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Triethylenetetramine dihydrochloride: Interactions and Conformations in two Anhydrous Structures and a Hydrate

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Abstract

Triethylenetetramine is a polyamine type chelating ligand for copper (II), which is currently used, mainly in its dihydrochloride form, as an alternative to D-penicillamine against Wilson's disease. Because knowledge about the solid-state behavior of pharmaceuticals is a prerequisite for the development of an effective dosage form, the crystal structures of two triethylenetetramine dihydrochloride polymorphs have been determined and the infrared spectra and thermal expansion have been studied. No suitable crystals could be obtained of the two anhydrous forms, for which the structures have been solved from X-ray powder diffraction. Form I is monoclinic $P2_1/n$ with the cell parameters $a = 11.0475(4) \text{ \AA}$, $b = 4.87475(16) \text{ \AA}$, $c = 11.1178(4) \text{ \AA}$, and $\beta = 106.9826(13)^\circ$ leading to $V = 572.63(3) \text{ \AA}^3$ with $Z = 2$. Form II is also monoclinic $P2_1/c$ with cell parameters $a = 10.6734(6) \text{ \AA}$, $b = 12.3613(6) \text{ \AA}$, $c = 9.8479(7) \text{ \AA}$, and $\beta = 115.985(3)^\circ$ leading to a unit-cell volume of $V = 1167.95(12) \text{ \AA}^3$ with $Z = 4$. A recurring structural element is a ionic interaction between two chloride ions and two ammonium groups each organized in a diamond pattern present in the dihydrate (the salt is hygroscopic) and anhydrous form I. The molecular conformations are different in both anhydrous forms and in the dihydrate. Comparison of the thermal expansions demonstrates that form I has the smallest thermal expansion and thus possesses the strongest intermolecular interactions.

1 Introduction

The dihydrochloride salt of triethylenetetramine (N^1,N^2 -bis(2-aminoethyl)-1,2-ethanediamine, hydrochloride (1:2) and here abbreviated with TETA·2HCl, Figure 1), is a polyamine type chelating ligand for copper (II) and currently used as an alternative to D-penicillamine against Wilson's disease.¹ Due to its activity on copper homeostasis, TETA·2HCl is also being tested for numerous applications such as diabetes mellitus,² Alzheimer's disease,³ and even cancer.⁴

TETA was first synthesized in Germany in 1861 and in 1896 prepared as a dichloride salt.⁵ Its chelating activity was studied in 1925.⁵ Because TETA possesses four equally spaced nitrogen atoms, it fits the square-planar geometry in which Cu(II) is most stable. It strongly binds Cu(II) with a dissociation constant in the order of 10^{-15} mol/L at pH 7.0.⁵ For medical purposes, TETA has been used mainly in the form of the dihydrochloride salt, which is very soluble in water.^{5,6}

Figure 1. Chemical structure of triethylenetetramine dihydrochloride

Several TETA salts have been studied and a number of crystal structures has been solved: tetrafumarate trihydrate,⁷ disuccinate,^{7,8} tetramaleate dihydrate,^{7,8} tetrafumarate tetrahydrate,⁸ tetraparatoluenesulfonate tetrahydrate,⁹ and dinitrate.⁹ However, even though this substance has been known for over a century, the crystal structure of the TETA·2HCl dihydrate was only solved in 2000.¹⁰ The crystal structure has been reported in a study on a number of polyamine salts with halogen ions Cl^- , Br^- , and I^- .¹⁰ TETA·2HCl dihydrate was found to be isostructural with TETA·2HBr dihydrate and TETA·2HI dihydrate. They crystallize in the monoclinic space group $P21/c$ with $Z = 4$. The TETA chains are linear. Twelve hydrogen bonds are present per formula unit (leading to six unique hydrogen bonds as the asymmetric unit only contains half a TETA molecule). The chloride anions are four-coordinate and form the apex of a pyramid. The two additional protons on TETA are found

on the amine end groups as is expected considering the pKa values of the hydrochloride and the amino groups.^{10,11}

The existence of 2 polymorphs of anhydrous TETA·2HCl have been reported; form I is characterized by a melting range between 111° C to 132° C and form II by a melting range between 106° C to 126° C.¹² The crystal structures have never been elucidated, however. They will be presented in this paper together with their thermal expansion. In addition, the structures will be compared with that of the dihydrate. Infrared spectra of the two polymorphs will be provided too.

2 Material and methods

2.1 Materials

Triethylenetetramine dihydrochloride (99.4%, C₆H₂₀N₄Cl₂, 219.16 g mol⁻¹) was purchased from Aldrich (Steinheim, Germany) and used as such. Crystals were grown by slow evaporation from various solvents, including ethanol, acetone, dioxane, isopropanol, ethyl acetate and THF. All solvents were of analytical grade with purity ≥ 99%. From all solvents, crystals of the known hydrated form were obtained.¹⁰ As the commercial powder, form I, did not contain water, it was decided to solve the structure from X-ray powder diffraction data. A second polymorph, form II, could only be obtained by melting the commercial sample and recrystallization from the melt by quenching the liquid at ambient temperature. Therefore, also the structure of form II has been solved from X-ray powder diffraction as described below.

2.2 High-resolution X-ray powder diffraction

X-ray powder diffraction was performed on a transmission mode diffractometer using Debye–Scherrer geometry equipped with a cylindrical position-sensitive detector (CPS120) from INEL (France) containing 4096 channels (0.029° 2θ angular step)¹³ with monochromatic Cu-Kα₁ (λ = 1.54061 Å) radiation. For the measurements as a function of temperature, a liquid nitrogen 700 series Cryostream Cooler from Oxford Cryosystems (United Kingdom) was used.

Lightly ground specimens were introduced in a Lindemann capillary (0.7 mm diameter) rotating perpendicularly to the X-ray beam during the experiments to improve the average over the crystallite orientations. Room temperature data were collected for at least 12 hours per polymorph. For the temperature dependent measurements in the range from 100 K up to the respective melting points of phases I and II, the sample temperature was equilibrated for about 15 min followed by an acquisition time of ca. 1 hour at each temperature. The heating rate in between data collection was 1.33 K min⁻¹. For phase II, a specimen of phase I mixed with Lindemann glass was molten in a Lindemann capillary of 1.0 mm then cooled down to 293 K and left to recrystallize overnight after which the X-ray data were collected as described above. Samples prepared outside the capillary contained consistently some phase I.

2.3 Structure solution of forms I and II from powder diffraction

For the structure solutions, the program *DASH*¹⁴ and *TOPAS-Academic*¹⁵ were employed and the powder pattern was truncated to 52.6° in 2 θ (Cu $K\alpha_1$), corresponding to a real-space resolution of 1.75 Å. The background was subtracted with a Bayesian high-pass filter.¹⁶ Peak positions for indexing were obtained by fitting with an asymmetry-corrected pseudo-Voigt function.^{17,18}

2.3.1 Form I

Twenty-one peaks were indexed with the indexing program DICVOL04.¹⁹⁻²¹ A monoclinic unit cell was obtained with figures of merit $M(21) = 15.7$ and $F(21) = 24.5$ (0.0138, 62). Pawley refinement was used to extract integrated intensities and their correlations, from which the space group was determined using Bayesian statistical analysis.²² The space group $P2_1/n$ was returned as the most probable option. It was the space group with the highest symmetry. It resulted in a Pawley χ^2 of 2.46. Simulated annealing was used to solve the crystal structure from the powder pattern in direct space. The starting molecular geometry was taken from the published dihydrate structure from the CSD (reference code XAHWOS),¹⁰ and only half of the triethylenetetramine molecule was used considering the unit-cell volume (573 Å³) and the symmetry elements. In 30 simulated annealing runs, the same crystal structure was found 30 times. The profile χ^2 of the best solution was 8.81, which is less than four times the Pawley χ^2 ; these are good indications that the correct solution has been found.

For the Rietveld refinement, data out to $90^\circ 2\theta$ were used, which corresponds to 1.1 Å real-space resolution. The Rietveld refinement was carried out with *TOPAS-Academic*.¹⁵ Bond lengths, bond angles and planar groups were subjected to suitable restraints, including bonds to H atoms, based on the distances found in the structure XAHWOS. A global B_{iso} was refined for all non-hydrogen atoms, with the B_{iso} of the hydrogen atoms constrained at 1.2 times the value of the global B_{iso} . The inclusion of a preferred-orientation correction with the March-Dollase formula²³ was tried for directions (100), (010) and (001). No difference to the R_{wp} value was observed. The molecular geometry was checked with *Mogul*,²⁴ which compares each bond length and bond angle to corresponding distributions from single-crystal data.

2.3.2 Form II

20 peaks were indexed with the indexing program DICVOL04.¹⁹⁻²¹ A monoclinic unit cell was obtained with figures of merit $M(20) = 12.1$ and $F(20) = 27.3$ (0.0175, 42). The exact same monoclinic unit cell was also found by TOPAS Academic.²⁵ Pawley refinement was used to extract integrated intensities and their correlations, from which the space group was determined using Bayesian statistical analysis.²² The space group $P2_1/c$ was returned as the most probable option, which was the one with the highest symmetry. It resulted in a Pawley χ^2 of 2.73. Simulated annealing was used to solve the crystal structure from the powder pattern in direct space. In first instance, this did not lead to any solution. Taking into consideration that form II needed to be prepared in the capillary, preferred orientation was included into the analysis. After some trial and error, the preferred orientation direction (1 3 0) appeared to return the best result and it was used for the simulated annealing. In 100 runs, the 20 crystal structures with the lowest χ^2 were the same. The profile χ^2 of the best solution was 7.82, which is about three times the Pawley χ^2 ; these are reasonable indications that the correct solution has been found.

For the Rietveld refinement, data out to $90^\circ 2\theta$ were used. A preferred-orientation correction with the March-Dollase formula²³ was used with direction (1 3 0). Other directions were tried, but did not lead to a better fit. The molecular geometry was checked with *Mogul*,²⁴ which compares each bond length and bond angle to corresponding distributions from single-crystal data.

Supplementary crystallographic data can be found in the CCDC, deposit numbers 1014992 and 1014993 for form I and form II respectively, and obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif/.

2.4 Parametric Pawley and Rietveld refinements

The lattice parameters as a function of temperature have been determined with Pawley fits to the known unit cells using TOPAS Academic.¹⁵ The X-ray patterns for each temperature were fitted simultaneously with global diffraction setup constants and a global zero error. For the parametric Rietveld refinements, the atom coordinates of the structure were also defined globally, whereas the unit-cell parameters were allowed to refine independently for each temperature.

2.5 Hirshfeld Surfaces and fingerprint plots.

Calculations were performed with CrystalExplorer v3.020^{26,27} with the experimental crystal geometries as input.¹⁰ Distance d_i is defined as the distance from the Hirshfeld surface to the nearest interior atom, and d_e is the distance from the surface to the nearest exterior atom. Plots of d_e against d_i , called fingerprint plots, offer the possibility to classify crystals by the nature of their intermolecular interactions and to rapidly identify structural similarities.²⁸

2.6 Isobaric thermal expansion tensor

The anisotropy of the intermolecular interactions can be investigated with the isobaric thermal expansion tensor, which is a measure of how the interactions change with temperature.²⁹ A small value for a tensor eigenvalue is commonly referred to as a “hard” direction and a large value as a “soft” direction.³⁰ The tensor was calculated by PASCAL software³¹ and was drawn by Wintensor.³²

2.7 Infrared spectrometry

Infrared spectrometry was carried out with a Fourier transform Perkin-Elmer Septum spectrometer 1000 using the Spectrum 1000 analysis software. Spectra were recorded at room temperature from 500 to 4000 cm^{-1} . Samples were measured directly in the solid state without the need of a matrix.

3 Results

3.1 Crystal structures of forms I and II

The Rietveld refinement for the structure of form I progressed smoothly and produced a good fit with $\chi^2 = 1.585$, $R'_p = 11.523$, $R'_{wp} = 11.091$ (values after background correction), $R_p = 1.903$ and $R_{wp} = 2.512$ (values before background subtraction). B_{iso} refined to $1.47(9) \text{ \AA}^2$. The cell parameters of phase I and its structure solution data by powder diffraction can be found in Table 1. The structure is monoclinic, space group $P2_1/n$ and has a unit-cell volume of $572.64(3) \text{ \AA}^3$ with $Z = 2$ and $Z' = 1/2$. The result of the Rietveld refinement is shown in Figure 2a and the crystal packing in Figure 2b.

For phase II, the Rietveld refinement produced a reasonable fit with $\chi^2 = 1.935$, $R'_p = 27.473$, $R'_{wp} = 22.528$ (values after background correction), $R_p = 2.114$ and $R_{wp} = 2.959$ (values before background subtraction). B_{iso} refined to $1.1(2) \text{ \AA}^2$. The high R-values are the result of preferred orientation that has been difficult to fully compensate for. The cell parameters of phase II, determined with powder diffraction, can be found in Table 1. The structure is monoclinic, space group $P2_1/c$ and has a unit-cell volume of $1167.95(12) \text{ \AA}^3$ with $Z = 4$ and $Z' = 1$. The result of the Rietveld refinement is shown in Figure 2a and the crystal structures in Figure 2c.

Figure 2. Results of the structure resolutions by X-ray powder diffraction **a.** Rietveld refinements against the powder diffraction patterns **b.** Crystal structure of form I **c.** Crystal structure of form II. Hydrogen atoms omitted for clarity.

3.2 Powder diffraction data as a function of temperature

The cell parameters and the unit-cell volumes of form I, form II, and the dihydrate increase linearly with temperature (Table 2). The volumes of the asymmetric unit (in Å³) as a function of temperature for the three forms are given by:

$$\text{form I (Z = 2):} \quad V_{\text{I}} / Z = 282.04(8) + 0.0172(3) T \quad (1)$$

$$\text{form II (Z = 4):} \quad V_{\text{II}} / Z = 282(1) + 0.039(3) T \quad (2)$$

$$\text{dihydrate (Z = 2):} \quad V_{\text{2H}_2\text{O}} / Z = 319.9(2) + 0.0337(5) T \quad (3)$$

The eigenvalues of the thermal expansion tensor of forms I and II, and the dihydrate are compiled in Table 3. The 3D tensors can be found in Figure 3. In the 3 structures, the thermal expansion is constant with temperature but not isotropic. The maximum expansion is along **e**₃ for forms I and II and is comparatively large for form II. The minimum expansion can be found along **e**₁ in the 3 forms.

Figure 3. Graphical representation of the thermal expansion tensors of forms I, II, and the dihydrate at 300 K³²

3.3 Infrared measurements

The IR spectra of forms I and II are presented in Figure 4 (a list of absorption peaks is provided in the supporting information). In both spectra, the absence of a broad peak around 3600 cm⁻¹ demonstrates the absence of water. The two IR spectra are different as would be expected for conformational polymorphs. They contain characteristic peaks for the ammonium group, confirming the transfer of the hydrochloride proton to the TETA molecule. The N-H stretch (secondary amine and ammonium groups) frequencies are different in forms I and II. This is consistent with the different hydrogen-bond networks for the two polymorphs. Moreover, the N-H frequencies of form I are higher than those of form II (3419

vs. 3285 cm^{-1}). This is an indication for the increase in strength of the hydrogen bonds in form I.

Figure 4. Infrared transmittance spectra of the two TETA·2HCl polymorphs I and II. Spectra are shifted for clarity

4 Discussion

4.1 Conformations

TETA is a flexible molecule with seven torsion angles (Table 4). In the dihydrate, the molecule is linear (Figure 5) and its molecular center is located on an inversion center of the unit cell. Therefore, there are only 3 independent torsion angles and because the molecule is linear all the angles have a value of approximately 180° . The point group symmetry of the molecule is C_i , or D_{2h} disregarding the hydrogen atoms, as the molecule is linear. The same linear configuration has been observed for the tetrafumarate trihydrate salt⁷ and for the salt with TETA and *p*-toluenesulfonic acid (1:4).⁹ In these two salts all four amine groups are protonated, however.

The point group symmetry of the TETA molecule in form I is C_i , for it is also located on an inversion center of the unit cell. However, the D_{2h} symmetry is lost, because the molecule is not completely linear; the torsion angle N1-C1-C2-N2 is $-73.7(3)^\circ$ (Figure 5 and Table 4). Its configuration can also be found in the salt of TETA with succinate (ratio 1:2), in which all four amine groups are protonated.⁷ In form II, the molecule is neither linear (Figure 4) nor

placed on an inversion center. The torsion angles all differ and range from $44.7(1.6)$ to $163.5(1.2)^\circ$ in absolute values. This configuration has not been reported in the literature.

Figure 5. Conformations of TETA in the dihydrate (left-hand side), form I (center), and form II (right-hand side)

4.2 Packing in the two anhydrous TETA·2HCl polymorphs compared to the dihydrate

In form I and in the dihydrate, the asymmetric unit contains only half a TETA molecule and a chloride ion (in the case of the dihydrate, the asymmetric unit also contains a water molecule). In form II, the whole TETA molecule and two chloride anions can be found in the asymmetric unit. Even though TETA is used throughout the text, it is clear from all three structures that hydrochloride has donated its proton to the terminal amine groups. Thus TETA in these structures actually refers to TETA·2H⁺.

The molecular packings of the two anhydrous structures have been presented in Figures 2b and 2c. In form I, the TETA molecules are linear, except for the terminal NH₃⁺ (see Figure 5). The TETA molecules form layers parallel to the *ab* plane (Figure 2) with a distance between each other of $c/2$. Whereas the molecules within each layer are parallel, the molecules of subsequent layers have different orientations; in one layer they are oriented in the direction **a + b** and in the adjacent layer in the direction **a - b** (Figure 2). The chloride ions can be found between the TETA layers in columns along the *b* axis. The formation of layers separated by anions is an often-recurring element in structures with TETA as many examples can be found in the literature.^{7,9,10}

In form II, the TETA molecules are sickle shaped instead of linear (Figure 5). As in form I, the TETA molecules form parallel layers (Figure 2) interchanged by chloride columns along the b axis. The distance between the layers is again $c/2$. As can be seen in Figure 2, chloride columns can also be observed along the c axis, part of them running through a circular area defined by the circular part of two TETA molecules in adjacent layers.

In the dihydrate, layers of TETA molecules can be observed parallel to the bc plane.¹⁰ Within the layers, adjacent TETA molecules are shifted by half a molecule along the c axis and they possess two specific orientations with a 30° difference between each other. The water molecules and chloride ions possess their respective columns in between these layers along the a axis. Moreover, also the TETA molecules form columns along the a axis. All three structures represent different packings highlighting the flexibility of the TETA molecule.

4.3 Intermolecular interactions

4.3.1 Hydrogen bonds

In form I, three unique hydrogen bonds have the terminal amine group $N1H_3^+$ as donor (Table 5). $N2$ on a different TETA molecule is acceptor of one of those. Another hydrogen bond is connected to the chloride ion inside the asymmetric unit and the third one is connected to a chloride ion outside of the asymmetric unit (See Table 5 for the molecular coordinates). It should be mentioned that a slightly weaker hydrogen bond with $N2-H$ as donor is also bound to the chloride ion in the asymmetric unit (see Table 5). This leads to five hydrogen bonds connected to TETA (of which two between TETA and Cl^- (x,y,z)) in the asymmetric unit and an additional sixth one only connected to the chloride ion in the asymmetric unit. Thus the TETA molecule takes part in ten hydrogen bonds, four of which are with the two adjacent TETA molecules that make up the molecular layers parallel to the ab plane of the unit cell (Figure 6a). The six others are linked to the chloride ions that interconnect the different layers of the TETA molecules (Figure 6b). The chloride ion forms the top of a tetrahedron, which is linked to both $N1$ and $N2$ of the same TETA molecule (Figure 6c). This explains the deviating torsion angle (Table 4) of an otherwise linear molecule. Moreover, the chloride ion on top of the tetrahedron of hydrogen bonds possesses above the tetrahedron a triangular interaction with two more hydrogen atoms on two different molecules: $H1a$ ($x + \frac{1}{2}, -y + \frac{1}{2}, z + \frac{1}{2}$) and $H2b$ ($x + \frac{1}{2}, -y + 1.5, z + \frac{1}{2}$).

As mentioned above the layers or sheets of TETA molecules are held together by hydrogen bonds, which are described by graph sets such as $C_1^1(5)$ and $C_2^2(16)$. The infinite chains formed by the chloride ions are in part described by $C_1^2(4)$ and rings formed with two chloride ions are described by $R_2^4(8)$ (Figure 6b). Considering the fact that the distances between the chloride ions and the donors in these rings are small and also that both the chloride ions and the ammonium groups are charged, it must be one of the main backbones of the structure of form I.

Figure 6. Hydrogen-bond patterns in form I **a.** between TETA molecules **b.** Ionic interactions between chloride ions and ammonium groups on TETA molecules (graph set $R_2^4(8)$) **c.** Hydrogen bonds and other interactions around the chloride ion

In form II, for which the entire TETA molecule is part of the asymmetric unit, TETA has seven hydrogen bonds, all with chloride ions. The chloride ion Cl1 possesses four hydrogen bonds and Cl2 possesses three (Table 5). To both terminal NH_3^+ groups (N1 and N4) two chloride ions are connected. It can be seen in Table 5 that the sickle shape form of the TETA molecules is stabilized by two chloride ions connecting to two different amine groups on a single TETA molecule: one Cl1 ($-x + 1, -y + 1, -z + 1$) is linked to N1 and N3, if not by hydrogen bond than at least by electrostatic interactions (to N3), and one Cl2 ($-x + 1, y - \frac{1}{2}, -z + \frac{1}{2}$) is linked to N3 and N4. The Cl1 ions form tetrahedrons with two molecules linking to N1 and N3 on a single TETA molecule ($-x+1, -y+1, -z+1$) and to N2 on another TETA molecule (x, y, z) (Figure 7). This tetrahedron is mirrored by a second Cl1 ion ($-x+1, -y+1, -z+1$), binding to N1 and N3 of

the other TETA molecule (x, y, z) and to N2 on the first TETA molecule ($-x+1, -y+1, -z+1$). In addition to the interaction in the shape of a tetrahedron, an additional hydrogen bond to the N1 on a third TETA ($-x + 1, y - \frac{1}{2}, -z + \frac{1}{2}$) exists.

Figure 7. Ionic and hydrogen-bond interactions of Cl1 in form II.

Cl2 ($-x + 1, y - \frac{1}{2}, -z + \frac{1}{2}$) is linked to N4 on two different TETA molecules (x, y, z and $-x, y - \frac{1}{2}, -z + \frac{1}{2}$), forming an infinite chain with graph set $C^1_2(7)$. In addition, Cl2 is involved in a hydrogen bond to N3 on one of those TETA molecules (x, y, z). The chloride ions stabilize the sickle shape of the TETA molecules and keep the structure together by interconnecting the TETA molecules by hydrogen bonds and electrostatic interactions.

For the dihydrate, each TETA molecule is involved in twelve hydrogen bonds, which means six in the asymmetric unit (Table 5, the asymmetric unit contains only half a TETA molecule). Four hydrogen bonds exist with four different chloride ions and two hydrogen bonds with two different water molecules. No hydrogen bonds exist directly between different TETA molecules. Thus the layers of TETA molecules are linked via the water molecules and the chloride ions. Water is involved in three different hydrogen bonds, two connected to TETA molecules and one to a chloride ion. The chloride ion is the apex of a shallow pyramid formed by four hydrogen bonds involving three TETA molecules ($-x, -y + 1, -z + 1$; $x + 1, y, z$; $x + 1, -y + 1.5, -z - \frac{1}{2}$) and a water molecule ($-x - 1, -y + 1, -z + 1$) and from this apex another hydrogen bond exists with the ammonium group in the asymmetric unit. More information on the structure of the dihydrate can be found in the literature.¹⁰

In Table 5, it can be observed that the TETA molecule possesses most hydrogen bonds in the dihydrate –twelve in total–, then form I with eight hydrogen bonds, and then form II in which TETA possesses only seven hydrogen bonds. This explains at least in part the ease of TETA to form the dihydrate, as it is thoroughly stabilized by the additional hydrogen bonds.

Figure 8. Fingerprint plots²⁸ of the TETA molecule in the dihydrate, in form I and in form II. From top to bottom: all intermolecular interactions together, Cl $\cdots$ H interactions, N $\cdots$ H, H $\cdots$ H, and O $\cdots$ H interactions. The d_i, d_e occurrence increases from deep blue to light blue.

4.3.2 Fingerprint plots

Because the hydrogen bond patterns are complex and different for each form, Hirshfeld surfaces have been calculated for the TETA molecules in the three different structures. To facilitate comparison, the Hirshfeld surfaces have been converted into fingerprint plots.²⁸

The Cl...H interactions (Figure 8, second row from the top) are found in the upper left corner and these interactions are present in all three structures. The strengths (distances) are also equal in each structure, although they seem a bit stronger for form I. This is obviously due to the many hydrogen bonds that are formed between the TETA cations and the chloride anions. Interactions between N and H are clearly not important in form II; however in the dihydrate and in form I they are particularly strong (short). The symmetry observed for form I confirms that the interaction between N and H occurs between TETA molecules, whereas the single peak in the dihydrate points to the fact that the main N...H interaction is due to hydrogen atoms of the water molecules. Strength-wise the interactions are the same, but the relative occurrence of stronger interactions is higher in the dihydrate, as can be judged from the light blue color in the tip of the spike. The H-H interactions are important in all three structures. The single spike in the dihydrate corresponds to the N-H...O interaction, which is obviously absent in the two anhydrous forms.

4.3.3 Thermal expansion

The thermal expansion is constant over the entire temperature range for the dihydrate, form I, and form II (Table 3). All cell parameters increase linearly within measurement error and the thermal coefficients are positive, confirming that there are no contractions.^{33,34} The coefficients range from 3 to 80 MK⁻¹, which is in the same range as those observed for tienoxolol³³ and a number of tyrosine derivatives.³⁵ The expansion is anisotropic, although in the dihydrate α_{22} and α_{33} are virtually the same. In addition, the expansion in the hard direction, the most limited expansion, is much smaller in forms I and II, than in the dihydrate (α_{11} being 3.5, 4.5, and 13.0 MK⁻¹ respectively).

Figure 9. Projections of the thermal expansion tensors in relation to the unit cell **a.** for the dihydrate, **b.** for form I, and **c.** for form II. Hydrogen atoms have been omitted for clarity.

In the dihydrate, the thermal coefficient along **e₁** (approximately along the unit-cell *c* axis) is relatively small with 13.0 MK⁻¹ (Table 3, Figure 9a). It corresponds to the hard direction of the crystal, along which the intermolecular interactions are the strongest, in this case the ionic interaction between the chloride ion and the ammonium end groups. They form a diamond shape pattern as can be seen in Figure 10. A proliferation of hydrogen bonds without substantial ionic interactions causes the thermal expansion in the other directions to be fairly isotropic.

Figure 10. Diamond shape pattern in the dihydrate made up by the ionic interaction involving two chloride ions and two ammonium end groups.

The thermal expansion is lowest for form I in comparison to the two other forms. The hard direction is $\mathbf{e}_1$ with a tensor coefficient of 3.8 MK^{-1} (Table 3, Figure 9b), which coincides with the line-up of the before-mentioned diamond configuration of two chloride ions and two ammonium groups representing the major ionic interaction in the crystal (Figure 6b). A similar pattern can be seen repeated in the dihydrate (Figure 10), but the interactions involved are weaker considering the thermal expansion coefficients.

Form I's soft direction is along $\mathbf{e}_3$ (31.8 MK^{-1}) roughly along the main diagonal of the ac plane. Along this direction the layers of TETA are mainly connected by van der Waals interactions; however, each chloride ion interacts relatively strongly (distances of 2.946 and 2.852 Å) with two hydrogen atoms of two TETA molecules in the adjacent layer. The resulting thermal expansion of 32 MK^{-1} is therefore still relatively low for the soft direction, in particular in comparison with the thermal expansion along $\mathbf{e}_2$ equivalent to the b axis of the unit cell. The latter direction contains the double hydrogen bonds between the TETA molecules in the layer along the b axis and it has an expansion coefficient of 25 MK^{-1} . The strength of the hydrogen bonds in form I is confirmed by the results obtained by infrared.

In form II, the hard direction is along the diagonal of the ac plane ($\mathbf{e}_1$). This again represents the ionic interaction involving chloride ions linked to ammonium and amino groups on several TETA molecules forming an infinite chain of ionic interaction. Strangely enough the softest direction $\mathbf{e}_3$, along b , also contains a ionic infinite chain involving Cl⁻ and the ammonium group at the handle side of the sickle shape; however, this chain is buckled and the expansion may be the result of an alignment of the molecules along the b axis.

5 Conclusion

The crystal structures of two TETA·2HCl polymorphs have been determined by X-ray powder diffraction at room temperature. Form I is monoclinic with space group $P2_1/n$ and its unit-cell volume is $572.63(3) \text{ Å}^3$ with $Z = 2$. Form II is monoclinic with space group $P2_1/c$ and its unit-cell volume is $1167.95(12) \text{ Å}^3$ with $Z = 4$.

Specific ionic interactions between the ammonium end groups and the chloride ions are a recurring theme in the structures of the two anhydrous forms and the dihydrate, for example

the diamond pattern formed by two chlorides and two ammonium groups that occur in both the dihydrate and form I. However, the conformations of the TETA molecule are different in all structures. It demonstrates its flexibility. The structures are all distinct, even though they are built up from the same elements. It can also be seen that water is readily incorporated in the structure as the TETA molecules have considerably more hydrogen bonds in the hydrate than in the anhydrous forms. Whereas form I also forms hydrogen bonds between different TETA molecules, form II relies completely on hydrogen bonds with the chloride ion as intermediate. In particular the chloride – ammonium interactions play an important role in all three structures.

Although the dihydrate has by far the most hydrogen bonds, thermal expansion demonstrates that form I is the crystal with the strongest interactions as its thermal expansion is clearly smaller than the other two forms. All structures have strong ionic interactions that can be recognized by the hard directions in the thermal expansion. Extensive hydrogen bond networks mainly control the thermal expansion in the other directions. In this respect it is surprising to observe the high value of 80 MK⁻¹ for form II along **e**₃, while there is clearly an infinite chain of ionic interactions in combination with hydrogen bonds. It is probably because the infinite chain is relatively isolated from the other intermolecular interactions and because this chain is buckled providing room for alignment.

Supporting Information

Infrared absorption frequencies for form I and form II.

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Tables

Table 1. Crystal structure and refinement data at 298 K of triethylenetetramine dihydrochloride forms I and II

Form I	Form II	Common details
$a = 11.04754(34)$	$a = 10.67338(57)$	$C_6H_{20}N_4Cl_2$
$b = 4.87475(16)$	$b = 12.36132(59)$	$Mr = 219.16 \text{ g mol}^{-1}$
$c = 11.11783(37)$	$c = 9.84791(72)$	Specimen shape: cylinder, $10 \times 0.7 \text{ mm}$ (1.0 for form II)
$\beta = 106.9826(13)^\circ$	$\beta = 115.9852(28)^\circ$	Diffractometer INEL CPS 120
$V = 572.631(32)$	$V = 1167.95(12)$	Specimen mounting: Lindemann glass capillary 0.7 mm (form II 1.0 mm)
Monoclinic $P2_1/n$	Monoclinic $P2_1/c$	Specimen mounted in transmission mode
$Z = 2$	$Z = 4$	Scan method: curved detector
$D_x = 1.27 \text{ g cm}^{-3}$	$D_x = 1.25 \text{ g cm}^{-3}$	Absorption correction: none
Cu $K\alpha 1$ radiation	Cu $K\alpha 1$ radiation	Profile function: modified Thompson-Cox-Hastings pseudo-Voigt
$\mu = 0.87 \text{ mm}^{-1}$	$\mu = 0.62 \text{ mm}^{-1}$	H-atom parameters restrained
$2\theta_{\min} = 5.022^\circ$	$2\theta_{\min} = 5.006^\circ$	Weighting scheme based on measured s.u.'s $w = 1/\sigma(Y_{\text{obs}})^2$
$2\theta_{\max} = 89.99^\circ$	$2\theta_{\max} = 89.97^\circ$	$(\Delta/\sigma)_{\max} = 0.001$
Increment in $2\theta = 0.029^\circ$	Increment in $2\theta = 0.029^\circ$	Refinement on I_{net}
$R_p = 1.572$	$R_p = 1.529$	
$\chi^2 = 1.598$	$\chi^2 = 1.935$	
	reflections 954	

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reflections 471	parameters 220	Crystal structure – form I
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Table 2. Lattice parameters for triethylenetetramine dihydrochloride form I, form II, and its dihydrate as a function of the temperature^a

T (K)	<i>a</i> (Å)	<i>b</i> (Å)	<i>c</i> (Å)	β (°)	<i>V</i> (Å ³)
Form I					
293	11.059	4.879	11.128	107.005	574.27
290	11.058	4.878	11.126	107.014	573.89
260	11.052	4.875	11.121	107.064	572.78
230	11.048	4.871	11.116	107.105	571.78
200	11.044	4.868	11.114	107.149	570.93
150	11.035	4.863	11.106	107.223	569.29
120	11.031	4.860	11.102	107.251	568.48
320	11.059	4.881	11.125	106.968	575.067
350	11.067	4.887	11.132	106.912	576.05
380	11.074	4.891	11.136	106.865	577.15
385	11.075	4.892	11.138	106.862	577.53
390	11.075	4.893	11.139	106.857	577.67
Form II					
293	10.679	12.364	9.863	116.001	1170.47
293	10.684	12.366	9.880	116.039	1172.87
225	10.663	12.311	9.849	115.896	1163.11
250	10.670	12.331	9.863	115.945	1167.03

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275	10.677	12.351	9.874	115.987	1170.52
320	10.695	12.388	9.896	116.030	1178.16
340	10.701	12.406	9.926	116.004	1184.39
293	10.691	12.372	9.880	116.025	1174.36
360	10.703	12.442	9.876	116.154	1180.54
370	10.715	12.452	9.895	116.244	1184.21
375	10.711	12.459	9.917	116.186	1187.55
dihydrate					
200	4.721	10.654	13.007	93.210	653.21
250	4.731	10.677	13.016	93.188	656.46
275	4.736	10.688	13.022	93.177	658.18
300	4.742	10.701	13.024	93.158	659.86
300	4.742	10.703	13.024	93.154	660.01

^aThe Rietveld refinement and Pawley refinement led to the same results within error, therefore only the Pawley results have been reported here.

Table 3. Thermal expansion tensor eigenvalues and eigenvectors obtained for forms I and II, and the dehydrate of triethylenetetramine dihydrochloride

Eigenvectors ^a				Eigenvalues (MK ⁻¹)	
	<i>a</i>	<i>b</i>	<i>c</i>		
Form I					
e₁	0.691	0	−0.723	α_{11}	3.80(20)
e₂	0	−1	0	α_{22}	24.91(80)
e₃	0.719	0	0.695	α_{33}	31.78(32)
Form II					
e₁	−0.727	0	−0.687	α_{11}	4.5(4.8)
e₂	−0.545	0	0.838	α_{22}	47.0(5.0)
e₃	0	1	0	α_{33}	80.5(3.4)
dihydrate					
e₁	− 0.288	0	− 0.958	α_{11}	13.0(8)
e₂	0	−1	0	α_{22}	43.8(5)
e₃	0.998	0	0.060	α_{33}	44.6(5)

^aas a function of the unit cell parameters

Table 4. Torsion angles (°) of triethylenetetramine dichloride in forms I, II, and the dihydrate

Torsion	form I	form II	dihydrate
N1-C1-C2-N2	-73.7(3)	74.5(1.3)	178.83(9)
C1-C2-N2-C3	172.9(3)	-159.1(1.1)	177.80(9)
C2-N2-C3-C4*	-177.3(3)	81.7(1.2)	-179.63(9)
N2-C3-C4-N3*	-180.00(3)	44.7(1.6)	-180.00(9)
C3-C4-N3-C5*	177.3(3)	-163.5(1.2)	179.63(9)
C4-N3-C5-C6*	-172.9(3)	-56.5(1.6)	-177.80(9)
N3-C5-C6-N4*	73.7(3)	-76.1(1.4)	-178.83(9)

*because of the symmetry in form I and the dihydrate C4=C3, N3=N2, C5=C2, C6=C1 and N4=N1

Table 5. Hydrogen bonds in form I, form II and the dihydrate in the asymmetric unit^a

	Distance (Å)			Angle (°)
	D – H	H...A	D...A	D-H...A
Form I				
N1 – HN1c...N2 ⁱ	0.92(2)	2.03(2)	2.917(5)	161.6(1.1)
N1 – HN1a...Cl ⁱⁱ	0.887(10)	2.57(10)	3.133(3)	169.3(1.0)
N1 – HN1b...Cl ⁱⁱⁱ	0.928(13)	2.219(12)	3.135(4)	168.8(1.0)
N2 – HN1b...Cl ⁱⁱ	0.829(85)	2.556(95)	3.374(4)	169.50(28)
C1-H1a...Cl ⁱⁱⁱ	0.958(11)	2.852(13)	3.739(3)	154.60(97)
Form II				
N1 – HN1a...Cl1 ^{iv}	0.89	2.506	3.309	150.40
N1 – HN1b...Cl1 ^v	0.95(4)	2.21(5)	3.11(2)	158(4)
N2 – HN2...Cl1 ⁱⁱ	0.80(5)	2.51(4)	3.297(16)	165(4)
N3 – HN3...Cl1 ^{iv}	0.78(7)	3.35(5)	3.208(18)	93(5) ^b
N3 – HN3...Cl2 ^{vi}	0.78(7)	2.48(6)	3.20(2)	153(6)
C4-H4b...Cl2 ^{vi}	0.98(5)	2.74(5)	3.540(1)	138(4)
N4 – HN4c...Cl2 ^{vi}	0.89(5)	2.98(5)	3.42(2)	112(3)
N4 – HN4b...Cl2 ^{vii}	0.90(5)	2.74(4)	3.317(16)	123(4)
Dihydrate				
N1-H3...Cl ^{viii}	0.875(17)	2.466(18)	3.2993(13)	159.3(1.5)
N1-H4...Cl ^{ix}	0.915(18)	2.319(18)	3.1911(14)	159.2(1.5)

N1...Cl ⁱⁱ			3.388(1) ^b	
N1-H5...O1 ^x	0.915(16)	1.876(16)	2.7593(15)	161.8(1.4)
N2-H6...Cl ^{xi}	0.831(17)	2.702(18)	3.5287(12)	173.3(1.4)
O1-H2...N2 ⁱⁱ	0.874(19)	1.880(16)	2.7485(14)	172.1(1.8)
O1-H1...Cl ^{xii}	0.759(19)	2.492(19)	3.2467(13)	173.2(19)

Symmetry codes: (i) $x, y - 1, z$; (ii) x, y, z ; (iii) $-x + \frac{1}{2}, y - \frac{1}{2}, -z + 1.5$; (iv) $-x + 1, -y + 1, -z + 1$; (v) $-x + 1, y + \frac{1}{2}, -z + \frac{1}{2}$; (vi) $-x + 1, y - \frac{1}{2}, -z + \frac{1}{2}$; (vii) $x - 1, y, z$; (viii) $-x, -y + 1, -z + 1$; (ix) $x - 1, y, z$; (x) $-x - 1, y + \frac{1}{2}, -z + 1.5$; (xi) $x - 1, -y + 1.5, z + \frac{1}{2}$; (xii) $-x - 1, -y + 1, -z + 1$;

^aBoth the dihydrate and form I have only half a TETA molecule in the asymmetric unit

^bThis may not be a hydrogen bond in accordance with its definition, but the donor – acceptor distance and the fact that the acceptor Cl[−] is charged imply nevertheless the presence of an electrostatic interaction

For Table of Contents us only

Triethylenetetramine dihydrochloride forms strong ionic interactions, such as the diamond patterns with NH_3^+ and Cl^- as shown, that clearly affect the thermal expansion of the crystal. In combination with configurational versatility and a multitude of hydrogen bonds, it leads to several distinct crystal structures.

Chemical structure of triethylenetetramine dihydrochloride
17x3mm (600 x 600 DPI)

Results of the structure resolutions by X-ray powder diffraction a. Rietveld refinements against the powder diffraction patterns b. Crystal structure of form I c. Crystal structure of form II. Hydrogen atoms omitted for clarity.

91x66mm (288 x 288 DPI)

Results of the structure resolutions by X-ray powder diffraction a. Rietveld refinements against the powder diffraction patterns b. Crystal structure of form I c. Crystal structure of form II. Hydrogen atoms omitted for clarity.
90x63mm (288 x 288 DPI)

Results of the structure resolutions by X-ray powder diffraction a. Rietveld refinements against the powder diffraction patterns b. Crystal structure of form I c. Crystal structure of form II. Hydrogen atoms omitted for clarity.

28x9mm (300 x 300 DPI)

Results of the structure resolutions by X-ray powder diffraction a. Rietveld refinements against the powder diffraction patterns b. Crystal structure of form I c. Crystal structure of form II. Hydrogen atoms omitted for clarity.
28x9mm (300 x 300 DPI)

Graphical representation of the thermal expansion tensors of forms I, II, and the dihydrate at 300 K
31x12mm (300 x 300 DPI)

Infrared transmittance spectra of the two TETA·2HCl polymorphs I and II. Spectra are shifted for clarity
47x27mm (600 x 600 DPI)

dihydrate

form I

form II

Conformations of TETA in the dihydrate (left-hand side), form I (center), and form II (right-hand side)
82x66mm (300 x 300 DPI)

Hydrogen-bond patterns in form I a. between TETA molecules b. Ionic interactions between chloride ions and ammonium groups on TETA molecules (graph set R24(8)) c. Hydrogen bonds and other interactions around the chloride ion
50x61mm (300 x 300 DPI)

Hydrogen-bond patterns in form I a. between TETA molecules b. Ionic interactions between chloride ions and ammonium groups on TETA molecules (graph set R24(8)) c. Hydrogen bonds and other interactions around the chloride ion
39x39mm (300 x 300 DPI)

Hydrogen-bond patterns in form I a. between TETA molecules b. Ionic interactions between chloride ions and ammonium groups on TETA molecules (graph set R24(8)) c. Hydrogen bonds and other interactions around the chloride ion
50x23mm (300 x 300 DPI)

Ionic and hydrogen-bond interactions of Cl1 in form II.
70x37mm (300 x 300 DPI)

Fingerprint plots of the TETA molecule in the dihydrate, in form I and in form II. From top to bottom: all intermolecular interactions together, Cl···H interactions, N···H, H···H, and O···H interactions. The di,de occurrence increases from deep blue to light blue.
136x225mm (300 x 300 DPI)

Projections of the thermal expansion tensors in relation to the unit cell a. for the dihydrate, b. for form I, and c. for form II. Hydrogen atoms have been omitted for clarity.
64x84mm (300 x 300 DPI)

Projections of the thermal expansion tensors in relation to the unit cell a. for the dihydrate, b. for form I, and c. for form II. Hydrogen atoms have been omitted for clarity.
82x137mm (300 x 300 DPI)

Projections of the thermal expansion tensors in relation to the unit cell a. for the dihydrate, b. for form I, and c. for form II. Hydrogen atoms have been omitted for clarity.

64x84mm (300 x 300 DPI)

Diamond shape pattern in the dihydrate made up by the ionic interaction involving two chloride ions and two ammonium end groups.
70x44mm (300 x 300 DPI)

Triethylenetetramine dihydrochloride forms strong ionic interactions, such as the diamond patterns with NH_3^+ and Cl^- as shown, that clearly affect the thermal expansion of the crystal. In combination with configurational versatility and a multitude of hydrogen bonds, it leads to several distinct crystal structures.

34x21mm (300 x 300 DPI)