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Cimetidine, $C_{10}H_{16}N_6S$, form C: crystal structure and modelling of polytypes using the superspace approach

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The H2 antagonist cimetidine forms many polymorphs, several of which have resisted structural analysis thus far. Using single-crystal X-ray measurements obtained from synchrotron radiation, the crystal structure of cimetidine form C has been solved. This layered structure crystallizes in space group $C2/c$ with an unusually large lattice parameter, $a = 82.904 \text{ \AA}$. The thickness of each layer L is equal to $a' = a/6 = 13.82 \text{ \AA}$, and $a = 6a'$ originates from a sixfold $LLLL'L'L'$ sequence with L and L' differing by $0.5b$. This packing is reminiscent of polytypic stacking in metals. A $(3 + 1)$ -dimensional superspace model is derived and used to explain and predict many polytypic modifications. This model is characterized by (i) the $(3 + 1)$ -dimensional symmetry group $X2/c(\alpha 0 \gamma)00$, where $X = 0\frac{1}{2}0\frac{1}{2}$; (ii) the lattice parameter a' and modulation vector $\mathbf{q} = 1/n(\mathbf{a}^*)$; (iii) the atomic positions of a single molecule of cimetidine form C; (iv) the primary variable, $1/n$. The model reproduces the previously solved structure, the 6M polytype, and generates the related polytypes nM with lattice parameter $a_{nM} = na'$ for $n = 1, 2, 3, 4$ and 5 . A comparison of powder X-ray diffraction patterns available for cimetidine form C with those simulated for the nM polytypes suggests that the powder samples published previously probably contain a mixture of various polytypes.

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1. Introduction

Cimetidine, *N*-cyano-*N'*-methyl-*N''*-{2-[(4-methyl-5-imidazolyl)-methylthio]ethyl}guanidine, is a well known antagonist for H2 receptors located on the surface of stomach parietal cells. It inhibits acid secretion induced by histamin, gastrin or penta-gastrin, whereby it contributes to the healing of gastric ulcers. Cimetidine has been exceptionally successful on the market and became one of the first blockbuster drugs. Shortly after being introduced into therapy in 1976 (Brimblecombe *et al.*, 1975; Bavin *et al.*, 1976), it was discovered that cimetidine produces a number of crystal modifications. Four crystal modifications and a number of pseudopolymorphs were described and characterized by different methods: IR spectroscopy (Hegedüs & Görög, 1985), X-ray diffraction (Hadicke *et al.*, 1978; Kojic Prodic *et al.*, 1979; Shibata *et al.*, 1983), synchrotron X-ray powder diffraction (Cernik *et al.*, 1991), atomic force microscopy (Danesh *et al.*, 2000), scanning thermo microscopy (Sanders *et al.*, 2000) and differential scanning calorimetry (Bauer-Brandl, 1996). A fifth modification has been described (Bencsik *et al.*, 1992), but could not be reproduced even by high-throughput crystallization experi-

ments (Dova *et al.*, 2005). Polymorphs have different physical properties and hence the choice of the best polymorph for specific drug formulations is essential for effective drug manufacture and optimal performance. Understanding the relationship between molecular conformation, crystal structure and polymorph suitability in a drug formulation remains a significant challenge.

The explicit crystal structures of modifications A and D (Fig. 1) were solved quite early on using single-crystal X-ray diffraction (XRD) (Hadicke *et al.*, 1978; Shibata *et al.*, 1983). Modification A is used as tablets on the market, but D is not because it is difficult to compress (Bauer-Brandl, 1996). Interestingly, despite their very different mechanical properties and distinct crystal structures, the thermodynamic stabilities of A and D in terms of heat of fusion are extremely close to each other: they can hardly be distinguished experimentally and are 'practically isoenergetic' (Bauer-Brandl, 1996). Using the explicit crystal structures, the relationships between these 'isoenergetic' polymorphs A and D have been studied in detail using solution calorimetry, and the results have been compared with *in silico* methods based on force fields (Bauer-

Brandl *et al.*, 1999). This is not the case for modifications B and C. They are particularly interesting because from the thermochemical data it may even be speculated that at least modification C is also 'isoenergetic' with A and D. Although these polymorphs have been known for a long time, the structure of neither B nor C has yet been solved. Both modifications B and C display needle-shaped crystals and are therefore of less practical value, since they resist processing on a larger scale. The needles cannot even be crystallized thick enough to enable standard single-crystal XRD structure analysis.

The current work uses synchrotron radiation to solve the structure of modification C from small single crystals. This polymorph has also been referred to as Form IV by Kojic-Prodic *et al.* (1979) and as Form B by Shibata *et al.* (1983), according to XRD reference patterns 00-032-1586 and 00-036-1639 (PDF2; ICDD, 2005), respectively. The structure solution of this polymorph is useful, first of all from a general point of view to better understand the complex system of the 'iso-energetic' cimetidine polymorphs, and secondly to study the published powder diffractograms, some of which (Kojic-Prodic *et al.*, 1979; Shibata *et al.*, 1983) still cannot be clearly attributed to specific crystal modifications.

In addition to solving the crystal structure of cimetidine C by traditional means, we apply the superspace model to describe the crystal structure as a commensurately modulated

structure. This allows us to explain the difference between the reference powder diffraction patterns on the basis of the coexistence of polytypic modifications, which are modelled and described in the present work. The experimentally studied polytype called 6M refers to a monoclinic unit cell packed with six similar structural layers alternating periodically along the *a* axis with two different positions. We also predict and describe polytypes 1M, 2M, 3M, 4M and 5M.

Polytypism is a well known phenomenon and the reader can refer to the literature (Krishna, 1983; Ferraris *et al.*, 2004) for inorganic compounds. Generally, methods of polytype analysis concern the description of a packing of topologically identical layers and their stacking order/disorder (OD). The OD groupoid is one of the most efficient techniques used in traditional crystallography (Dornberger-Schiff & Grell-Niemann, 1961; Merlino, 1997). The absence of specific software to allow a simple analysis of polytypic modifications, including their identification and prediction, is the main weakness of the method. The superspace approach and corresponding software [for instance, *JANA2006* by Petříček *et al.* (2006)], which is based on higher-dimensional crystallography, avoid this weakness. A recent review of organic molecular compounds with modulated crystal structures (Schönleber, 2011) shows an increasing interest in the superspace concept in the field of organic materials. The powerful tools associated with this approach have also been applied to the description of both polytypic (Arakcheeva & Chapuis, 2006) and polytypoid (Perez-Mato *et al.*, 1999) families of inorganic compounds. However, the elaborated arsenals on polytypism are still practically unused by small-molecule chemistry. One can mention the description of stacking disorder in tris(bicyclo[2.1.1]hexeno)benzene, and related examples, as one of only a few analyses of polytypic modifications formed by a small molecule (Birkedal *et al.*, 2003; Bürgi *et al.*, 2005). At the same time, some polymorphic modifications of small-molecule compounds can be considered as polytypes. Polytypes differ from polymorphs in being characterized by different packing of identical molecules, while molecules of different polymorphs have different conformations. For instance, aspirin forms two polymorphs, which are certainly polytypes (Bond *et al.*, 2011).

Polytypism phenomena are of importance not only from a theoretical point of view for the discussion of crystal structures in general but also, particularly in the case of small organic molecules used as drugs, for the definition of the respective drug substance itself with implications for quality, handling and medical agency registration issues.

2. Experiments and methods

2.1. Preparation

Cimetidine raw material was donated by NextPharma (NextPharma Arzneimittel GmbH, Göttingen, Germany; identification No. 327900). Distilled water was used as solvent. Form C was crystallized by cooling a 5% (*m/m*) aqueous solution rapidly from 353 to 278 K without agitation (Hegedüs

Figure 1
The molecular conformations of cimetidine forms A and D. The figure was produced using the PLATON program (Spek, 2009) on the basis of atomic parameters reported by Hadicke *et al.* (1978) and Shibata *et al.* (1983) for A and D, respectively.

Table 1

Details of the single-crystal synchrotron XRD experiments, crystallographic data and characteristics of structure refinements of cimetidine form C polytype 6M.

Corresponding data in CIF format are included as part of the supplementary material.

Crystal data	3D (supercell) model	(3 + 1)D (superspace) model
Chemical formula	C ₁₀ H ₁₆ N ₆ S	C ₁₀ H ₁₆ N ₆ S
Chemical formula weight	252.36	252.36
Crystal system	Monoclinic	Monoclinic
(Super) space group	C2/c	$X2/c(\alpha 0 \gamma)00;\dagger$ $X = 0\frac{1}{2}0\frac{1}{2}$
Temperature (K)	100	100
<i>a</i> , <i>b</i> , <i>c</i> (Å)	82.904 (10) 4.8500 (10) 18.760 (5)	13.817 (1) 4.8500 (10) 18.760 (5)
β (°)	74.340 (19)	74.340 (19)
Modulation vector	–	$\mathbf{q} = 1/6\mathbf{a}^*$
<i>V</i> (Å ³)	7263 (3)	1210.5 (5)
<i>Z</i>	24	4
<i>D_x</i> (Mg mm ^{−3})	1.3842	1.3842
μ (mm ^{−1})	0.34	0.34
Crystal size (mm)	0.1 × 0.02 × 0.01	0.1 × 0.02 × 0.01
Crystal form, colour	Needle, transparent colourless	Needle, transparent colourless
Data collection		
Diffractometer	mar345	mar345
Radiation type, λ (Å)	Synchrotron, 0.8000	Synchrotron, 0.8000
Data collection method	Image plate	Image plate
No. of measured, independent and observed reflections	15754, 4668, 3822	15754, 4668, 3822
Criterion for observed reflections	$I > 5\sigma(I)$	$I > 5\sigma(I)$
<i>R</i> _{int}	0.0382	0.0382
<i>q</i> _{max} (°)	22.46	22.46
Range of <i>h</i> , <i>k</i> , <i>l</i> , <i>m</i>	−88 → <i>h</i> → 87 −5 → <i>k</i> → 5 −20 → <i>l</i> → 20	−14 → <i>h</i> → 14 −5 → <i>k</i> → 5 −20 → <i>l</i> → 20 −3 → <i>m</i> → 2
Refinement		
Refinement on	<i>F</i>	<i>F</i>
<i>R</i> _{all} [<i>F</i> > 3σ(<i>F</i>)], ω <i>R</i> (<i>F</i>), <i>S</i>	0.0457, 0.0582, 4.54	0.0458, 0.0582, 4.56
<i>R</i> _{main} [<i>F</i> > 3σ(<i>F</i>)], ω <i>R</i> (<i>F</i>)	–	0.0417, 0.0548
<i>R</i> _{1st} [<i>F</i> > 3σ(<i>F</i>)], ω <i>R</i> (<i>F</i>)	–	0.0417, 0.0564
<i>R</i> _{2nd} [<i>F</i> > 5σ(<i>F</i>)], ω <i>R</i> (<i>F</i>)	–	0.0477, 0.0595
<i>R</i> _{3rd} [<i>F</i> > 5σ(<i>F</i>)], ω <i>R</i> (<i>F</i>)	–	0.0642, 0.0666
No. of reflections	4668	4668
Main	–	775
1st order satellites	–	1527
2nd order satellites	–	1592
3rd order satellites	–	774
GOF	4.15	4.16
No. of parameters	460	460
H-atom treatment	Constrained	Constrained
Weighting scheme	Based on measured s.u.'s, ω = 1/[σ ² (<i>F</i>) + 0.0001 <i>F</i> ²]	Based on measured s.u.'s, ω = 1/[σ ² (<i>F</i>) + 0.0001 <i>F</i> ²]
(<i>D</i> / <i>s</i>) _{max}	<0.001	<0.0001
Δρ _{max} , Δρ _{min} (e Å ^{−3})	0.40, −0.41	0.41, −0.4

† Symmetry operations: (1) x_1, x_2, x_3, x_4 ; (2) $-x_1, x_2, -x_3 + \frac{1}{2}, -x_4$; (3) $-x_1, -x_2, -x_3, -x_4$; (4) $x_1, -x_2, x_3 + \frac{1}{2}, x_4$; (5) $x_1, x_2 + \frac{1}{2}, x_3, x_4 + \frac{1}{2}$; (6) $-x_1, x_2 + \frac{1}{2}, -x_3 + \frac{1}{2}, -x_4 + \frac{1}{2}$; (7) $-x_1, -x_2 + \frac{1}{2}, -x_3, -x_4 + \frac{1}{2}$; (8) $x_1, -x_2 + \frac{1}{2}, x_3 + \frac{1}{2}, x_4 + \frac{1}{2}$.

& Görög, 1985; Bauer-Brandl, 1996). The crystals obtained form transparent colourless needles.

2.2. Synchrotron radiation XRD experiments

Single-crystal diffraction data were collected on beamline BM01A at the Swiss–Norwegian Beamlines (SNBL), ESRF, Grenoble. A needle-like crystal of size about 100 × 20 × 10 μm was selected from the batch as prepared and mounted onto a cryoloop. A total of 178 diffraction frames were collected using a Marresearch mar345 image-plate detector with a rotation angle of 2° per frame. A sample temperature of 100 K was maintained throughout the measurement using a nitrogen gas flow from an Oxford Cryostream. A focused beam with a wavelength of 0.8000 Å was selected with an Si(111) monochromator. Integration of the images and indexing of the diffraction reflections were performed using *CrysAlisPRO* (Agilent Technologies, 2011). A total of 15 754 measured intensities were used for the structure determination.

The synchrotron powder XRD (PXRD) data were collected at room temperature on beamline BM01B at the SNBL, in capillary mode using a wavelength of 0.697 Å selected by an Si(111) monochromator. High angular resolution was achieved by using Si(111) analyser crystals, and the data were obtained in the 1–30° 2θ range with a step size of 0.005°. The PXRD data were used for refinement of the lattice parameters at room temperature.

2.3. Crystal structure using the classical approach

Using single-crystal data collected at 100 K, the three-dimensional model was obtained and refined using *JANA2006* (Petříček *et al.*, 2006). *PLATON* was used for graphical illustrations (Spek, 2009). The structure solution was obtained in space group *C2/c* with lattice parameters *a* = 82.904 (10), *b* = 4.8500 (10), *c* = 18.760 (5) Å and β = 74.340 (19)°. The model was refined successfully with anisotropic atomic displacement parameters to *R* = 0.0457. H atoms were constrained with distances N–H = 0.87 Å and C–H = 0.87 Å for –CH₂– and –NH₂– groups, and C–H = 0.96 Å for –CH₃ groups. The residual electron density with extrema of 0.40 and −0.41 e Å^{−3} indicated that no additional atoms are present. The main characteristics of the structure refinement are given in Table 1. The corresponding characteristics of 51 non-H atoms and 48 H atoms are listed in the supplementary material for this paper (Tables S1 and S2; data are also provided in CIF format¹). The supplementary crystallographic data for the refined structure of cimetidine form C have in addition been deposited with the Cambridge Structural Database (CSD; Allen, 2002) (refcode CCDC 898404). These data can be obtained free of charge from the CSD via http://www.ccdc.cam.ac.uk/data_request/cif.

¹ Supplementary data are available from the IUCr electronic archives (Reference: HE5576). Services for accessing these data are described at the back of the journal.

2.4. Crystal structure using the superspace approach

The superspace approach is based on the $(3 + d)$ -dimensional group symmetry ($d = 1, 2$ or 3) and can be applied for both incommensurately and commensurately modulated structure refinements (Janssen *et al.*, 2007; van Smaalen, 2007). In particular, this approach results in a refined $(3 + d)$ -dimensional superspace model. A commensurately modulated structure can be refined as both a three-dimensional supercell model and a $(3 + d)$ -dimensional superspace model with identical structural characteristics. This can be confirmed by a superspace–supercell model transformation, an example of which has been reported by Martinez-Garcia *et al.* (2009) for $d = 1$. However, the $(3 + d)$ -dimensional superspace model can also be used to generate a family of related structures (Arakcheeva & Chapuis, 2008), which provide a tool for structure modelling and prediction. Since the structure of cimetidine form C can be considered as commensurately modulated, this approach was used here for the modelling of a polytypic family. *JANA2006* was used for the $(3 + 1)$ -dimensional superspace model refinements, for the superspace–supercell transformations and for modelling.

The $(3 + 1)$ -dimensional $[(3 + 1)D]$ superspace group used for the description of the commensurately modulated structure is $X2/c(\alpha 0 \gamma)00 (3 + 1)D$ with unit-cell centring $X = 0\frac{1}{2}0\frac{1}{2}$, modulation vector $\mathbf{q} = 1/6(\mathbf{a}')^*$ and lattice parameters $a' = a/6 = 13.817$, $b = 4.850$, $c = 18.760$ Å and $\beta = 74.34^\circ$ (100 K). In the superspace model, only 17 non-H and 16 H atoms forming a single molecule need to be included in the list of atoms. This atomic set defines the basic structure. All details of the model construction and refinement are described in Appendix A.

Figure 2

Molecule I of cimetidine form C. Two projections are shown: perpendicular (right) and normal (left) to the imidazole ring.

The quality of the superspace model refinement is identical to the refinement of the three-dimensional model (Table 1). This three-dimensional (3D) model can be also called a supercell model, because $a_{3D} = 6a'_{(3+1)D}$. The superspace–supercell structure transformation shows identical (within 0–1 s.u.) corresponding atomic parameters (supplementary material, Table S1). This confirms the validity of the $(3 + 1)$ -dimensional superspace description of the refined structure.

2.5. Modelling based on the superspace model

The general principles of the modelling were formulated, justified and tested with the example of some inorganic compounds (Arakcheeva & Chapuis, 2006, 2008). They are applied here to an organic material for the first time. Accordingly, the $(3 + 1)$ -dimensional superspace model yields (i) the $(3 + 1)$ -dimensional group symmetry and a general expression of the modulation vector $\mathbf{q}$; (ii) a basic structure, which is defined by a unit cell and a number of atoms occupying certain Wyckoff sites; and (iii) variables characterizing the structure modulations and the free parameters defining the modulation vector $\mathbf{q}$. The modelling of the structure manifold is based on the variation of a primary variable.

The refined $(3 + 1)$ -dimensional superspace model of cimetidine form C is used here for the structure modelling. It is precisely the variation of $\mathbf{q}$ which is responsible for the structure manifold in the polytypic family of cimetidine form C.

3. Results and discussion

3.1. Molecular structure of cimetidine form C

The crystal structure of form C consists of three symmetry-independent molecules, I, II and III (Fig. 2), which are very similar to each other, as shown by overlays of the molecules in Fig. 3. The interatomic distances and angles (supplementary material, Tables S4 and S5, respectively) are very similar to those reported for form D (Shibata *et al.*, 1983), although no intramolecular hydrogen bonds can be observed in form C.

Figure 3

Fit of molecules constituting the crystal structure of form C. Overlaps of I and II, I and III, and II and III are shown on the left, in the middle and on the right, respectively.

The molecule can be described as linear (Fig. 2). The angles between the planar imidazole ring and the guanidine group are small: 17.95, 10.95 and 21.64° for molecules I, II and III, respectively. The planes of the linking C2—C5—S and S—C6—C7—N3 groups are also slightly tilted, with angles of 8.9–11.2°. The planes of both the imidazole ring and the guanidine group are approximately orthogonal to the linking groups, with the corresponding angles varying from 79.9 to 89.7°. Detailed characteristics of the planes are available in the supplementary material, Table S6. The torsion angles characterizing the similarity of the three molecules are given in Table 2.

3.2. Crystal packing of cimetidine form C

The crystal packing is shown in Figs. 4 and 5. Similar layers, labelled *L* in these figures and hereinafter, extend in the *bc* plane. A single layer consists of parallel molecules bonded 'head-to-tail' by N3—H···N2 and N1—H···N5 hydrogen

Table 2

Torsion angles (°) in the three symmetry-independent molecules.

Angle	Molecule I	Molecule II	Molecule III
N2—C2—C5—S	−88.3 (4)	−86.7 (4)	−86.3 (4)
C3—C2—C5—S	90.6 (4)	89.7 (4)	92.3 (4)
C2—C5—S—C6	−169.7 (3)	−170.6 (3)	−170.5 (3)
C5—S—C6—C7	179.4 (3)	176.2 (3)	−176.3 (3)
S—C6—C7—N3	−180.00	177.4 (2)	−177.7 (3)
C6—C7—N3—C8	91.4 (4)	91.4 (4)	91.3 (4)
C7—N3—C8—N4	−174.7 (3)	−174.7 (3)	−173.9 (3)
C7—N3—C8—N5	4.6 (5)	4.3 (5)	5.0 (5)

Figure 4

A single *L* layer (top) and the connection of adjacent layers by hydrogen bonds in the crystal structure of cimetidine form C. I, II and III indicate the corresponding molecules.

Figure 5

Packing of molecules in cimetidine form C polytype 6M. The *ac* (left) and *ab* (right) structure projections are shown. Red circles mark the centres of molecules associated with the positions of S1 atoms. *L* and *L'* are defined by $y \approx 0$ and $y \approx 0.5$, respectively, for the centres of the molecules. I, II and III denote the corresponding molecules.

Table 3

Crystallographic characteristics of the modelled polytypes 1M, 2M, 3M, 4M and 5M of cimetidine form C and the experimentally observed polytype 6M at 295 K.

Characteristic	1M	2M	3M	4M	5M	6M
Sequence of L layers†	L	$L'L$	$L'LL$	$L'LL'L'$	$L'L'LL'L'$	$L'L'LLLL'L'$
Supercell model						
Space group	$P2/c$	$C2/c$	$P2/c$	$C2/c$	$P2/c$	$C2/c$
Lattice parameter a_x^* (Å)	$a = a' = 13.827$	$a = 2a' = 27.654$	$a = 3a' = 41.481$	$a = 4a' = 55.308$	$a = 5a' = 69.135$	$a = 6a' = 82.962$
Superspace model§						
$\mathbf{q}$ vector, t_0	$\mathbf{q} = 1\mathbf{a}^*, t_0 = 0$	$\mathbf{q} = 1/2\mathbf{a}^*, t_0 = 0$	$\mathbf{q} = 1/3\mathbf{a}^*, t_0 = 0$	$\mathbf{q} = 1/4\mathbf{a}^*, t_0 = 1/8$	$\mathbf{q} = 1/5\mathbf{a}^*, t_0 = 0$	$\mathbf{q} = 1/6\mathbf{a}^*, t_0 = 0$

† L or L' indicates the layer with location of S1 atoms at about $y = 0$ and $y = 0.5$, respectively. ‡ The lattice constants $b = 4.887$, $c = 19.132$ Å and $\beta = 73.749^\circ$ are identical for all the listed models. § The $(3+1)$ D superspace group is identical for all polytypes and is $X2/c(\alpha 0 \gamma)00$. The a' lattice constant of the basic $(3+1)$ D superspace unit cell is also the same for all polytypes and is $a' = 13.827$ Å.

bonds (Fig. 4, top). These bonds link the molecules along both the c and b axes, because they have characteristic inclinations relative to both axes. Along the a -axis direction, adjacent L layers are linked to each other by $N4-H \cdots N6$ hydrogen bonds (Fig. 4, bottom). Detailed characteristics of the intermolecular hydrogen bonds are listed in the supplementary material, Table S7.

Along the a axis, a single L layer has a thickness $a' = a/6 = 13.817$ Å (Fig. 4, top). The unusually long lattice parameter $a = 6a' = 82.904$ Å results from a sequence of six L layers, each with a relative shift of 0 or $0.5b$. As can be deduced from Fig. 5, the sequence of L layers can be described as $LLLL'L'L'$ along the a axis. L and L' are characterized by $y \simeq 0$ and $y \simeq 0.5$, respectively, for the centres of the molecules constituting the corresponding layer. The centre of each molecule is associated with the position of atom S1.

3.3. Assumption of a polytypic family for cimetidine form C

The refined structure shows that each L layer can be connected to either an L or an L' layer, and the connections LL , $L'L$, $L'L'$ and LL' are stable. This means that polytypes characterized by different sequences of L and L' are very probable for cimetidine form C. The refined structure, which is called polytype 6M, is one of them. The notation 6M indicates that the monoclinic unit cell consists of six similar layers alternating periodically along the a axis with different locations.

In general, any sequence of L and L' along the a axis can be postulated for the crystal packing. Moreover, the sequence of the layers can be either periodic or aperiodic. We limited ourselves to the generation and description of periodic sequences, which consist of less than six layers per period and maintain the monoclinic twofold axis and the c -glide plane. For this purpose, we used the method based on the $(3+1)$ -dimensional superspace model (Arakcheeva & Chapuis, 2008).

3.4. Characteristics of the $(3+1)$ -dimensional superspace model of cimetidine form C

This model was obtained from the $(3+1)$ -dimensional superspace model refinement of cimetidine form C polytype

6M. The superspace model is characterized by (i) the $(3+1)$ -dimensional superspace group $X2/c(\alpha 0 \gamma)00$ with unit-cell centring $X = 0\frac{1}{2}0\frac{1}{2}$ and modulation vector $\mathbf{q} = \alpha(\mathbf{a}')^* + \gamma\mathbf{c}^*$; (ii) the basic structure defined by the lattice parameters $a_{(3+1)D} = a' = a/6 = 13.817$, $b = 4.850$, $c = 18.760$ Å and $\beta = 74.34^\circ$ (numerical values valid at 100 K), and atomic positions of a single molecule of cimetidine form C (Appendix A); and (iii) the fixed characteristics of the molecule domain occupation width $\Delta = 0.5$ and central point $x_4 = 0$. The primary variable of the model is the coefficient α in the modulation vector $\mathbf{q}$.

Figure 6
Scheme illustrating the different sequence of L and L' along the a axis as a function of the modulation vector $\mathbf{q} = \alpha(\mathbf{a}')^*$ and t_0 . The sequence can be deduced from the intersections of a black solid line with black (L') and grey (L) (orange in the electronic version of the journal) domains. The L domain is defined by the central point $x_4 = 0$ and width $\Delta = 0.5$. L and L' domains are related by the unit-cell centring $X = 0\frac{1}{2}0\frac{1}{2}$. The coefficient α in the $\mathbf{q}$ vector expression is equal to the tangent of the angle between the black solid line and the x_1 axis.

3.5. Modelling of nM polytypes of cimetidine form C

The superspace model mentioned above was used for the modelling of possible polytypes. The primary variable is the coefficient α in the modulation vector, while $\gamma = 0$ is a specific feature of the model. Using this superspace model, different sequences of L and L' layers packed along the a axis can be modelled by varying α and t_0 , which is the zero point in the fourth, x_4 , axis (Fig. 6). In this model, n sections of a single molecule domain, which is defined on the x_4 axis with central point $x_4 = 0$ and width $\Delta = 0.5$ (Fig. 6), reproduce the nM structure characterized by $\mathbf{q} = 1/n(\mathbf{a}')^*$. The superspace-supercell transformation with $\alpha = 1/6$ reproduces a supercell [with $a_{6M} = 6a'_{(3+1)D}$] of polytype 6M characterized by the sixfold periodic sequence of layers $LLLL'L'L'$ (Fig. 5). The superspace-supercell transformation with $\alpha = 1/n$ (where n is an integer) reproduces a supercell [with $a_{nM} = na'_{(3+1)D}$] of polytype nM characterized by the periodic sequence of nL layers. With this method, the structural characteristics of various supercell models were obtained for the five simplest polytypes, 1M, 2M, 3M, 4M and 5M. The corresponding sets of atomic coordinates and graphical illustrations of the molecular

Figure 7

Comparison of the 00-032-1586 and 00-036-1639 XRD patterns (CCD PDF2) with the patterns simulated for the modelled, 1M, 2M, 3M, 4M and 5M, and the experimental, 6M, polytypes. The wavelength 1.540 Å (Cu) was used for the simulation.

Table 4

Characteristics of hydrogen bonds in polytypes 1M, 2M, 3M, 4M and 5M modelled for cimetidine form C and the experimentally observed polytype 6M.

Problematic characteristics for the structure stabilization are indicated by bold type.

Hydrogen bond between L layers.

Characteristic	1M	2M	3M	4M	5M	6M
N4—H (Å)	0.87	0.87	0.86–0.89	0.86–0.88	0.85–0.89	0.87
H...N6 (Å)	2.61	1.97	1.78–1.89	1.9–2.0	1.95–2.14	2.08–2.19
N4...N6 (Å)	3.44	2.32	2.43–2.49	2.63–2.79	2.71–2.95	2.85–3.00
N4—H...N6 (°)	160.7	102.5	129–131	141–148.9	146–155	148–153.5

Hydrogen bonds within the L layers.

Characteristic	1M	2M	3M	4M	5M	6M
N3—H...N2						
N3—H (Å)	0.86	0.86	0.86–0.89	0.86–0.88	0.86–0.89	0.87
H...N2 (Å)	2.18	2.22	2.14–2.23	2.17–2.24	2.14–2.25	2.17–2.25
N3...N2 (Å)	2.99	3.03	2.96–3.05	2.99–3.04	2.98–3.06	2.98–3.06
N3—H...N2 (°)	156.5	156	153.7–156	154–155.5	153–156	154–155.4
N1—H...N5						
N1—H (Å)	0.85	0.85	0.85–0.89	0.86–0.87	0.85–0.92	0.87
H...N5 (Å)	2.60	2.60	2.08–2.90	2.20–2.83	2.00–2.95	2.12–2.87
N1...N5 (Å)	3.33	3.33	2.93–3.62	3.02–3.56	2.87–3.67	2.94–3.61
N1—H...N5 (°)	146.5	146.6	141–159	143–156.5	139.4 –159	145–156.7

packing are given in the supplementary material (Tables S8–S12 and Figs. S2–S6).

Using PXRD synchrotron radiation data taken at 295 K, the lattice parameters of polytype 6M were refined as $a = 82.962$ (2), $b = 4.8874$ (1), $c = 19.1323$ (5) Å and $\beta = 73.749$ (7)°. These lattice parameters were applied for the simulation of the PXRD patterns (Fig. 7) of polytypes 1M, 2M, 3M, 4M and 5M.

The crystallographic characteristics including space group and lattice parameters valid at 295 K as well as the sequence of the L and L' layers in the supercell are listed in Table 3 for each of the modelled polytypes. Only values for $\alpha = 1/n$ ($n = 1, 2, 3, 4, 5$) were used here in the modulation vector $\mathbf{q} = \alpha(\mathbf{a}')^*$. However, it should be mentioned that α might be either any rational (in a periodic structure) or any irrational (in aperiodic incommensurately modulated structures) number.

3.6. Estimation of the validity of the nM polytypes

Since the molecule in the superspace model is fixed to the configurations appearing in the refined 6M structure, only the connections between molecules, *i.e.* the characteristics of the hydrogen bonds, are different in the modelled structures. The analysis of the hydrogen bonds gives us a criterion to evaluate the structures. These characteristics are listed in Table 4 alongside those experimentally observed for the 6M structure. The hydrogen bonds appearing inside the L layers are mainly similar in the experimental and modelled structures. The most problematic value, 139.4°, is the N5—H1 n 1...N1 angle calculated for polytype 5M. This value is less than 145° as observed in the experimental structure; however, it is accep-

table for a hydrogen bond. A few hydrogen bonds calculated for the interlayer interactions are more problematic for 1M, 2M and 3M. The distances $\text{H}\cdots\text{N6} = 2.61 \text{ \AA}$ and $\text{N4}\cdots\text{N6} = 3.44 \text{ \AA}$ calculated for 1M are too long in comparison to the values of $2.08\text{--}2.19 \text{ \AA}$ and $2.85\text{--}3.00 \text{ \AA}$, respectively, observed for 6M. The $\text{N6}\cdots\text{H1n4}\cdots\text{N4}$ angle equal to 102.5° in 2M and $129\text{--}131^\circ$ in 3M is too small in comparison to the range of $148\text{--}153.5^\circ$ observed in 6M. The hydrogen bonds calculated for 4M and 5M are similar to the corresponding hydrogen bonds observed in 6M. Therefore, 4M and 5M can be considered as very probable structures to exist under certain conditions of preparation.

It should be mentioned that the proposed structures are only models. They may also be stabilized by packing distortion, which can better fit the intermolecular interactions while keeping the main structural features and, therefore, the general appearance of the powder XRD patterns. We report here the patterns simulated for the polytypes (Fig. 7).

3.7. Analysis of powder XRD patterns reported for cimetidine form C

Two powder XRD patterns of cimetidine form C are available in the CCD PDF2 database. These reference patterns, 00-032-1586 and 00-036-1639, are compared with the patterns simulated for the six polytypes (Fig. 7).

The 00-036-1639 pattern is of extremely poor quality for the identification of the phase. It exhibits long lattice parameters and monoclinic symmetry, a characteristic of cimetidine form C. This pattern consists of only five lines. Taking into account that these lines probably originate from an experimental diffractogram with a high level of background, poor resolution and broad reflections (Shibata *et al.*, 1983), this pattern might be better associated with the pattern calculated for 2M, because this is the only one to show strong reflections at $2\theta \approx 30^\circ$. However, the strongest reflection of the 2M pattern is at $2\theta \approx 22^\circ$, which is missing in 00-036-1639.

The five lines of the 00-036-1639 pattern are quite different from the corresponding lines of the reference pattern 00-032-1586 (the maximal shift is about 0.5° for the strongest line at about 27.1°). The reference pattern 00-032-1586 exhibits a larger number of lines (Fig. 7). The $0\text{--}9^\circ$ 2θ range, which is the most informative for the recognition of polytypic modification, is missing in this pattern. Three lines located between 9 and 15° with hkl 002, $2n\ 0\ 0$ and $2n\ 0\ 2$ and the single $2n\ 0\ 4$ line at 20.1° are noncharacteristic because they exist in all nM polytypes. The qualitative comparison of the rest of the pattern shows that 5M and 6M give the best fit of the 00-032-1586 reference pattern with the exception of two lines in the vicinity of 22° , which are fitted with 3M and 4M. Probably, the sample that was used for this powder XRD pattern consists of a mixture of several polytypes.

4. Conclusions

An efficient method for the modelling of polytypic families is presented with a study of the cimetidine form C polymorph as

an example. This method is based on exploiting the $(3+1)$ -dimension superspace model and has not yet been properly recognized in the literature.

The experimentally studied structure of cimetidine form C can be equivalently refined using the traditional supercell structure model and the $(3+1)$ -dimensional superstructure model. While the traditional technique gives us only a standard description of one more crystal packing pattern of the small-molecule compound, the superspace model offers some additional opportunities. Here, we demonstrate that this model is a powerful tool for the prediction and characterization of polytypic modifications. Thus, with these tools, we are able to explain the polyvariant PXRD characteristics of cimetidine polymorph form C.

The powerful method of polytype modelling based on a superspace model may be also exploited in other cases. For instance, for acetylsalicylic acid (aspirin), different molecular packing schemes resulting in two polytypic modifications and their intergrowth were described (Bond *et al.*, 2007, 2011) and attributed to 'isoenergetic' structures similar to the present case for cimetidine (Wen & Beran, 2012). It therefore appears useful to consider such polytypic modifications using a similar superspace model adapted for the respective molecules to understand better the significance of polytype structures of drug substances.

APPENDIX A

$(3+1)\text{D}$ superspace model

The $X2/c(\alpha 0\gamma)00$ group ($X = 0\frac{1}{2}0\frac{1}{2}$ relates to the centring of the unit cell in four-dimensional space) was selected for the $(3+1)\text{D}$ model in order to keep the monoclinic centrosymmetry and the c -glide plane, and to reproduce the C centring of the three-dimensional model characterized by the unit cell with $a = 6a'$. The a' parameter is six times less than the corresponding a parameter of the three-dimensional structure. Consequently, the h index of each experimental hkl reflection used in the three-dimensional model was expressed as $h = 6h' + m$, where h' and m are integers or 0, so that each three-dimensional index hkl was transformed into the $(3+1)\text{D}$ index $h'klm$. The structure was refined as commensurate with $\mathbf{q} = 1/6(\mathbf{a}')^*$ and $t_0 = 0$. Only 17 non-H and 16 H atoms corresponding to a single molecule need to be included in the list of atoms (Table S3 of the supplementary material; data are also provided in CIF format). The centre of the molecule was associated with the S atom. The occupation $\Delta = 0.5$ at the central point $x_4 = 0$ characterizes a single position of the molecular domain. The refined translation and rotation modulations of the molecule are less than one s.u. Small differences between the three independent molecules forming the corresponding supercell were reproduced by the refinement of positional and anisotropic displacement parameter modulations of each non-H atom. Similarly to the three-dimensional model, all H atoms were constrained to ride on the corresponding non-H atoms. The characteristics of the refinement quality reached with this $(3+1)\text{D}$ model are

practically identical to those obtained with the three-dimensional supercell model (Table 1). This is not surprising because the number of refined parameters appears to be identical in the two cases. The coordinates, isotropic displacement parameters and Fourier amplitudes of the displacive modulation function are given for each atom of the single molecule in Table S3 of the supplementary material. These parameters were transformed into the list of atomic positions corresponding to the supercell, which is identical to the unit cell of the three-dimensional model. The transformed coordinates appear to be equal to those refined in the three-dimensional model to within 0–1 standard deviations (supplementary material, Table S3).

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