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# Interaction of thiamine with anions in the triclinic form of thiamine iodide: 3-[(4-amino-2-methylpyrimidin-5-yl)-methyl]-5-(2-hydroxyethyl)-4-methyl-1,3-thiazol-3-ium iodide 1.25-hydrate

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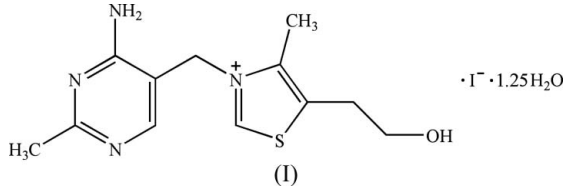
The asymmetric unit of the title compound, $C_{12}H_{17}N_4OS^+\cdot I^-\cdot 1.25H_2O$, contains two crystallographically independent molecules. Both formula units assume the usual *F* conformation and have the hydroxyethyl group disordered over two sites, each with half occupation. Two thiamine cations are linked by hydrogen bonds into a cyclic dimer. These dimers are further connected by base-pairing hydrogen bonds into a chain along [010]. The stacked dimers form channels, which are occupied by iodide anions. The cations and anions are associated by N—H···I hydrogen bonds, C—H···I interactions and I···thiazolium ring close contacts. The interactions between thiamine and the iodide anions are similar to those observed in monoclinic thiamine iodide 1.5-hydrate [Hu & Zhang (1993). *J. Inclusion Phenom. Mol. Recognit. Chem.* **16**, 273–281].

## Comment

Thiamine (vitamin $B_1$) in the form of pyrophosphate is a co-enzyme for a number of enzyme systems catalysing the transfer of acyl or aldehyde groups and the decarboxylation of $\alpha$-keto acids (Krampitz, 1969). The catalytic processes involve the recognition and reaction of a substrate anion such as pyruvate at the C1 site of the thiazolium group (refer to molecule *A* in Fig. 1 for atomic numbering, unless otherwise indicated). Structural studies of thiamine–anion compounds as models of host–guest interactions have revealed two distinct types of interaction between thiamine and anions (Aoki *et al.*, 1993; Cramer *et al.*, 1988). One of these is of the form C1—H···anion···pyrimidine ring, *i.e.* an anion accepts a hydrogen bond from atom C1 of the thiazolium group and makes a close contact with the pyrimidine ring of the same molecule, and the other is of the form N4—H···anion···thiazolium ring, where an anion or an electronegative atom accepts a hydrogen bond from the amine group and forms an electrostatic contact with the thiazolium ring. These two interactions have been defined as type I and type II anion bridges, respectively (Hu *et al.*, 1999). Thiamine interacts with an anionic group near the active C1 position through a type I anion bridge, serving as a model for thiamine–substrate interactions based on the fact that the enzymatic reactions proceed through C1-substituted thiamine intermediates (Breslow, 1958).

The construction of host frameworks which trap anionic or neutral guests through the use of hydrogen-bonding, electrostatic and $\pi$–$\pi$ interactions is one of the goals of organic crystal engineering (Beatty, 2003; Biradha, 2003; Desiraju, 1995; Etter, 1991; Videnova-Adrabińska, 1996). Thiamine, as a naturally occurring cationic host, provides multiple sites that serve as hydrogen-bond donors or acceptors to form various hydrogen-bonded supramolecular arrays on which anion guests are adsorbed (Aoki *et al.*, 1993; Hu *et al.*, 2001*b*). For example, one-dimensional chains in the $ClO_4^-$ (Aoki *et al.*, 1988; Kozioł *et al.*, 1987) and $BF_4^-$ salts (Aoki *et al.*, 1990; Hu *et al.*, 2001*a*) of thiamine, a triple helical chain in the $SCN^-$ salt (Hu & Zhang, 1993*a*) and a two-dimensional network in the tetraphenylborate salt (Hu *et al.*, 2005) have all been observed to date. In this regard, we are interested in how anions interact with supramolecular assemblies of thiamine. Generally, thiamine–anion compounds can be isolated in two forms, where the thiamine is present in the protonated form (Hth), with a proton on the pyrimidine N2 atom, or the unprotonated form (th). The structures of a protonated compound, $(Hth)I_2$ (Lee & Richardson, 1976), and an unprotonated compound, $(th)I\cdot 1.5H_2O$, (II), in the monoclinic form (Hu & Zhang, 1993*b*), have been reported. We report here an unprotonated triclinic form, $(th)I\cdot 1.25H_2O$, (I).




(I)

The asymmetric unit of (I) contains two crystallographically independent thiamine cations, denoted *A* (containing atom S1) and *B* (containing atom S2) (Fig. 1), two iodide ions and 2.5 water molecules distributed over one fully and three half-occupied sites. The thiamine cations are monovalent with an unprotonated pyrimidine ring (atoms N2 of cation *A* and N6 of cation *B* are unprotonated). The dimensions of the pyrimidine groups are in agreement with those found in the unprotonated monoclinic compound, (II). The C8—N2—C11 and C20—N6—C23 bond angles are 115.9 (5) and 114.9 (6)° in (I), comparable with values of 115.4 (7) and 115.9 (8)° in (II), but smaller than that of 119.0° in protonated $(Hth)I_2$. Thiamine cations *A* and *B* both adopt an *F* conformation in terms of the torsion angles: $\varphi_T = -4.4$ (8) and $\varphi_P = -79.6$ (7)° for cation *A*, and −6.6 (8) and −80.1 (7)°, respectively, for cation

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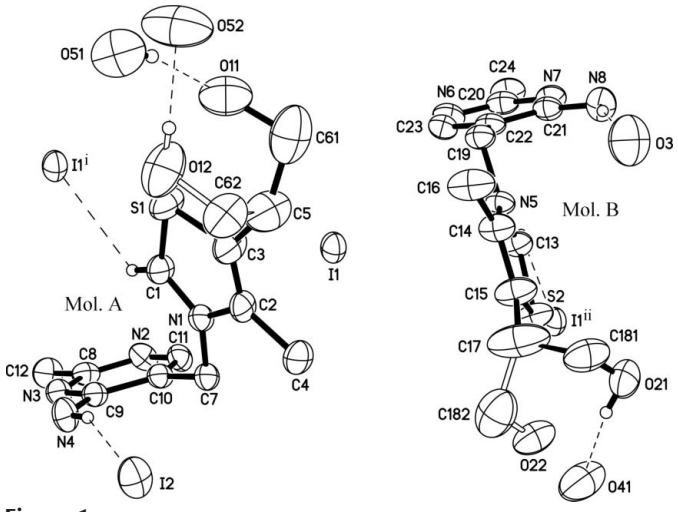


**Figure 1**
The molecular structure of (I), showing the atom-numbering scheme. The disordered hydroxyethyl groups are distinguished by solid and open bonds. Displacement ellipsoids are drawn at the 30% probability level. H atoms have been omitted for clarity, except those involved in hydrogen bonds. Dashed lines denote hydrogen bonds and C—H···I interactions. [Symmetry codes: (i) $1-x, 1-y, 1-z$; (ii) $2-x, 1-y, 1-z$.]

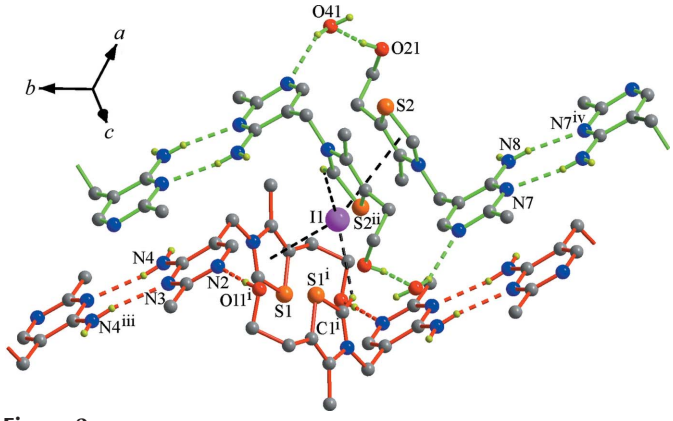


**Figure 2**
Hydrogen-bonded chains formed by cyclic dimers, which are connected through the base-pairing (dashed lines). Most H atoms have been omitted for clarity. [Symmetry codes: (i) $1-x, 1-y, 1-z$; (ii) $2-x, 1-y, 1-z$; (iii) $1-x, 2-y, 1-z$; (iv) $2-x, -y, 1-z$.]

*B* [$\varphi_T$ = C10—C7—N1—C1 (or C22—C19—N5—C13) $\simeq 0°$ and $\varphi_P$ = N1—C7—C10—C9 (or N5—C19—C22—C21) $\simeq \pm 90°$ for the *F* conformation; Blank *et al.*, 1976].

The hydroxyethyl side chains of both *A* and *B* are disordered, each over two half-occupied positions, and fold back towards the thiazolium groups to make a close contact between the S and hydroxy O atoms (values for cation *B* are given in square brackets): S1···O11[O12] = 2.893 (13) Å [3.075 (12) Å] and S2···O21[O22] = 3.142 (15) Å [2.923 (15) Å]. This close contact is a common feature in thiamine structures.

A water molecule (O3) acts as a type II anion bridge to link the two aromatic rings of *B* by accepting a hydrogen bond from atom N8 (Table 1) and making a close contact with the thiazolium ring [closest distance O3···N5 = 3.038 (11) Å]. This type of water bridge has also been observed in (II) and in some hydrated thiamine compounds (Aoki *et al.*, 1988, 1990; Pletcher *et al.*, 1972), where the water O atom takes part in an electrostatic interaction with the positively charged thiazolium ring, in most cases the closest contact being with the quarternary N atom. Atom I2 accepts a hydrogen bond from atom N4 of *A* but is involved in a quite loose contact with the thiazolium ring, where the closest distance between atom I2 and the thiazolium ring is I2···C2 of 4.039 (8) Å. In a rigorous sense, the type II anion bridge does not exist for *A* in (I). This is also the case with monoclinic (II) [closest distance I···C2 = 4.083 (7) Å]. In contrast, the type II anion bridge is active in (Hth)$I_2$ (Lee & Richardson, 1976).

It is noteworthy that the I···thiazolium distance in protonated Hth·$I_2$ [closest distance I···N1 = 3.68 Å] is evidently shorter than those in (I) and (II). A similar situation has also been observed in unprotonated (th)Br·1.5$H_2O$ (Hu & Zhang, 1992) and protonated (Hth)$Br_2$·0.5$H_2O$ (Thompson & Richardson, 1977) (Table 2). As to the type I anion bridge, atom I1 simultaneously forms two C—H···I interactions with C1—H1 of cation *A* at $(1-x, 1-y, 1-z)$ and C13—H13 of cation *B* at $(2-x, 1-y, 1-z)$ (Table 1), but the distances between I1 and the pyrimidine rings are too long to be considered significant interactions [closest distances I1···$N3^i$ = 4.885 (5) Å for *A* and I1···$C21^{ii}$ = 5.050 (6) Å for *B*; symmetry codes: (i) $1-x, 1-y, 1-z$; (ii) $2-x, 1-y, 1-z$]. Thus, a type I anion bridge does not form in (I). Interestingly, a type I anion bridge is present in the protonated Cl, Br and I salts, but is also absent in the unprotonated Cl and Br salts and in (II), as indicated by the long anion–pyrimidine distances listed in Table 2. However, an inspection of the other thiamine salts with various inorganic anions, including $NO_3^-$ (Ishida *et al.*, 1984; Yang *et al.*, 1987), $ClO_4^-$ (Aoki *et al.*, 1988; Kozioł *et al.*, 1987), $BF_4^-$ (Aoki *et al.*, 1990; Hu *et al.*, 2001*a*) and $PF_6^-$ (Aoki *et al.*, 1988), shows the common existence of type I anion bridges in these compounds, regardless of whether the thiamine has a protonated or unprotonated pyrimidine ring.

The crystal packing in (I) is dominated by intermolecular hydrogen bonds involving thiamine and water molecules (Table 1). For the first part of the disorder (atoms C61/O11/C181/O21/O41/O51), a cyclic dimeric unit is constructed by self-association of cation *A* and its centrosymmetric partner through O11—H···$N2^i$ hydrogen bonds (Fig. 2). Cations *B* also form a centrosymmetric cyclic dimer through the intervention of water molecules *via* O21—H···O41—H···$N6^{ii}$ hydrogen bonds. These cyclic dimers are further linked by a self-complementary pyrimidine–pyrimidine interaction involving a pair of N4—H···$N3^{iii}$ hydrogen bonds for *A* (or N8—H···$N7^{iv}$ for *B*), which is a supramolecular synthon frequently observed in thiamine structures [symmetry codes: (iii) $1-x, 2-y, 1-z$; (iv) $2-x, -y, 1-z$]. These base-pairing interactions connect the cyclic dimers into chains extending along [010]. The chains formed by cations *A* and *B*, respectively, are arranged alternately with the cyclic dimers aligned, thus forming a channel along [100] (Fig. 3). This arrangement of the *A* and *B* chains is stabilized by $\pi$–$\pi$ interactions between the pyrimidine rings of cations *A* and *B* at $(x, 1+y, z)$, with a centroid–centroid distance of 3.554 (1) Å, and by O11···H—

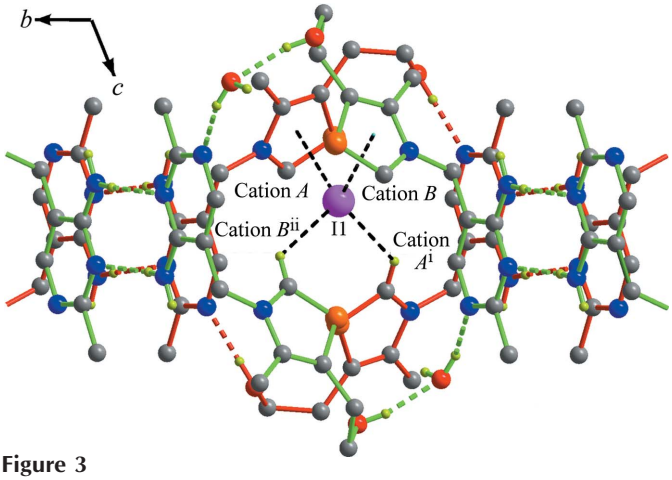


**Figure 3**
A top view (along [100]) of the stacking of the cyclic dimers, showing an iodide ion, surrounded by thiamine cations in a cavity, interacting with four thiazolium groups through C—H···I and I···thiazolium ring interactions (dashed lines). Most H atoms have been omitted for clarity. [Symmetry codes: (i) $1-x, 1-y, 1-z$; (ii) $2-x, 1-y, 1-z$.]

O51—H···O21$^{vii}$ hydrogen bonds [symmetry code: (vii) $x-1, y, z$].

The thiamine cations are self-associated into a similar chain structure for the second disorder group (atoms C62/O12/C182/O22/O52). One difference from the first disorder group is that now cyclic dimer *A* is mediated by water molecules (O12—H···O52—H···N2$^{i}$), while cyclic dimer *B* is formed directly by hydrogen bonds between the hydroxy group and a pyrimidine N atom (O22—H···N6$^{ii}$). It is interesting to note that the channel formed by the stacking of the cyclic dimers serves as an anion tunnel, with I atoms arranged through it. As shown in Fig. 3, atom I1, lying in a cavity surrounded by four thiazolium rings, is involved in two C—H···I interactions with two thiazolium groups, as mentioned above, and two electrostatic interactions with the other two thiazolium groups, with I1 located over the ring planes. The distances between I1 and the centroids of the thiazolium rings are 3.7759 (6) and 3.8252 (6) Å. This binding mode of an iodide anion to thiamine cations is similar to that found in monoclinic (II). A major difference is that the cyclic dimer consists of cations *A* and *B* in (II) and thus is noncentrosymmetric.

In summary, although two types of anion bridges have frequently been observed in thiamine compounds, halide salts do not follow this rule. A similar hydrogen-bonded network of thiamine cations, which captures iodide anions in a unique mode, has been observed in both triclinic (I) and monoclinic (II), indicating the robustness of these supramolecular synthons. The results could be helpful for understanding the interactions between thiamine and anions in enzyme systems, and may also provide useful information for developing supramolecular host frameworks that selectively adsorb anionic guests.

## Experimental

Compound (I) was prepared by reacting thiamine nitrate (0.065 g, 0.2 mmol) and zinc iodide (0.064 g, 0.2 mmol) in water (20 ml). The solution was set aside to crystallize at ambient temperature. Colourless crystals of (I) suitable for X-ray analysis were obtained after two weeks and were washed with water and methanol.

### *Crystal data*

$C_{12}H_{17}N_4OS^+\cdot I^-\cdot 1.25H_2O$
$M_r$ = 414.78
Triclinic, $P\overline{1}$
$a$ = 11.9437 (10) Å
$b$ = 12.5913 (12) Å
$c$ = 13.8768 (13) Å
$\alpha$ = 104.900 (1)°
$\beta$ = 100.968 (2)°
$\gamma$ = 115.129 (1)°
$V$ = 1715.6 (3) Å$^3$
$Z$ = 4
Mo $K\alpha$ radiation
$\mu$ = 2.00 mm$^{-1}$
$T$ = 293 K
0.21 × 0.17 × 0.05 mm

### *Data collection*

Bruker APEX CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
$T_{min}$ = 0.679, $T_{max}$ = 0.907
9403 measured reflections
6271 independent reflections
5141 reflections with $I > 2\sigma(I)$
$R_{int}$ = 0.015

### *Refinement*

$R[F^2 > 2\sigma(F^2)]$ = 0.053
$wR(F^2)$ = 0.156
$S$ = 1.09
6271 reflections
418 parameters
8 restraints
H-atom parameters constrained
$\Delta\rho_{max}$ = 1.62 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.98 e Å$^{-3}$

**Table 1**
Hydrogen-bond geometry (Å, °).

| $D$—H···$A$ | $D$—H | H···$A$ | $D$···$A$ | $D$—H···$A$ |
|---|---|---|---|---|
| C1—H1···I1$^{i}$ | 0.93 | 2.98 | 3.643 (6) | 129 |
| C13—H13···I1$^{ii}$ | 0.93 | 3.02 | 3.623 (6) | 124 |
| N4—H4$A$···N3$^{iii}$ | 0.86 | 2.26 | 3.112 (7) | 172 |
| N4—H4$B$···I2 | 0.86 | 2.86 | 3.667 (5) | 158 |
| N8—H8$A$···N7$^{iv}$ | 0.86 | 2.23 | 3.079 (8) | 170 |
| N8—H8$B$···O3 | 0.86 | 1.96 | 2.793 (9) | 164 |
| O11—H1$A$···N2$^{i}$ | 0.85 | 1.81 | 2.665 (15) | 178 |
| O12—H12···O52 | 0.81 | 2.33 | 2.85 (2) | 123 |
| O21—H21···O41 | 0.82 | 1.84 | 2.637 (18) | 165 |
| O22—H22···N6$^{ii}$ | 0.82 | 1.92 | 2.632 (14) | 146 |
| O3—H3$A$···I2$^{v}$ | 0.83 | 2.73 | 3.526 (9) | 161 |
| O3—H3$B$···O51$^{vi}$ | 0.82 | 2.12 | 2.78 (2) | 137 |
| O3—H3$B$···O52$^{vi}$ | 0.82 | 1.88 | 2.59 (2) | 144 |
| O41—H41$A$···N6$^{ii}$ | 0.82 | 2.26 | 2.982 (16) | 148 |
| O51—H51$A$···O11 | 0.80 | 1.96 | 2.73 (3) | 162 |
| O51—H51$B$···O21$^{vii}$ | 0.82 | 2.16 | 2.97 (2) | 172 |
| O52—H52$A$···N2$^{i}$ | 0.82 | 2.14 | 2.957 (16) | 179 |

Symmetry codes: (i) $-x+1, -y+1, -z+1$; (ii) $-x+2, -y+1, -z+1$; (iii) $-x+1, -y+2, -z+1$; (iv) $-x+2, -y, -z+1$; (v) $x, y-1, z$; (vi) $x+1, y, z$; (vii) $x-1, y, z$.

The hydroxyethyl groups of cations *A* and *B* are disordered, each over two positions. Three of the four water sites are also disordered. From the hydrogen-bonding scheme, atoms O41 and O51 belong to the same disorder group as atoms O21 and O11 (referred to as the first disordered part in the *Comment*), while atom O52 is occupied simultaneously with atom O12 in the second disorder group. (We use the term 'disorder group' as defined in the CIF dictionary.) The occupancy factors were initially refined to 0.474 (7) and 0.536 (7) for parts 1 and 2, respectively, and they were fixed at 0.50 in the final refinement. Bond-length restraints were applied to the disordered C—C and C—O bonds of the disordered hydroxyethyl groups [1.54 (1) and 1.45 (1) Å, respectively]. C-bound H atoms were positioned geometrically and refined as riding atoms, with C—H = 0.93

(CH), 0.97 ($CH_2$) or 0.96 Å ($CH_3$) and N—H = 0.86 Å, and with $U_{iso}(H) = 1.2U_{eq}(C,N)$. H atoms of the hydroxy group and water molecules were located from difference Fourier maps and were constrained in the refinements, with $U_{iso}(H) = 1.2U_{eq}(O)$. H atoms on O11, O12, O22 and O51, as well as on C12 and C24, were fixed in the final refinement to avoid short intermolecular H···H distances. The highest residual electron density was found 0.91 Å from I2 and the deepest hole 0.75 Å from I2.

Data collection: *SMART* (Bruker, 2007); cell refinement: *SAINT* (Bruker, 2007); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *SHELXTL* (Sheldrick, 2008) and *DIAMOND* (Brandenburg, 1999); software used to prepare material for publication: *SHELXTL*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FA3240). Services for accessing these data are described at the back of the journal.

**Table 2**
Distances between the anion and the pyrimidine or thiazolium ring in the anion bridges I (C1—H···A···P) and II (N4—H···A···T) (Å).

A refers to the anion, T to an atom in the thiazolium ring and P to an atom in the pyrimidine ring.

| Compound | A | P | A···P | A | T | A···T | Reference |
|---|---|---|---|---|---|---|---|
| (Hth)$Cl_2$·$H_2O$ | Cl | N2 | 3.484 | Cl | C2 | 3.369 | Kraut & Reed (1962) |
| (th)Cl·$H_2O$ | Cl | C9 | 4.414 | O† | N1 | 3.125 | Pletcher *et al.* (1972) |
| (Hth)$Br_2$·0.5$H_2O$ | Br | C8 | 3.601 | Br | C2 | 3.509 | Thompson & Richardson (1977) |
| (th)Br·1.5$H_2O$ | Br | C9 | 4.806 | Br | N1 | 3.991 | Hu & Zhang (1992) |
| (Hth)$I_2$ | I | N2 | 3.857 | I | N1 | 3.683 | Lee & Richardson (1976) |
| (th)I·1.5$H_2O$ | I | C9 | 4.910 | I | C2 | 4.083 | Hu & Zhang (1993*b*) |
| (th)I·1.25$H_2O$ | I1 | N3 | 4.885 (5) | I2 | C2 | 4.039 (8) | This work |
| | I1 | C21 | 5.050 (6) | O3† | N5 | 3.038 (11) | |

† These are water O atoms.

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