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Host–Guest Interactions of Thiamine with Anions. Crystal Structure of Thiamine Iodide Sesquihydrate

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Abstract. The crystal structure of thiamine iodide sesquihydrate has been determined by X-ray diffraction methods as a host–guest model for coenzyme–substrate interactions. The asymmetric unit contains two chemical units. Both the thiamine molecules A and B, which are crystallographically independent, assume the usual *F* conformation and have a disordered hydroxyethyl side chain. An iodide anion (or a water molecule) bridges the pyrimidine and thiazolium rings of molecule A (or B) by forming a hydrogen bond with the amino group and an electrostatic contact with the thiazolium ring to stabilize the molecular conformation. In the crystal the thiamine molecules self-associate to form a pipe-like polymeric structure, in which four thiamine hosts surround an iodide guest and hold it through C(2)–H···I hydrogen bonds and thiazolium···I electrostatic interactions. Crystal data: $C_{12}H_{17}N_4OS^+ \cdot I^- \cdot 1.5\ H_2O$, monoclinic, $P2_1/c$, $a = 12.585(2)$, $b = 25.303(5)$, $c = 12.030(2)$ Å, $\beta = 115.15(1)°$, $V = 3468(1)$ Å^3, $Z = 8$, $D_c = 1.606$ g cm^{-3}, $R = 0.045$ for 3328 observed reflections.

Key words: Thiamine compound, X-ray crystal structure, host–guest interaction, hydrogen bonding.

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1. Introduction

Thiamine (**1**; vitamin B_1), in the form of the pyrophosphate, is a coenzyme for a number of enzymic processes among the most prominent of these being the α-keto acid decarboxylases and transketolases. The reaction intermediate could be a C(2)-substituted derivative of thiamine pyrophosphate [1], according to the observation that thiazolium salts easily lose a proton at C(2). The interactions of thiamine with anions have recently received particular attention because the binding of guest anions by host thiamine could have mechanistic implications [2, 3]. In the thiamine–anion compounds there are two types of interactions between the host that adopts the common *F* conformation and the guests [4]. One of them has the form

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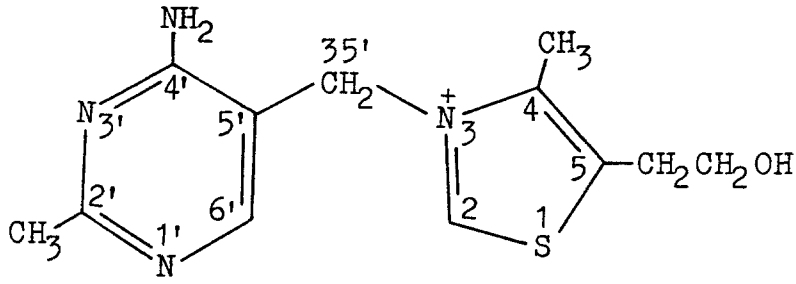

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of an N(41′)–H···X···thiazolium ring (X = anion or electronegative atom), that is, the anion X forms a hydrogen bond with N(41′)H and an electrostatic interaction with the thiazolium ring of the same thiamine, and the other has the form of a C(2)–H···X···pyrimidine ring. These two interactions of the anion-bridge have been considered to be important in affecting the conformation of thiamine. The latter can also serve as a model for the substrate anion fixation near the catalytic C(2) site in the enzyme system.

Generally thiamine–anion compounds crystallize in two forms, the protonated form with a proton on the pyrimidine N(1′) atom and the free-base form. The structure of thiamine iodide hydroiodide, the protonated form, has been studied [5]. We report here the structure of thiamine iodide sesquihydrate, the free-base form, to further examine the interactions between thiamine and anions. This work provides some new structural aspects for thiamine–anion compounds.

2. Experimental

2.1. Preparation of the Crystal

Thiamine · I · 1.5 H_2O was prepared by mixing aqueous solutions of thiamine · Cl · HCl and NaI in a 1 : 2 molar ratio and adjusting the pH to about 5 with several drops of dilute NaOH solution. Colourless crystals formed after a few days in two crystalline forms in the same batch; rectangular plates which are the previously reported thiamine iodide hydroiodide [5] and rhomboidal plates, unstable in air, which is the compound reported here.

2.2. X-Ray Crystal Structure Analysis

Crystal data: $C_{12}H_{17}N_4OS^+ \cdot I^- \cdot 1.5\ H_2O$, formula weight = 419.28, monoclinic, space group $P2_1/c$, $a = 12.585(2)$, $b = 25.303(5)$, $c = 12.030(2)$ Å, $\beta = 115.15(1)°$, $V = 3468(1)$ Å^3, $Z = 8$, $D_c = 1.606$ g cm^{-3}, $\mu(\text{Mo}K_\alpha) = 19.5$ cm^{-1}, $F(000) = 1672$.

A crystal of dimensions 0.14 × 0.42 × 0.62 mm was sealed in a glass capillary with a small quantity of mother liquor. Intensity data were collected on a Nicolet

R3m/E four-circle diffractometer with graphite-monochromated MoK_α radiation ($\lambda = 0.71069$ Å). The cell parameters were obtained from a least-squares fitting of diffractometer setting angles for 20 reflections in the 2ϑ range of 11.7 to 21.8°. A total of 5364 independent reflections were measured up to $2\vartheta = 48°$ using ω scan mode, scan width of 1.39° and scan speed of 5.86°/min. Of these reflections 3328 with $I > 3\sigma(I)$ were considered observed. Two standard reflections were monitored every 98 reflections and showed an intensity variation less than 2.7%. Lp and empirical absorption corrections were applied; max. and min. transmission coefficients were 0.94 and 0.69.

The structure was solved by the heavy-atom method and refined by block-diagonal least-squares, minimizing the function $\sum w(F_o - |F_c|)^2$. The hydroxyethyl side chains for both thiamines A and B and two of the three water molecules were disordered, each atom in two positions. The occupancy factors for these disordered atoms were estimated on the basis of their electron densities. The non-hydrogen atoms were refined anisotropically, except those of the minor disordered hydroxyethyl groups which were refined isotropically. The hydrogen atoms, except those attached to water molecules and to disordered groups, were located on a difference map and fixed in the final cycles of the refinements($U = 0.06$ Å^2). The final R value was 0.045, R_w 0.066 and S 1.10 for 3328 observed reflections, where $w = 1/[\sigma^2(F_o) + 0.0026(F_o)^2]$. The maximum shift/e.s.d. was equal to 0.02. The maximum height in the final difference map was 0.54 eÅ^{-3}.

Atomic scattering factors were taken from the *International Tables for X-ray Crystallography* [6]. All calculations were performed using the SHELXTL program system [7].

3. Results and Discussion

The final atomic coordinates of the non-hydrogen atoms are listed in Table I. Hydrogen bonds are given in Table II. Lists of bond lengths and angles, coordinates of the H atoms, anisotropic thermal parameters and structure factors have been deposited. Figure 1 shows the molecular structure with atomic numbering scheme. Figures 2 and 3 depict the molecular packing.

3.1. Molecular Structure

The asymmetric unit contains two independent thiamine cations A and B, two iodide anions and three water molecules. The molecular dimensions of the thiamine cations are similar to those of other free-base forms of thiamine [4]. As expected, the average N(1′)–C(2′) bond length (1.33 Å) and C(6′)–N(1′)–C(2′) bond angle (115.7°) are smaller than the corresponding values in the N(1′)-protonated structures [3, 5]. Both A and B have a disordered hydroxyethyl side chain, which folds back towards the thiazolium ring to make a close contact between S(1) and O(53): O(53A)[O(53A)′]···S(1A) = 3.14(1)[2.86(2)] and O(53B)[O(53B)′]···S(1B) =

TABLE I. Atomic coordinates and equivalent isotropic thermal parameters for non-hydrogen atoms.

Atom	x	y	z	U_{eq}[a]
I(1)	1.21149(4)	0.28163(2)	−0.44481(5)	0.0588(2)
I(2)	0.77831(5)	0.05639(2)	−0.05842(5)	0.0722(3)
O(w1)	0.5731(6)	0.4033(3)	−0.2636(7)	0.100(4)
O(w2)[b]	0.496(1)	0.0786(5)	−0.522(1)	0.140(8)
O(w2)′[b]	0.429(2)	0.031(1)	−0.586(2)	0.14(1)
O(w3)[b]	0.032(1)	0.4267(7)	0.180(1)	0.19(1)
O(w3)′[b]	−0.045(2)	0.4113(7)	0.109(2)	0.093(9)
S(1A)	1.2186(2)	0.1510(1)	−0.2894(2)	0.080(1)
C(2A)	1.0972(6)	0.1849(3)	−0.1996(7)	0.058(3)
N(3A)	1.0386(5)	0.1613(2)	−0.0929(5)	0.045(2)
C(4A)	1.0883(6)	0.1148(3)	−0.0781(7)	0.054(3)
C(5A)	1.1884(7)	0.1040(3)	−0.1769(7)	0.067(4)
C(41A)	1.0354(7)	0.0859(3)	0.0413(7)	0.060(4)
C(51A)[b]	1.276(1)	0.0593(6)	−0.194(1)	0.061(6)
C(51A)′[b]	1.239(3)	0.0458(6)	−0.205(3)	0.07(1)[c]
C(52A)[b]	1.244(1)	0.0154(5)	−0.262(1)	0.066(6)
C(52A)′[b]	1.362(3)	0.060(1)	−0.245(3)	0.083(8)[c]
O(53A)[b]	1.258(1)	0.0329(4)	−0.3777(9)	0.114(7)
O(53A)′[b]	1.416(2)	0.0814(8)	−0.372(2)	0.114(7)[c]
C(35′A)	0.9316(6)	0.1851(3)	0.0048(6)	0.050(3)
N(1′A)	0.8963(5)	0.3312(3)	−0.0310(7)	0.068(3)
C(2′A)	0.8356(6)	0.3290(3)	−0.0973(7)	0.057(3)
N(3′A)	0.8003(5)	0.2859(2)	−0.1347(5)	0.055(3)
C(4′A)	0.8318(6)	0.2377(3)	−0.1064(6)	0.047(3)
C(5′A)	0.8975(6)	0.2360(3)	−0.0341(6)	0.050(3)
C(6′A)	0.9261(6)	0.2833(3)	0.0009(8)	0.062(4)
C(21′A)	0.7994(8)	0.3807(3)	−0.1332(8)	0.075(4)
N(41′A)	0.7947(5)	0.1957(3)	−0.1442(6)	0.061(3)
S(1B)	0.2229(2)	0.34680(9)	−0.1051(2)	0.070(1)
C(2B)	0.3348(6)	0.3111(3)	−0.1988(7)	0.056(3)
N(3B)	0.3951(4)	0.3342(2)	−0.3055(5)	0.048(2)
C(4B)	0.3508(6)	0.3838(3)	−0.3159(7)	0.060(4)
C(5B)	0.2553(7)	0.3961(3)	−0.2123(7)	0.072(4)
C(41B)	0.4045(8)	0.4139(4)	−0.4317(9)	0.085(4)
C(51B)[b]	0.194(1)	0.4524(4)	−0.177(1)	0.071(7)
C(51B)′[b]	0.164(2)	0.4375(9)	−0.206(2)	0.041(6)[c]
C(52B)[b]	0.069(1)	0.4416(6)	−0.146(1)	0.080(7)
C(52B)′[b]	0.192(2)	0.477(1)	−0.124(2)	0.065(7)[c]
O(53B)[b]	0.0102(9)	0.4159(4)	−0.0245(9)	0.086(5)
O(53B)′[b]	0.171(1)	0.4574(6)	−0.008(1)	0.068(4)[c]
C(35′B)	0.4993(6)	0.3101(3)	−0.4060(6)	0.051(3)

TABLE I. Continued.

Atom	x	y	z	U_{eq}[a]
N(1′B)	0.5356(5)	0.1637(3)	−0.3864(6)	0.067(3)
C(2′B)	0.5980(6)	0.1637(3)	−0.3189(7)	0.062(3)
N(3′B)	0.6325(5)	0.2062(2)	−0.2786(6)	0.058(3)
C(4′B)	0.5997(6)	0.2541(3)	−0.3031(6)	0.054(3)
C(5′B)	0.5335(6)	0.2578(3)	−0.3734(6)	0.054(3)
C(6′B)	0.5068(6)	0.2107(3)	−0.4132(7)	0.062(4)
C(21′B)	0.6348(8)	0.1122(3)	−0.2904(8)	0.079(5)
N(41′B)	0.6348(6)	0.2966(3)	−0.2612(6)	0.068(3)

[a] Equivalent isotropic U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

[b] Disordered atoms; occupancy factors: 0.65 for O(w2), O(w3), C(51A), C(52A), O(53A), C(51B), C(52B) and O(53B) and 0.35 for O(w2)′, O(w3)′, C(51A)′, C(52A)′, O(53A)′, C(51B)′, C(52B)′ and O(53B)′.

[c] Refined with isotropic thermal parameters.

2.99(1)[3.00(2)] Å (sum of van der Waals radii for O···S is 3.32 Å [8]). This close contact is a rather common feature in thiamine structures.

3.2. Factors Affecting the Conformation of Thiamine and Host–Guest Interaction

The conformation of two aromatic rings with respect to the methylene C(35′) can be described in terms of torsion angles φ_T = C(5′)–C(35′)–N(3)–C(2) and φ_P = N(3)–C(35′)–C(5′)–C(4′) [9]. Although a wide range of conformations is accessible to a free thiamine, the principle conformations observed in the crystalline state are the F-form ($\varphi_T \simeq 0$, $\varphi_P \simeq \pm 90°$) and the S-form ($\varphi_T \simeq \pm 100$, $\varphi_P \simeq \pm 150°$). For this structure the torsion angles, φ_T = 2.5(11) (A) and −2.5(11)° (B) and φ_P = 81.8(8) (A) and −80.5(8)° (B), correspond to the usual F conformation. It has been demonstrated by several authors [10, 11] that the anion-bridge between the pyrimidine and thiazolium rings consisting of an N(41′)–H···X hydrogen bond and an X···thiazolium ring electrostatic interaction can stabilize the conformation of thiamine; the size of the anionic group to which the X belongs is also an important factor to determine which conformation is preferred. This type of anion-bridge is maintained in the present structure. I(2) bridges the two aromatic rings of A through a hydrogen bond with N(41′A) and a somewhat loose contact with the thiazolium A [the closest distance I(2)···C(4A) = 4.083(7) Å]. In a similar manner, O(w1) associates with the two aromatic rings of B [the closest distance O(w1)···N(3B) = 3.05(1) Å]. From an inspection of the other thiamine salts with inorganic anions, we recognize similar anion-bridges in spite of a different

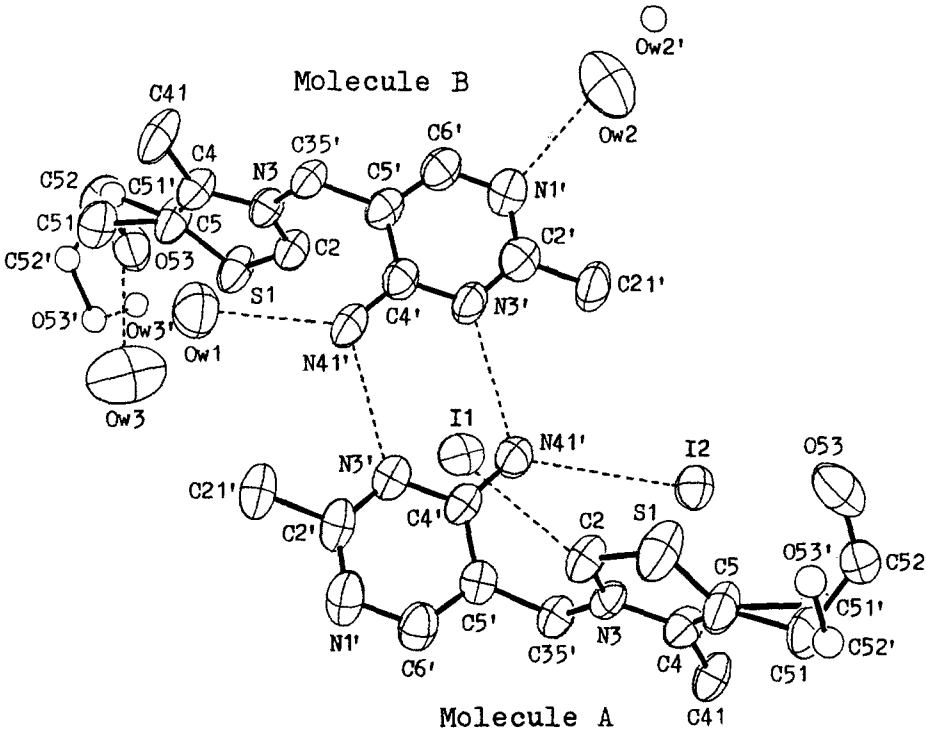

Fig. 1. Molecular structure of thiamine · I · 1.5 H_2O shown as 50% probability ellipsoids. Circles denote the minor disordered positions. Hydrogen bonds are indicated by broken lines.

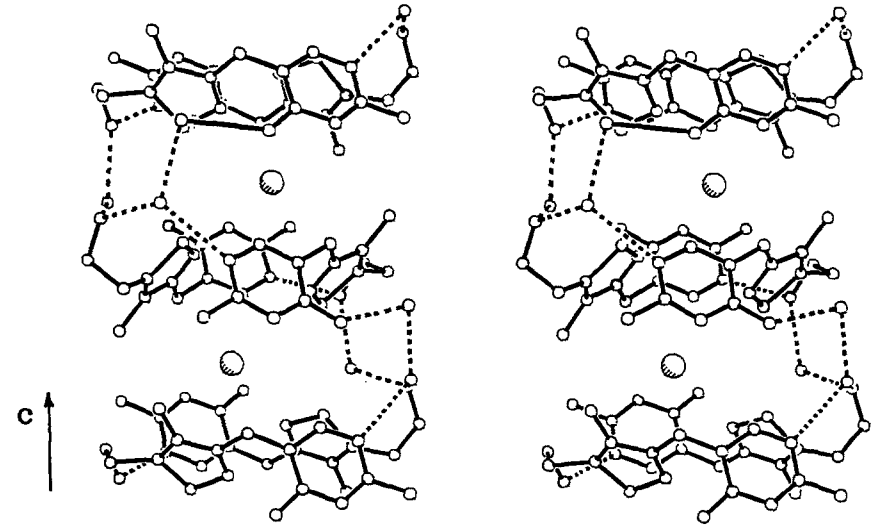

Fig. 2. Stereoscopic view of the molecular packing. Broken lines denote hydrogen bonds.

TABLE II. Hydrogen bonds[a].

Donor	Acceptor	Symmetry for A	D···A(Å)	H···A(Å)	D–H···A(°)
C(2A)–H	I(1)	x, y, z	3.626(7)	2.98	119
N(41′A)–H1	N(3′B)	x, y, z	3.108(9)	2.20	179
N(41′A)–H2	I(2)	x, y, z	3.655(6)	2.79	145
C(2B)–H	I(1)	$x-1, \frac{1}{2}-y, z-\frac{1}{2}$	3.636(7)	3.08	114
N(41′B)–H1	N(3′A)	x, y, z	3.068(9)	2.11	173
N(41′B)–H2	O(w1)	x, y, z	2.81(1)	1.87	165
O(w1)	O(w2)	$x, \frac{1}{2}-y, z-\frac{1}{2}$	2.68(2)		
O(w1)	I(2)	$x, \frac{1}{2}-y, \frac{1}{2}+z$	3.536(7)		
O(w2)	N(1′B)	x, y, z	2.87(2)		
O(w2)	O(53A)	$x-1, y, z$	2.98(2)		
O(w2)′	O(53A)′	$x-1, y, z$	2.82(4)		
O(w2)′	O(w1)	$x, \frac{1}{2}-y, \frac{1}{2}+z$	2.71(2)		
O(w3)	I(2)	$x-1, \frac{1}{2}-y, z-\frac{1}{2}$	3.43(1)		
O(w3)	O(53B)	x, y, z	2.60(2)		
O(w3)′	O(53B)′	x, y, z	2.73(2)		
O(w3)′	N(1′A)	$x-1, y, z$	2.93(2)		
O(53A)	O(w3)	$1+x, \frac{1}{2}-y, \frac{1}{2}+z$	2.82(2)		
O(53A)′	N(1′B)	$1+x, y, z$	2.53(2)		
O(53B)	N(1′A)	$x-1, y, z$	2.60(1)		
O(53B)′	O(w2)′	$x, \frac{1}{2}-y, z-\frac{1}{2}$	3.00(2)		

[a] The hydrogen atoms attached to the water molecules and O(53) atoms were not located.

geometry for the monoatomic halide [5, 12–15], linear SCN^- [4], planar NO_3^- [16], tetrahedral BF_4^- [4] and ClO_4^- [3, 17] and octahedral PF_6^- [17] anions. In all of these structures the thiamine cations assume the *F* conformation. This is in accord with the conclusion from crystallographic studies of the polyhalogenometal anion–thiamine compounds that the *F* conformation is a predominant form for smaller anionic groups [10, 18], since the dimensions of these anions (< 2.5 Å), estimated by the nonbonding distance between two adjacent atoms, are much smaller than those of the polyhalogenometal anions reported (3.2–4.0 Å).

Another type of anion-bridge, which was noted by Aoki *et al.* [11], involving a C(2)–H···X···pyrimidine ring interaction, has been frequently observed in thiamine structures which crystallize in the *F* conformer. This host–guest interaction further stabilizes the *F* conformer, and more importantly, it provides a model for the substrate recognition and fixation near to the active C(2) site through the non-covalent interactions. In the present structure, I(1) simultaneously accepts two hydrogen bonds from the C(2) atoms of A and B ($1+x, \frac{1}{2}-y, \frac{1}{2}+z$), but the I(1)···pyrimidine ring distances [4.774(1) (A) and 4.973(1)Å (B)] are considerably

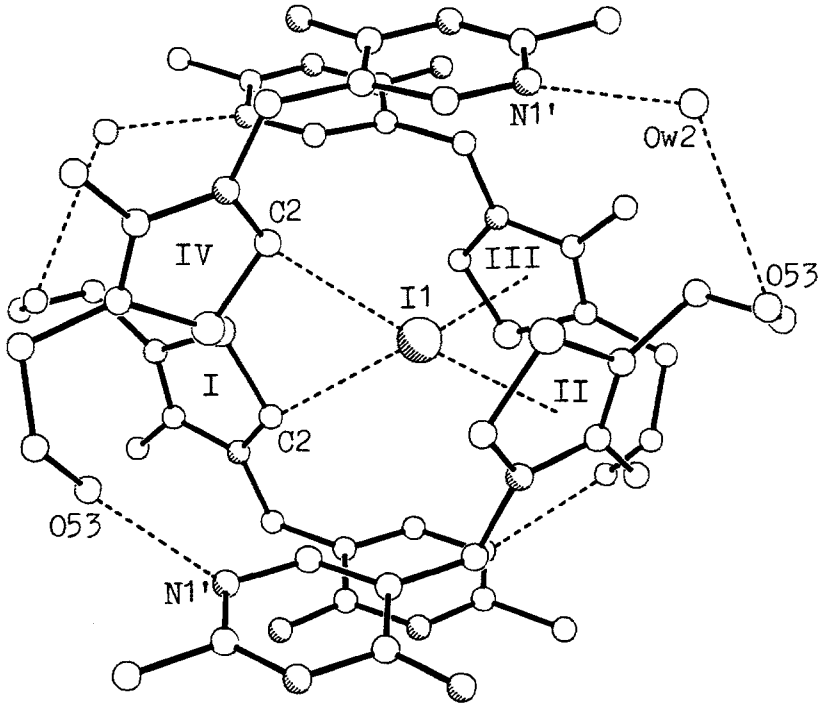

Fig. 3. Perspective view showing that four thiamine hosts [I: A(x, y, z), II: A($x, \frac{1}{2}-y, \frac{1}{2}+z$), III: B($1+x, y, z$), IV: B($1+x, \frac{1}{2}-y, \frac{1}{2}+z$)] hold an I(1) guest through C(2)–H···I(1) hydrogen bonds and I(1)···thiazolium ring close contacts (indicated by broken lines), and also showing the formation of cyclic dimers. Minor positions of the disordered atoms are ignored for clarity.

longer than the van der Waals distance, indicating the lack of the X···pyrimidine ring interaction. The case is similar to those found in thiamine · Br · 1.5 H_2O [15] and thiamine · Cl · H_2O [12]. In addition, I(1) is in contact with the thiazolium S atoms. The I(1)···S(1) distances are 3.818(3) Å for A and 3.750(2) Å for B. These I···S contacts are likely to be attractive interactions because the S atoms carry a partial positive charge. The tendency for thiazolium sulfur to contact with negative ions or electronegative atoms is a characteristic of thiamine structures [12]. It is therefore apparent that in the absence of the I···pyrimidine ring interaction, the thiamine host still captures a guest I^- ion in the vicinity of the C(2) site by the C(2)–H···I hydrogen bond and the S(1)···I electrostatic contact.

3.3. Self-Association of the Hosts and Packing Relations between the Hosts and Guests

The crystal packing shows an interesting aspect. A cyclic dimer is constructed by self-association of the two thiamine molecules through O(53)–H···N(1′) and

O(53)···H–O(w2)–H···N(1′) hydrogen bonds. The dimeric units are parallel to each other and further associate with each other by N(41′)–H···O(w1)–H···O(w2) and O(53)–H···O(w3)–H···O(53) hydrogen bonds in the *c* direction, as is shown in Figure 2 and Table II, to form a pipe-like polymeric structure. The minor disordered molecules also have a similar self-association mode (not shown in Figure 2). This distinct cationic polymer serves as an anion-tunnel having the iodide ions, I(1), arranged through it.

The packing relations between the hosts and guests are further shown in detail in Figure 3. Each anionic guest is held by four neighbouring thiamines in a cavity formed by the hosts. The four thiazolium moieties as near neighbours surround I(1), which accepts two hydrogen bonds from the C(2) atoms, as mentioned above, by lying on the planes of the two thiazolium rings, and at the same time, forms electrostatic contacts with the other two thiazolium rings by locating over the ring planes. The closest contacts of I(1) with the thiazolium rings are I(1)···N(3) = 3.65(7) Å for A $(x, \frac{1}{2} - y, \frac{1}{2} + z)$ and 3.63(7) Å for B $(1 + x, y, z)$. Moreover, I(1) is also surrounded by the four pyrimidine rings as far neighbours, two of which are coplanar with I(1) and the other two cap on I(1). The disposition of the guest I(1) closer to the thiazolium moieties than to the pyrimidine moieties is consistent with the suggestion by Breslow [1] that the thiazolium ring is the primary site of catalytic activity. In view of this observation we can expect that in the enzyme system the unique hydrogen-bonding and electrostatic interactions between the thiazolium moiety and the substrate anion, e.g. pyruvate anion, would play an important role in the substrate recognition and subsequent reactions.

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