-to-tail' cyclic dimer is also formed in $TMP^+ \cdot PF_6^-$.[10] For thiamine, the cyclic 'head-to-tail' dimer is found in H–thiamine·$2PF_6^-$,[10] thiamine·SCN^-,[20] thiamine·$SCN^- \cdot H_2O$,[20] H–thiamine·$PtCl_4^{2-}$,[33] H–thiamine·$PtCl_6^{2-}$,[6] and (H–thiamine)$_2$·$PtCl_6^{2-} \cdot 2Cl^-$,[6] through a hydrogen bond between N1′ and O53.

In **4**, as Fig. 4b shows, each TMP molecule is linked

to two others, to one molecule in a 'head-to-head' fashion through a pair of N4′1–H···N3′ hydrogen bonds and to the other in both 'tail-to-tail' fashion through a couple of O5d1–H···O5d2 hydrogen bonds and 'head-to-tail' one through an N4′1–H···O5d2 hydrogen bond, thus forming a one-dimensional molecular chain structure. Interestingly, the chain structure with the same molecular architecture forms in $TMP^{+}\cdot HPO_4^{-}$.[8]

In **5**, as shown in Fig. 5b, a 'head-to-tail' cyclic dimer is formed, but in this case through a pair of C6′–H···O5d3 hydrogen bonds, and at the same time, two $CF_3SO_3^{-}$ ions bridge between two TMP molecules through hydrogen bonds N1′–H···O9 at the 'head' and O8···H–O5d1 at the 'tail', thus creating an anion-bridged 'head-to-tail' macrocycle, TMP–anion–TMP–anion. This dimer unit is further linked to two neighboring dimers, in a 'tail-to-tail' manner through a pair of strong O5d2–H···O5d3 hydrogen bonds, resulting in the formation of a molecular column. For thiamine, the anion-bridged 'head-to-tail' macrocycle is observed in H–thiamine·$Pt(SCN)_6^{2-}$.[21]

In summary, thiamines self-associate in 'head-to-head' or 'head-to-tail' manners to frequently give well-defined higher-ordered structures,[21] while an additional 'tail-to-tail' self-assembly occurs for TMP; thus, the TMP–anion system is of interest in that novel and more complex supramolecular aggregates occur, possibly depending on the nature of the anion.

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