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1,2-Dimethyl-4-nitro-5-morpholinoimidazole and its hydrate: a case of a centrosymmetric–noncentrosymmetric ambiguity

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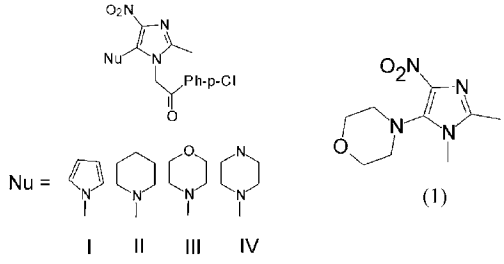
The compound studied is 1,2-dimethyl-4-nitro-5-morpholinoimidazole (1) in its anhydrous (1) and hydrated [(1)·H_2O] crystal forms. In spite of the strong electron-withdrawing effect of the nitro group, the unsubstituted N atom of the imidazole moiety retains its basic character and acts as an acceptor for intermolecular hydrogen bonds: either weak C—H···N bonds in (1) or strong O—H···N bonds, with the water molecules, in (1)·H_2O. The packing in (1) is determined by weak C—H···N and C—H···O hydrogen bonds, van der Waals interactions and the stacking of imidazole fragments. The crystal structure of (1)·H_2O is determined by strong O—H(water)···N3(imidazole) and O—H(water)···O(water) hydrogen bonds. This structure consists of a centrosymmetric 'matrix' of imidazole derivative molecules and locally noncentrosymmetric arrays of hydrogen-bonded water molecules. Each of these arrays is strictly homodromic, *i.e.* it runs only in one direction: ···H—O···H—O···H—O··· or ···O—H···O—H···O—H···. These homodromic domains are statistically distributed within the crystal.

1. Introduction

During our studies of nitroimidazole derivatives we found that 4-nitro-5-amino derivatives of imidazole were inactive towards protonation, although there were two potential proton acceptors in those molecules (Borowiak *et al.*, 1989; Wolska *et al.*, 1991, 1993, 1994; see scheme below). This molecular property was explained by the existence of a potential barrier that makes the basic centers (N3 of the imidazole moiety and the N atom of the amine substituent, Nu in the scheme below) inaccessible to proton attack (Wolska *et al.*, 1993). On the other hand, our recent study of the charge density distribution in 1-phenyl-4-nitroimidazole showed that the electron density of the N3 lone pair is clearly visible in the static deformation map (Kubicki *et al.*, 2002) and therefore the basicity of the imidazole moiety should be, at least in part, observed.



In the current study we present the crystal structures of 1,2-dimethyl-4-nitro-5-morpholinoimidazole (1) and its hydrate

Table 1
Experimental data.

	(1)	(1)·H_2O, 293 K	(1)·H_2O, 110 K
Crystal data			
Chemical formula	$C_9H_{14}N_4O_3$	$C_9H_{14}N_4O_3·H_2O$	$C_9H_{14}N_4O_3·H_2O$
M_r	226.24	244.26	244.26
Cell setting, space group	Monoclinic, $P2_1/m$	Triclinic, $P\bar{1}$	Triclinic, $P\bar{1}$
a, b, c (Å)	8.589 (2), 6.6750 (10), 10.657 (2)	10.1972 (11), 10.2908 (9), 11.1812 (12)	10.1087 (7), 10.2497 (8), 10.9623 (8)
α, β, γ (°)	90.00, 112.23 (3), 90.00	95.319 (8), 92.235 (9), 90.777 (8)	95.888 (6), 92.119 (6), 90.188 (6)
V (Å^3)	565.57 (19)	1167.2 (2)	1129.02 (14)
Z	2	4	4
D_x (Mg m^{-3})	1.329	1.437	1.437
Radiation type	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
No. of reflections for cell parameters	25	2644	4474
θ range (°)	8–15	5–20	5–25
μ (mm^{-1})	0.10	0.11	0.11
Temperature (K)	293 (2)	293 (2)	110 (1)
Crystal form, color	Block, colorless	Prism, colorless	Prism, colorless
Crystal size (mm)	0.3 × 0.2 × 0.15	0.3 × 0.15 × 0.1	0.3 × 0.15 × 0.1
Data collection			
Diffractometer	KM4 four-circle	Kuma KM4CCD κ-cradle	Kuma KM4CCD κ-cradle
Data collection method	ω–2θ	ω	ω
Absorption correction	None	None	None
No. of measured, independent and observed parameters	1140, 1068, 908	6520, 4860, 4180	17 221, 4891, 4823
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.033	0.011	0.025
θ_{max} (°)	25.0	27.0	27.0
Range of h, k, l	$0 \Rightarrow h \Rightarrow 10$ $0 \Rightarrow k \Rightarrow 7$ $-12 \Rightarrow l \Rightarrow 11$	$-12 \Rightarrow h \Rightarrow 12$ $-13 \Rightarrow k \Rightarrow 13$ $0 \Rightarrow l \Rightarrow 13$	$-12 \Rightarrow h \Rightarrow 12$ $-13 \Rightarrow k \Rightarrow 13$ $0 \Rightarrow l \Rightarrow 13$
No. and frequency of standard reflections	3 every 100 reflections	2 standard frames every 50 frames	2 standard frames every 50 frames
Intensity decay (%)	2	Not observed	Not observed
Refinement			
Refinement on	F^2	F^2	F^2
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.045, 0.091, 1.09	0.040, 0.113, 1.09	0.033, 0.080, 1.05
No. of relections	1068	4860	4891
No. of parameters	94	444	443
H-atom treatment	Mixture of independent and constrained refinement	Mixture of independent and constrained refinement	Refined independently
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.012P)^2 + 0.250P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0601P)^2 + 0.1765P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0376P)^2 + 0.4207P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	<0.0001	0.014	0.001
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.19, −0.16	0.18, −0.23	0.29, −0.24
Extinction method	*SHELXL*	*SHELXL*	None
Extinction coefficient	0.68 (2)	0.150 (7)	

Computer programs used: *Kuma KM4 Software* (Kuma Diffraction, 1992), *CrysAlis CCD* (Kuma Diffraction, 1999*a*), *CrysAlis Red* (Kuma Diffraction, 1999*b*), *SHELXS*97 (Sheldrick, 1997*a*), *SHELXL*97 (Sheldrick, 1997*b*), *Stereochemical Workstation* (Siemens, 1989).

(1)·H_2O. Our aim was to compare the different packing modes in these two structures. Moreover, in the hydrate structure we found an interesting case of the centro/noncentrosymmetric ambiguity.

2. Experimental

2.1. Synthesis

1,2-Dimethyl-5-morpholino-4-nitroimidazole was obtained in accordance with the following procedure: anhydrous 5-bromo-1,2-dimethyl-4-nitroimidazole (3 g, 13 mmol) was dissolved in absolute ethanol (15 ml) and then excess morpholine (4.75 g, 54 mmol) was added. The mixture was heated under reflux for 4 h and then cooled to room temperature. A solid material precipitated. Recrystallization from rectified ethanol (96%) gave slightly yellowish crystals of (1)·H_2O with m.p. 425–426 K, yield 2.76 g (94%). Analysis: calc. for $C_9H_{14}NO_3·H_2O$ (244.248): C 44.26, H 6.60, N 22.94; found: C 44.56, H 6.72, N 22.72%. ^{1}H NMR (300 MHz, DMSO-d_6); δ: 3.70–3.64 (m, 4H, H3 and H5 morpholine), 3.43 (s, 3H, 1-CH_3); 3.20–2.90 (m, 4H, H2 and H6 morpholine); 2.27 (s, 3H, 2-CH_3).

On the other hand, recrystallization from absolute ethanol gave small, colourless anhydrous crystals of (1) (of poor quality) with m.p. 448–449 K. Analysis: calc. for $C_9H_{14}NO_3$

Table 2
Hydrogen-bond data.

	D—H (Å)	H···A (Å)	D···A (Å)	D—H···A (°)
(1)				
C21—H21D···O54^{i}	0.84 (4)	2.87 (4)	3.487 (4)	132 (3)
C52—H52A···N3^{ii}	1.02 (2)	2.77 (2)	3.427 (3)	123 (2)
C11—H11C···O41^{iii}	0.90 (6)	2.60 (6)	3.456 (4)	159 (5)
C21—H21C···O41^{iii}	0.98 (5)	2.80 (6)	3.781 (4)	178 (4)
C21—H21C···O42^{iii}	0.98 (5)	2.73 (5)	3.466 (4)	133 (4)
(1)·H_2O at 110 (1) K				
O1W—H1WA···N3A	0.84 (2)	2.35 (2)	3.1523 (14)	158.6 (18)
O2W—H2WA···N3B	0.819 (19)	2.07 (2)	2.8899 (14)	176.2 (17)
O1W—H1WC···O1W^{iv}	0.80 (4)	2.04 (4)	2.832 (2)	170 (4)
O2W—H2WC···O2W^{v}	0.79 (4)	2.04 (4)	2.823 (3)	166 (5)
C11A—H11A···O41B^{vi}	0.967 (15)	2.612 (15)	3.4491 (17)	145.1 (11)
C52A—H52A···O41B^{vi}	0.994 (13)	2.824 (13)	3.7874 (15)	163.5 (10)
C56A—H56B···O42B^{vi}	0.997 (14)	2.815 (14)	3.7653 (15)	159.5 (10)
C11A—H11B···O54B^{vii}	0.960 (15)	2.447 (14)	3.2047 (16)	135.7 (11)
C55B—H55D···O42B^{vii}	0.973 (15)	2.447 (15)	3.3780 (16)	160.1 (12)
C11A—H11C···O41A^{viii}	0.972 (16)	2.592 (15)	3.4088 (19)	141.7 (11)
C21A—H21A···O42A^{viii}	0.957 (18)	2.597 (17)	3.4126 (18)	143.3 (13)
C52A—H52B···N3A^{viii}	0.968 (13)	2.759 (13)	3.4307 (17)	127.1 (10)
C52A—H52B···O41A^{viii}	0.968 (13)	2.801 (14)	3.7614 (15)	171.6 (10)
C55A—H55B···O42A^{ix}	0.972 (14)	2.735 (13)	3.4423 (17)	130.1 (10)
C11B—H11D···O41B^{x}	0.950 (14)	2.570 (14)	3.3651 (18)	141.4 (11)
C21B—H21F···O42B^{x}	0.974 (16)	2.590 (16)	3.4524 (18)	147.7 (12)
C52B—H52D···N3B^{x}	0.979 (13)	2.726 (13)	3.4710 (17)	133.3 (10)
C52B—H52D···O41B^{x}	0.979 (13)	2.896 (14)	3.8542 (15)	166.3 (10)
C11B—H11E···O54A^{xi}	0.970 (15)	2.473 (15)	3.3838 (16)	156.3 (12)
C21B—H21E···O54A^{xi}	0.960 (15)	2.749 (15)	3.4597 (16)	131.4 (11)
C21B—H21D···O41A^{iv}	0.963 (16)	2.655 (15)	3.2414 (16)	119.6 (11)
C52B—H52C···N3A^{xii}	0.997 (13)	2.713 (13)	3.6346 (18)	153.8 (10)

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

(226.233): C 47.78, H 6.24, N 24.77; found: C 47.68, H 6.43, N 24.52%.

Attempts to repeat this crystallization in order to obtain better crystals using absolute ethyl alcohol resulted in good-quality crystals of the hydrate. Also, numerous changes of solvents, crystallization conditions *etc.* produced crystals of the hydrate only.

2.2. X-ray crystallography

Crystal data, data collection and refinement parameters are summarized in Table 1.[1]

For (1) the systematic absences allowed the space groups $P2_1$ or $P2_1/m$; $P2_1/m$ was selected on the basis of the statistics of the $|E|$-value distribution and confirmed by successful structure solution and refinement. Two molecules per unit cell occupy special positions on the mirror plane.

For (1)·H_2O, which is triclinic, space-group choice and refinement is described in §3.1. Diffraction data were collected twice for this crystal. The first data set was collected at room temperature, and then, owing to problems with the presence/absence of the center of symmetry in relation to the H atoms of the water molecules (see §3.1 for details), the measurement was repeated at low temperature, 110 (1) K. The temperature was controlled with an Oxford Instruments cryosystem cooling device. At both temperatures, data collection was initially performed in six separate runs in order to cover the symmetry-independent area of the reciprocal space. An additional three runs were measured at 110 K to obtain a more complete set of data in the potential $P1$ space group. There were 782 and 1181 frames collected at room and low temperatures, respectively.

For both crystals only the Lorentz and polarization corrections were applied. In the case of the noncentrosymmetric space group $P1$ for (1)·H_2O, the block-diagonal method was used owing to the large correlation between parameters connected by the pseudo-center of symmetry. In other cases we applied the full-matrix least-squares method.

Non-H atoms were refined anisotropically. For (1) the positions of the H atoms were refined using the riding model and values 1.2 times the equivalent displacement parameters of the carrier atoms were assigned to their displacement parameters U_{iso}. Owing to the disorder of the H atoms of CH_3 groups, the occupancy factor of 0.5 was assigned to their two different orientations. They were also refined with the riding model and their isotropic displacement parameters were 1.2 times the U_{eq} value of the carrier atoms. For (1)·H_2O the treatment of the H atoms depended on the choice of the space group (see §3).

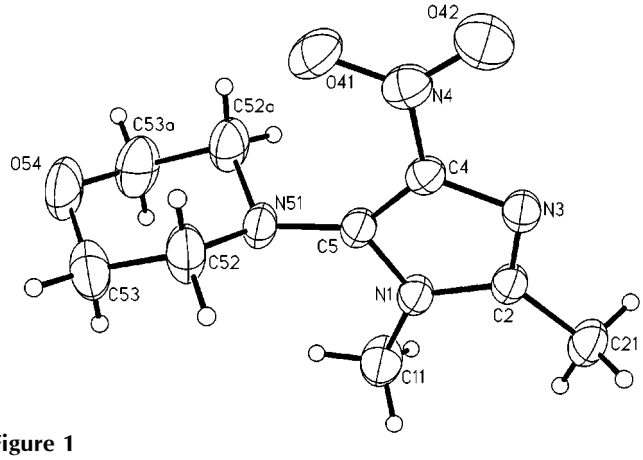


Figure 1
Displacement ellipsoid representation of molecule (1) (anhydrous form), together with the labeling scheme. Ellipsoids are drawn at the 33% probability level; H atoms are represented by spheres of arbitrary radii. Index a refers to the symmetry operation $x, \frac{1}{2}-y, z$.

[1] Supplementary data for this paper are available from the IUCr electronic archives (Reference: SN0030). Services for accessing these data are described at the back of the journal.

3. Results

3.1. (1)·H_2O: $P1$ or $P\bar{1}$ space group?

The structure of (1)·H_2O was initially solved and refined in the centrosymmetric $P\bar{1}$ space group, which was strongly suggested by the statistical analysis of the intensities: the probability that the structure is centrosymmetric was determined as 88% for the 110 K structure and 93% for the room-temperature structure. Also, to some extent, the number of molecules in the unit cell ($Z = 4$) seemed to be in favour of this alternative. The refinement went smoothly; all H atoms from the imidazole molecules were found in the difference-Fourier maps and successfully refined, but problems started with efforts to localize the H atoms of the water molecules. For each water molecule there were three $\Delta\rho$ peaks: one of them, the highest, was clearly the H atom connected *via* a hydrogen bond to the imidazole N3 atom, but we could not find a reasonable hydrogen-bonding scheme with any combination of the remaining peaks. Moreover, and more importantly, all these positions led to impossibly short H···H contacts of, for example, 1.2 Å between the molecules connected by a center of symmetry.

Therefore, we attempted to refine the structure in the noncentrosymmetric space group $P1$, with four symmetry-independent molecules. In this framework the hydrogen-bond pattern is very reasonable and clear; on the other hand, owing to the large correlations between parameters related by a pseudo-center of symmetry, we had to apply a block-diagonal refinement.

To obtain a better insight into this ambiguity we decided to repeat the measurement at a lower temperature (110 K) in order to measure the weak reflections more precisely. These reflections are known to be most sensitive to small noncentrosymmetric distortions (Schomaker & Marsh, 1979; Kassner *et al.*, 1993). In our case, the ratio $\Sigma F_o/\Sigma F_c$ for the weakest reflections (10% of the total) is 1.04 (2) for $P1$ and 1.33 (3) for $P\bar{1}$. This can be regarded as an indication towards the absence of a center of symmetry, but one has to be aware of the statement by Marsh (1999): '... when (and how) can one be certain that a structure should be described as exactly centrosymmetric rather than only approximately so? I believe that the correct answer, in the absence of conclusive noncrystallographic evidence is "never" (and "in no way")'.

The best results, in our opinion, were obtained with the assumption that the structure consists of a centrosymmetric 'matrix' of molecules of (1) and locally noncentrosymmetric homodromic arrays of hydrogen-bonded water molecules. Each of these arrays is strictly homodromic, *i.e.* it runs only in one direction: ···O—H···O—H···O—H··· or ···H—O···H—O···H—O, but these homodromic domains are statistically distributed within the crystals. Following this assumption we refined the structure of (1)·H_2O in the centrosymmetric $P\bar{1}$ space group, but the H atoms of the water molecules involved in O(water)—H···O(water) hydrogen bonds were assumed to be disordered over two alternative positions with s.o.f.'s equal to 0.5, defining two directions of hydrogen-bonded arrays.

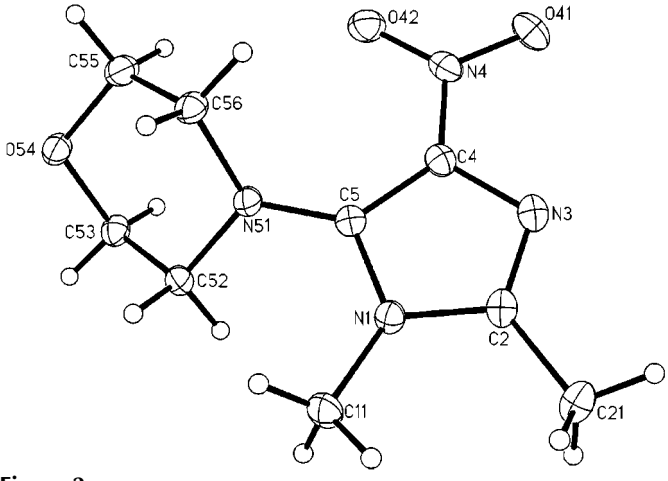


Figure 2
Displacement ellipsoid representation of molecule *A* of (1)·H_2O, together with the labeling scheme (low-temperature data). Ellipsoids are drawn at the 50% probability level; H atoms are represented by spheres of arbitrary radii.

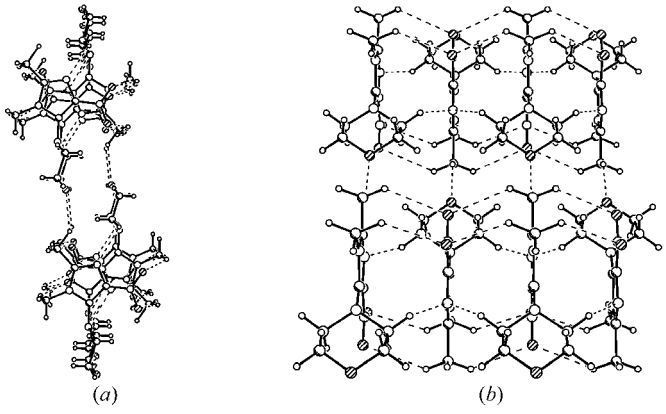


Figure 3
Molecular packing of (1) as seen approximately along (*a*) the *y* and (*b*) the *z* direction. Molecules are linked by weak C—H···O and C—H···N hydrogen bonds (depicted by dashed lines) to give infinite layers. Additional C—H···O and C—H···N hydrogen bonds and stacking of imidazole moieties connect the layers into a three-dimensional network.

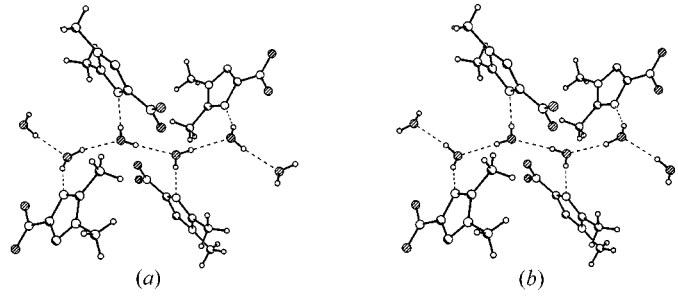


Figure 4
Main hydrogen-bonding motif in (1)·H_2O. Only strong hydrogen bonds involving water molecules are shown. In (*a*) a homodromic domain with the ···O—H···O—H···O—H··· sequence of hydrogen-bonded water molecules is indicated. (*b*) shows the other homodromic domain with the ···H—O···H—O···H—O··· sequence of hydrogen-bonded molecules. The morpholine substituent is removed for clarity.

Statistical descriptors for both models are similar (Table 1). The centrosymmetric model provides better s.u.'s of geometrical parameters and a better internal consistency for these parameters between symmetry-independent molecules. This can be rationalized by the inevitable presence of large correlations in the noncentrosymmetric model and also by the supposition that in the centrosymmetric model we actually observe the 'mean' structure, averaged over two, in fact, independent molecules.

3.2. Molecular structure of (1) and (1)·H_2O

The thermal ellipsoid representations for (1) and (1)·H_2O (molecule *A*), together with the numbering scheme, are shown in Figs. 1 and 2, respectively.

Bond distances and bond angles are typical. In the imidazole ring the double-bond character is partially preserved in the lengths of the C2—N3 and C4—C5 bonds.

The only statistically significant differences are caused by conformational differences. The C5—N51 bond lengths are sigificantly different: in (1) this bond length is 1.392 (3) Å, while in both symmetry-independent molecules of (1)·H_2O these lengths are equal at 1.342 (2) Å. That means a difference of *ca* 15σ. Even more significant are the changes observed in bond angles. The sum of the bond angles around the N51 atom in (1) is 345.0 (3)°, but in (1)·H_2O it is much larger, 357.2 (1)°. The differences in conformations can be visualized by comparing the dihedral angles between the imidazole ring plane and the central plane of the morpholine chair (*i.e.* the plane through the C52, C53, C55 and C56 atoms). In (1), owing to C_s symmetry, this angle is equal to 90°, while in (1)·H_2O the mean value of this angle is 54.8°. In (1) the nitro group has to be perfectly coplanar with the ideally planar imidazole ring. In the hydrate, imidazole rings are also planar [within a few s.u.'s the maximum deviation is 0.055 (8) Å] and the angles between the least-squares planes of the imidazole ring and nitro groups are small but statistically significant, up to 8.4 (4)°. As expected, the morpholine ring adopts a distorted chair conformation. While the noncrystallographic mirror plane passing through both heteroatoms is well preserved [perfectly in (1) owing to the molecular symmetry], the other noncrystallographic symmetry elements of an ideal D_{3d} chair are less well obeyed, obviously owing to the presence of different heteroatoms.

3.3. Molecular packing

In (1) the crystal packing is determined mainly by van der Waals interactions, weak C—H···O and C—H···N hydrogen bonds and partially by stacking of imidazole fragments (the distance between rings is equal to *b*/2, *i.e.* 3.337 Å; Fig. 3).

The crystal structure of the hydrate is determined mainly by the strong O—H(water)···N3 and O—H(water)···O(water) hydrogen bonds. The main intermolecular motif can be described as an infinite chain of hydrogen-bonded water molecules, with imidazole molecules connected to this chain (Fig. 4).

Two different domains with the hydrogen-bonding sequencies ···O—H···O—H···O··· (Fig. 4*a*) or ···H—O···H—O···H—O··· (Fig. 4*b*) are generated by different positions of only one H atom of each water molecule (refined with the fractional occupancy factor). The location of morpholinoimidazole moieties is the same in both types of domains. Additionally, a number of weak C—H···O interactions, involving all O atoms (from nitro and morpholine groups), causes a saturation of all potential hydrogen-bond acceptors. The hydrogen-bond data are listed in Table 2.

4. Conclusions

The crystal structures of (1) and its hydrate (1)·H_2O have been successfully determined from single-crystal X-ray diffraction. Both compounds crystallize in centrosymmetric space groups. However, (1)·H_2O is found to be locally noncentrosymmetric, with homodromic chains of hydrogen-bonded water molecules. The deviation from centrosymmetry concerns only one H atom of each water molecule in the chain that statistically occupies one of two positions. The location of the morpholinoimidazole moieties is the same in both types of chains.

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