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1-(2′-Aminophenyl)- and 1-(2′-hydroxyphenyl)-2-methyl-4-nitroimidazole: Crystallizing with two molecules in the asymmetric unit

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Abstract

Two similar 4-nitroimidazole derivatives, 1-(2′-aminophenyl)-2-methyl-4-nitroimidazole, $C_{10}H_9N_3O_3$, and 1-(2′-hydroxyphenyl)-2-methyl-4-nitroimidazole, $C_{10}H_{10}N_4O_2$, crystallize with two molecules in the asymmetric unit ($Z' = 2$). Packing conflicts may result from tendency towards closing hydrogen-bonded rings (dimer for amino-, and tetramer for hydroxy-derivative) and molecular stacking. These conflicts are solved in different ways in both compounds, due to the different nature of 2′-substituents, but in both cases the crystal structure involves multiple molecules in the asymmetry unit. The geometrical features of symmetry-independent molecules are similar. The nitro group is almost coplanar with the imidazole plane in amino derivative while it is significantly twisted in hydroxy-one.

Keywords: Crystal structure; Multiple molecules; Nitroimidazole derivatives; Hydrogen bonds; Weak intermolecular interactions

1. Introduction

Crystal packing is the result of the competition between different factors connected with close packing requirements and intermolecular interactions. Space-group symmetry results as a compromise, sometimes hard to achieve, and therefore more than one molecule may appear in the asymmetric unit. The literature dealing with this subject, which is crucial, for example, for crystal engineering or for the crystal structure prediction; is not that extensive as might be expected.

Historically, the statistical analysis of the presence of multiple molecules often accompanied papers dealing with the frequencies of different space groups (these analyses are reviewed by Brock and Dunitz, [1]). The problem of multiple molecules was further analyzed in detail by Steed [2]; recently even the dedicated website was created (http://www.dur.ac.uk/zprime).

The overall population of structures with $Z' > 1$ in the Cambridge Structural Database (CSD, [3]) is more or less constant over the years (but cf. Desiraju [4] and Anderson and Steed [5]) and is around 8.8%. Of course this proportion may change depending on the class of compounds, there are some classes for which the probability of finding $Z' > 1$ is significantly higher, for example, nucleosides and nucleotides (20.8%) or steroids (18.8%), as listed by Steiner [6]. The search in the November 2006 version of the CSD (Ver. 5.28, Jan. 2007 update) gives somewhat smaller values: 19.8% for nucleosides and nucleotides and 16.4% for steroids (with similar search conditions). It was also found that larger probability of finding multiple molecules exists also for monoalcohols [7] (the authors also suggested that the same should be the case for amino group) and for simple imidazole derivatives [8].

For some time we have studied weak intermolecular interactions in 4-nitroimidazole derivatives (e.g., [9,10]). This relatively simple molecule provides a convenient object for such studies: the degrees of freedom are few, one hydrogen bond acceptor is always available, stacking

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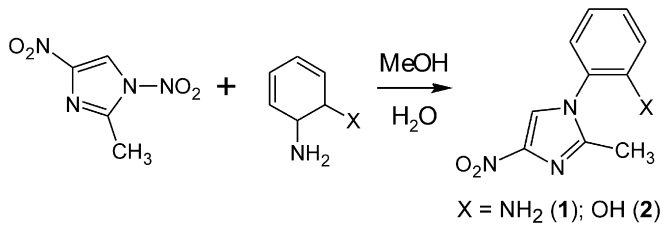

Scheme 1.

interactions are in principle possible, and by an appropriate choice of substituents one can focus on certain interactions. We have previously found interesting cases of $Z' = 2$ connected either with the differences in conformation or in intermolecular interactions [8].

Here, we report the crystal structures of two simple imidazole derivatives (Scheme 1): 1-(2′-aminophenyl)-2-methyl-4-nitroimidazole (1) and 1-(2′-hydroxyphenyl)-2-methyl-4-nitroimidazole (2). These compounds belong to a class of compounds having higher probability of crystallizing with $Z' > 1$, and in fact this is a case. CSD checks do not suggest any possibility for a missing symmetry between the independent molecules.

2. Experimental

The title compounds were synthesized by the *ANRORC* (Addition Nucleophile Ring Opening Ring Closure) reaction from 1,4-dinitro-2-methylimidazole and corresponding *ortho*-substituted aniline in methanol–water medium at room temperature with moderate yields. The syntheses were made in similar way described before by Suwiński and Salwińska [11] (Scheme 1).

Diffraction data were collected at 100(1)K by the ω-scan technique up to $2\theta = 60°$, on a KUMA-KM4CCD diffractometer [12] with graphite-monochromatized MoK_α radiation ($\lambda = 0.71073$ Å). The temperature was controlled by an Oxford Instruments Cryosystems cooling device. Frames (532) were measured for 1 and 2 (0.75° frame width). The data were corrected for Lorentz-polarization effects [13]. Accurate unit-cell parameters were determined by a least-squares fit of 2613 (1) and 2851 (2) reflections of highest intensity, chosen from the whole experiment. The structures were solved with SHELXS97 [14] and refined with the full-matrix least-squares procedure on F^2 by SHELXL97 [14]. Scattering factors incorporated in SHELXL97 were used. The function $\Sigma w(|F_o|^2\text{-}|F_c|^2)^2$ was minimized, with $w^{-1} = [\sigma^2(F_o)^2 + A\cdot P^2]$ ($P = [\text{Max}\ (F_o^2, 0) + 2F_c^2]/3$). The final values of the factor A are listed in Table 1. All non-hydrogen atoms were refined anisotropically, hydrogen atoms were located in subsequent difference Fourier maps and their positional and isotropic displacement parameters (one common parameter for each CH_3 group) were refined. Relevant crystal data are listed in Table 1, together with refinement details.

Crystallographic data (excluding structure factors) for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, Nos. CCDC-648297 (1) and CCDC-648298 (2). Copies of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK. Fax: +44(1223)336-033, e-mail: deposit@ccdc.cam.ac.uk, or www.ccdc.cam.ac.uk.

Table 1
Crystal data, data collection and structure refinement

Compound	1	2
Formula	$C_{10}H_{10}N_4O_2$	$C_{10}H_9N_3O_3$
Formula weight	218.22	219.20
Crystal system	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1/n$
a (Å)	11.0134(8)	10.5904(8)
b (Å)	10.0994(8)	17.9987(14)
c (Å)	18.6433(16)	10.9605(9)
β (°)	97.100(7)	100.563(6)
V (Å^3)	2057.6(3)	2053.8(3)
Z	8	8
D_x (g cm^{-3})	1.41	1.42
$F(000)$	912	912
μ (mm^{-1})	0.103	0.108
Crystal size (mm)	$0.2\times0.2\times0.05$	$0.15\times0.1\times0.1$
Θ Range (°)	4.85–26.4	3–25
hkl range	$-11 \leqslant h \leqslant 13$	$-12 \leqslant h \leqslant 11$
	$-12 \leqslant k \leqslant 11$	$-21 \leqslant k \leqslant 19$
	$-22 \leqslant l2 \leqslant 3$	$-13 \leqslant l \leqslant 13$
Reflections		
Measured	11984	11002
Unique (R_{int}) 4414	4156 (0.038)	3603 (0.042)
With $I > 2\sigma(I)$	2641	2398
Number of parameters	365	357
Weighting scheme		
A	0.07	0.05
$R(F)$ [$F^2 > 2\sigma(F^2)$]	0.049	0.040
$wR(F^2)$ [all refl.]	0.132	0.098
Goodness of fit	1.05	0.98
Max/min $\Delta\rho$ (e Å^{-3})	0.24/−0.24	0.24/−0.35

3. Discussion

3.1. Molecular geometry

Selected geometrical parameters are listed in Table 2. As far as the bond lengths and bond angles patterns are concerned, the differences between the symmetry-independent molecules are only of statistical nature. The normal probability plots [15,16] drawn for the bond length distribution in both cases are almost linear, the correlation coefficients between theoretical and experimental distributions are of ca. 0.97. Also the differences between 1 and 2 are small, with the notable exception of intraannular bond angles in the phenyl ring. These angles show the typical dependence on the kind of substituent (cf. Table 2); these differences are generally in agreement with the trends described by Domenicano and Murray-Rust [17].

As noted before [18] there is a statistically significant difference in the C–N–O angles of nitro group typical for 5-H imidazoles: the C4–N4–O41 (oxygen atom *cis* with respect to the N3 imidazole ring nitrogen) is, on

Table 2
Selected geometrical parameters (Å, °) with s.u.′s in parentheses (I and II are the least-squares planes of imidazole and phenyl rings, respectively)

	1A	1B	2A	2B
C4–N4–O41	118.9(2)	118.2(2)	118.9(2)	119.3(2)
C4–N4–O42	117.4(2)	118.0(2)	117.2(2)	117.1(2)
N3–C4–N4	120.0(2)	121.4(2)	121.5(2)	121.1(2)
C5–C4–N4	126.9(2)	126.0(2)	125.6(2)	126.4(2)
C11–C12–C13	116.3(2)	116.9(2)	118.2(2)	118.9(2)
C16–C11–C12	122.1(2)	121.8(2)	120.7(2)	121.5(2)
C12–C13–C14	121.0(2)	121.5(2)	120.5(2)	119.4(2)
C2–N1–C11–C12	100.3(2)	78.2(2)	69.6(3)	74.5(2)
C5–N1–C11–C12	103.3(2)	−107.3(2)	−120.0(2)	−106.9(2)
C2–N1–C11–C16	−76.5(2)	−100.292)	−110.1(2)	−106.8(2)
C5–N1–C11–C16	103.3(2)	74.4(2)	60.3(3)	71.8(3)
N3–C4–N4–O41	−3.4(3)	1.5(3)	7.7(3)	10.6(3)
N3–C4–N4–O42	176.6(2)	−179.3(2)	−173.6(2)	−168.7(2)
I/II	78.62(5)	76.54(7)	65.36(7)	73.10(6)
I/(NO_2)	3.2(2)	3.1(3)	8.6(2)	10.0(2)

average, 1.2° larger than C4–N4–O42 (i.e., oxygen atoms *trans* to N3).

The aromatic rings are almost planar. Generally, the imidazole rings are closer to ideal planarity (the deviations from the least-squares plane by five ring atoms are smaller than 0.0039(11) Å) than the phenyl ones, where there are surprisingly large deviations, as high as 0.0113(14) Å in 1 and 0.0107(14) Å in 2. The conformations of molecules 1 and 2 can be described by the dihedral angles between the benzene and nitroimidazole rings and between the imidazole ring and a nitro group (Table 2). In 1 the sense of twist is opposite in symmetry-independent molecules: the dihedral angle C2–N1–C11–C12 is larger than 90° in molecule A (100.3(2)°) while it is – by almost the same amount – smaller than 90° in B: 78.2(2)°.

The twist between the rings is large (65–78°), apparently in order to relieve the steric stress, while the nitro groups are close to coplanarity with the imidazole rings. It must be noted however, than in 2 the twist of the nitro group is relatively large, up to 10.0(2)° (Table 2).

3.2. Crystal packing and intermolecular interactions

In the structures of 1 and 2 relatively strong, "classical" hydrogen bonds are one of the primary factors in the building of crystal network. Hydrogen bond data are listed in Table 3. In 1 there is a heteromolecular (i.e., AB, consisting of two symmetry-independent molecules) dimer, connected by N–H···N (imidazole) hydrogen bonds (Fig. 1), while in 2 the O–H...N (imidazole) hydrogen bonds combine to form a centrosymmetric heteromolecular tetramer ABAB (Fig. 2). Using graph-set notation, [19–21], these rings can be described as $R^2_2(14)$ in 1 and $R^4_4(28)$ in 2. The tendency towards creating such closed structures might be the factor causing the packing conflict which, in turn, leads to the presence of multiple molecules in the asymmetry unit. The rings were often observed in the mono-hydroxy structures, but the factor responsible for this was connected with a possible conflict between the tendency towards ∼O–H···O–H∼. or ∼N–H···N–H∼ bonding – hydroxyl and amino groups can act almost equally well as hydrogen bond donor and acceptor – and close packing requirements. In 1 and 2 the imidazole nitrogen atom acts as an acceptor for the hydrogen bonds.

Table 3
Hydrogen bonds and other short contacts data (Å, °)

D	H	A	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (°)
1						
N12A	H12A	O42A^{i}	0.94(3)	2.09(3)	3.036(3)	174(2)
N12A	H12B	N3B^{ii}	0.93(3)	2.27(3)	3.166(2)	162(2)
N12B	H12C	N3A^{iii}	0.92(2)	2.24(2)	3.076(3)	151(2)
N12B	H12D	O41B^{iv}	0.89(3)	2.40(3)	3.213(3)	152(2)
C14A	H14A	O42B	0.94(2)	2.49(2)	3.191(3)	131.0(14)
C14A	H14A	O42A^{iii}	0.94(2)	2.60(2)	3.412(3)	143.9(15)
C14B	H14B	Cg1B^{v}	0.98(2)	2.87(2)	3.587(3)	130.1(15)
C21A	H21A	Cg2B^{v}	0.93(3)	2.94(3)	3.638(3)	133(2)
2						
O12A	H12A	N3B	0.90(3)	1.86(3)	2.745(2)	167(2)
O12B	H12B	N3A^{vi}	0.90(3)	1.90(3)	2.761(2)	159(3)
C16A	H16A	O42B^{vii}	0.95(2)	2.54(2)	3.435(3)	157(2)
C5A	H5A	O42B^{viii}	1.00(2)	2.44(2)	3.443(3)	179(2)
C13B	H13B	O41A^{vi}	0.99(2)	2.47(2)	3.436(3)	162.8(15)
C21B	H21D	O42A^{ix}	0.95(3)	2.60(3)	3.337(3)	135(2)
C15B	H15B	Cg2A^{x}	0.91(2)	2.80(2)	3.314(3)	117.3(14)
C14A	H14A	Cg2B^{viii}	0.95(2)	2.63(2)	3.270(3)	125.2(14)
C5B	H5B	Cg1A^{xi}	0.97(2)	2.92(2)	3.743(3)	143.5(14)

Cg symbol describes the centroid of the appropriate ring.
Symmetry codes: $^{i}-x,\ 0.5+y,1.5-z$; $^{ii}-1+x,y,z$; $^{iii}1+x,y,z$; $^{iv}x,\ ½-y,\ -0.5+z$; $^{v}-1-x,1-y,1-z$; ^{vi}–x,1 − y,1 − z; $^{vii}0.5-x,\ 0.5+y,\ 0.5-z$; $^{viii}0.5+x,\ 0.5-y,-0.5+z$; $^{ix}x,y,1+z$; $^{x}0.5+x,\ 0.5-y,\ 0.5+z$; $^{xi}-0.5+x,\ 0.5-y,\ 0.5+z$.

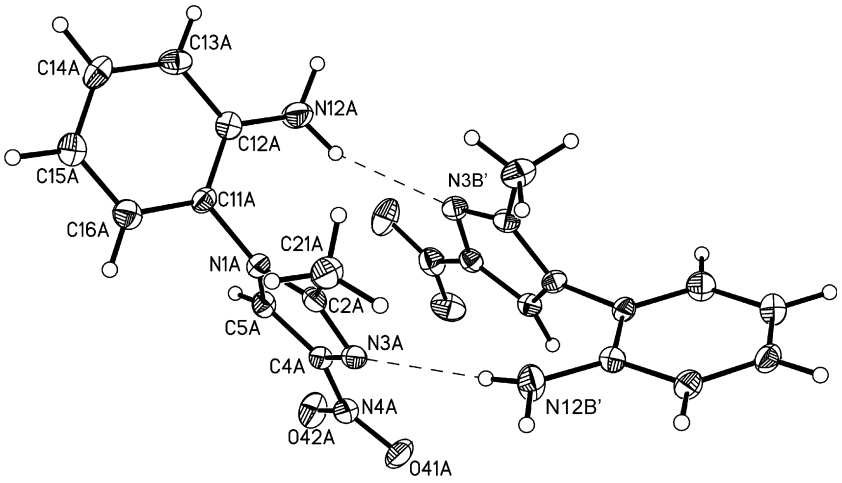

Fig. 1. The hydrogen-bonded dimer of 1 [26], with the labeling scheme of one of the molecules. Ellipsoids are drawn at 50% probability level, hydrogen bonds are shown as spheres with arbitrary radii. Hydrogen bonds are depicted as dashed lines. Symmetry code for a primed molecule: $-1+x, y, z$.

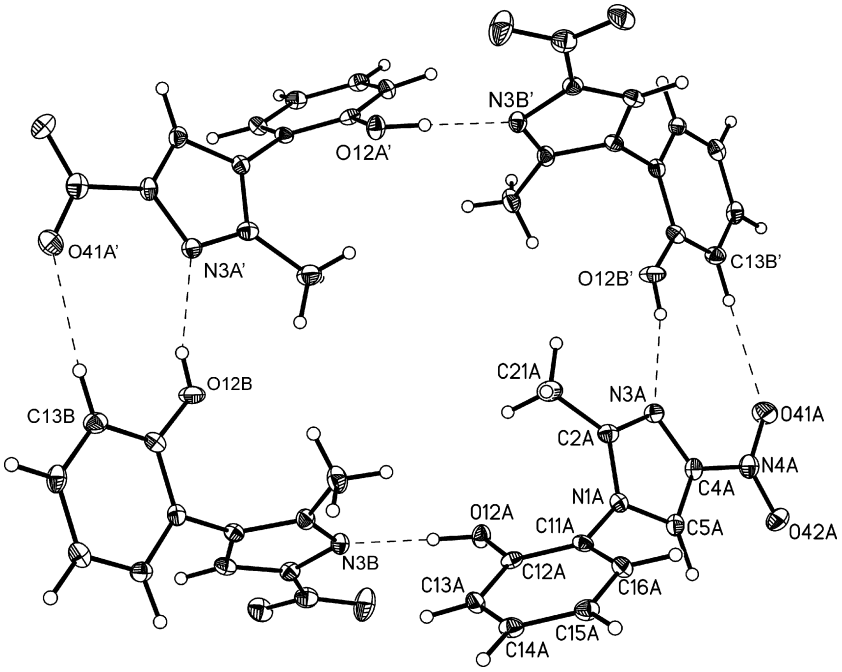

Fig. 2. The hydrogen-bonded tetramer of 2 [26], with the labeling scheme of one of the molecules. Ellipsoids are drawn at 50% probability level, hydrogen bonds are shown as spheres with arbitrary radii. Hydrogen bonds are depicted as dashed lines. Symmetry code for primed molecules: $-x,1-y,1-z$.

Only few examples of similar supramolecular structures can be found among substituted imidazoles located via CSD searches. In the crystal structure of 2-amino-5-(4-chlorophenyl)-1-methylimidazole [22] the asymmetric unit contains four molecules, two of which are connected into a pseudo-centrosymmetric heteromolecular dimer, while two other molecules form homomolecular centrosymmetric dimers. All these motifs are formed by N–H···N(imidazole) hydrogen bonds. The structure of 3-chloro-1-(4-nitro-5-piperidinylimidazol-1-yl)propan-2-ol [23] has also $Z' = 4$. In this case these molecules are connected into two heteromolecular dimers by means of O–H···N hydrogen bonds (actually all these bonds are three-centered, with oxygen atom from nitro group as additional acceptor). More commonly, multiple molecules are connected in chains of O–H···N bonds (e.g., (6-(imidazol-1-ylmethyl)pyrid-2-yl)methanol [24]), or in more complicated structures, that often contain also rings, for amino-substituted imidazole derivatives (e.g., 4-ethyl-5-(*N*-methyl-*N*-phenylamino)-imidazole-2-carboxamide [25]).

In 1, the hydrogen-bonded rings pack in the crystals *via* π–π stacking interactions, the angle between the mean planes is 2.6(1)°. The distance between the centroids of imidazole rings is 3.658(2) Å; and the distance perpendicular to the planes of almost parallel rings is as short as 3.321 Å. Hydrogen bonded dimers are con-

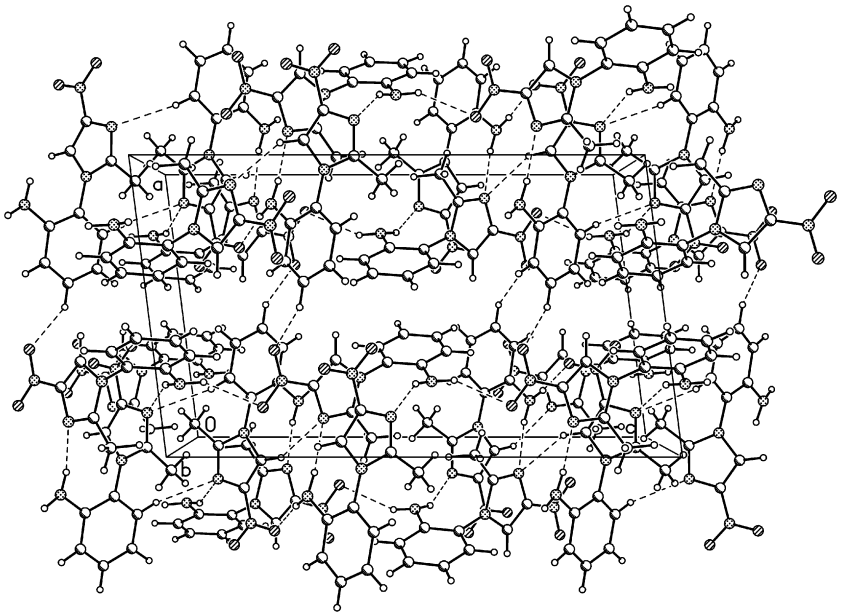

Fig. 3. The crystal packing of 1 as seen along [0 1 0] direction. Hydrogen bonds are depicted as dashed lines. [26].

nected into chains by means of homomolecular N–H···O (nitro) hydrogen bonds (Fig. 3). The hydrogen bond structure can be therefore regarded as two families of homomolecular C(9) chains, that are interwoven into the rings described earlier. Some other short C–H···N, C–H···O and C–H···π contacts may supply further coulombic stabilization in the crystal structures (Table 3), and they take part in formation of the three-dimensional structure.

In 2, the tetramers are connected into chains along [101] directions by relatively short and directional C5A-H5A···O (nitro, B) contacts (Fig. 4). Almost equally strong C–H···O bonds act as secondary interactions within the dimers (Fig. 1). Some weaker C–H···O and C–H···π contacts might be found in the crystal structure (Table 3).

4. Conclusions

The main motifs in the crystal structures of two 1(2′-(hydrogen bond donor)phenyl)-2-methyl-4-nitroimidazoles, where "hydrogen bond donor" is an amino group in 1 and hydroxyl group in 2, are closed, hydrogen-bonded rings: dimers in case of 1, tetramers in 2. The packing conflict between the tendency to form such dimers and other packing requirements can be regarded as the reason for the presence, in both cases, two symmetry independent

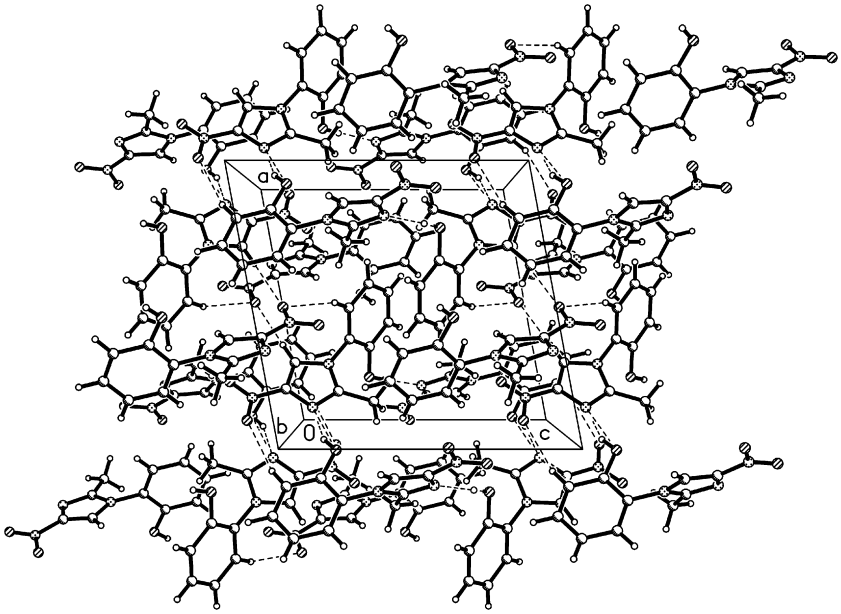

Fig. 4. The crystal packing of 2, as seen along [0 1 0] direction. Hydrogen bonds are depicted as dashed lines [26].

molecules in asymmetric part of the unit cell. The geometry of the molecules is not significantly differ, one could only realize the opposite sense of the twisting angles between the imidazole and phenyl groups in 1. Weaker hydrogen-bond-type interactions connect the closed structure: dimers and tetramers into three dimensional networks.

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