

# Substituent and Solvent Effects on Intermolecular Interactions in Crystals of *N*-Acylhydrazone Derivatives: Single-Crystal X-ray, Solid-State NMR, and Computational Studies

Liliana Mazur,<sup>\*,†</sup> Katarzyna N. Jarzembska,<sup>‡,§</sup> Radosław Kamiński,<sup>‡,§</sup> Krzysztof Woźniak,<sup>‡</sup> Edyta Pindelska,<sup>∥</sup> and Monika Zielińska-Pisklak<sup>∥</sup>

<sup>†</sup>Department of Chemistry, Maria Curie-Skłodowska University, Maria Curie-Skłodowska Square 2, 20-031 Lublin, Poland

<sup>‡</sup>Department of Chemistry, University of Warsaw, Pasteura 1, 02-093 Warszawa, Poland

<sup>§</sup>Department of Chemistry, University at Buffalo, The State University of New York, Buffalo, New York 14260-3000, United States <sup>||</sup>Department of Pharmacy, Medical University of Warsaw, Banacha 1, 02-097 Warszawa, Poland

#### Supporting Information

**ABSTRACT:** New crystalline forms of hydrated and anhydrous *N*-acylhydrazones are reported. The studied crystal structures were determined by single-crystal X-ray diffraction at 90 or 100 K. Transferred aspherical atom model (TAAM) structure refinements were performed with the aid of the most recent version of the University at Buffalo Databank (UBDB). The resulting crystal structures were analyzed in terms of molecular conformations, intermolecular interaction energies, and crystal packing motifs. For this purpose, solid-state NMR studies and theoretical calculations were conducted supplementarily. It was found that all studied hydrazones adopt the *E* configuration around the azine N–N bond and imino N=C function in the solid state, whereas the hydrazide N–N–C=O moiety exhibits the *E* and *Z* arrangement in the *N*-acyl and *N*-aroyl derivatives, respectively. The constrained energy scans confirmed the *E* conformation of the hydrazide unit and the *E* arrangement of pyridine and hydrazone N atoms as the most stable ones. The association modes in the studied crystals are dominated by strong hydrogen



bonds of the N–H…O or N–H…N-type involving the amide group as a proton donor. Consequently, as indicated by lattice energy calculations, a significant increase in the crystal cohesive energy per asymmetric unit is observed when water molecules are incorporated into the crystal structure, because this enables efficient saturation of the hydrogen bond acceptor and donor atoms. On the other hand, a substantial contribution of  $\pi \dots \pi$  stacking interactions to the overall stabilization of the crystal nets was also found. Thus, when more bulky phenyl substituents are introduced, the cohesive energy becomes more favorable.

### 1. INTRODUCTION

The chemistry of *N*-acyl- and *N*-aroylhydrazones (NAHs) has been the subject of much interest in recent years. Many papers and reviews concerning the use of hydrazone derivatives in organic<sup>1</sup> and organometallic<sup>2</sup> syntheses, as well as their potential applications in analytical chemistry<sup>3</sup> and medicine,<sup>4</sup> have been published. *N*-acylhydrazones, which can be readily obtained by condensation of aldehydes or ketones with acylhydrazines in the presence of acid catalysts,<sup>5</sup> represent a class of azomethine compounds (Scheme 1). In general,

# Scheme 1. Possible Isomers of Acetyl- And Aroylhydrazone Derivatives<sup>6,8</sup>



hydrazones are organic compounds bearing the  $C^2 = N^2 N^1$ moiety, where the double C=N bond is conjugated with the lone electron pair of the terminal N<sup>1</sup> atom. Both nitrogen atoms of the hydrazone group are nucleophilic, whereas the azine C<sup>2</sup> atom has both electrophilic and nucleophilic character and constitutes the most reactive center of the hydrazone moiety. In the case of N-acyl- and N-aroylhydrazones, the presence of an additional C=O donor site induces an extended  $\pi$ -electron delocalization along the whole C<sup>1</sup>(=O)N<sup>1</sup>HN<sup>2</sup>= C<sup>2</sup> fragment. These structural and electronic features determine the physicochemical properties and biological activities of NAHs to a large extent. Commonly, the acylhydrazone unit adopts a planar geometry; however, the planarity might be broken in the case of steric hindrance between substituents around the C=N bond.<sup>6</sup> Due to presence of the double C=N bond, unsymmetrical hydrazones may appear in the form of E/

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Z configurational isomers. Additionally, their N-acyl and Naroyl derivatives can exist in solution as a mixture of conformational isomers, because of the hindered rotation around the C-N amide bond. Therefore, in total four isomers are possible. What is more, some aroylhydrazones can be involved in keto–enol tautomeric interconversion.<sup>7</sup> The E-Zisomerization of hydrazones resulting from temperature and solvent effects, pH value, or UV irradiation can occur. Different tautomeric and isomeric forms have different physicochemical and spectral properties and can be distinguished according to the corresponding IR, UV-vis, and NMR spectra. On the basis of quantum-chemical calculations, it was established that among various conformational possibilities provided by the discussed hydrazone derivatives, acylhydrazones exist mainly in the EE' form (Scheme 1) with E configuration for both imine and amide groups and s-trans junction between both functions. In turn, in the case of aroylhydrazone crystal structures, the EZ' form is commonly encountered.<sup>8</sup> The conformational behavior and E-Z isomerization of certain hydrazone derivatives was studied in DMSO and CDCl<sub>3</sub> solutions by NMR and HPLC techniques.<sup>6a</sup> It was found that N-aroylhydrazones exist primarily as the EZ' isomers whereas a mixture of both forms was found for acyl derivatives, with variable stoichiometric ratios, depending on the solvent polarity.

Due to the capability of reacting with electrophilic and nucleophilic reagents, hydrazones and their aldehyde derivatives are widely used in organic chemistry, especially in condensation, cyclization, and cycloaddition reactions for synthesis of heterocyclic compounds.<sup>1a,5b</sup> *N*-Acylhydrazones can serve as stable imine equivalents, which can react with various nucleophiles. Chiral hydrazide products can be used as building blocks and transformed into various chiral nitrogencontaining compounds by cleavage of the N–N bond.<sup>1b,c</sup> The *N*-acyl groups often play important roles as templates for metal catalysis, which facilitate stereochemical control.<sup>1</sup> Furthermore, synthetic flexibility of hydrazones, selectivity, and sensitivity toward transition metal ions make them attractive as ligands in coordination chemistry.

Given the scope of applications, it is not surprising that the chemistry of *N*-acyl- and *N*-aroylhydrazones has attracted particular attention in recent years. Many researchers have synthesized these compounds as target structures and evaluated their physicochemical and biological properties. However, studies devoted to their crystal structures seem to be rather limited. For these reasons and as a part of the wider project devoted to structural, electronic, and antiproliferative properties of selected 2-pyridinecarboxaldehyde hydrazones, a comprehensive single-crystal X-ray analysis and computational investigations were performed. The aim of this work was to gain insight into the influence of the type of  $C^1$ -substituent on the conformational preferences of 1-5 (Scheme 2) and the intermolecular interaction patterns in their crystals. Additionally, solvent aspects constitute an interesting subject and thus

Scheme 2. General Synthetic Route of Studied Hydrazones (R = H (1), Me (2), Ph (3), 2-Cl- $C_6H_5(4)$ , 2-NH<sub>2</sub>- $C_6H_5(5)$ ) and a Numbering Scheme



will be explored. Experimental methods together with theoretical computations shall shed some light on the preferred conformations of the studied molecules as well as provide qualitative and quantitative information about crystal architecture and energetics, main molecular motifs, intermolecular interactions, and water content contribution to the crystal lattice stability. Finally, this work is enriched with solid-state NMR spectroscopy, which is a complementary technique to Xray crystallography. Thanks to these experiments, the purity of the studied solid systems was evaluated, and hence the relative stability of selected crystals was established.

#### 2. EXPERIMENTAL SECTION

**2.1. Synthesis and Materials.** All chemicals and solvents were purchased from commercial sources (Sigma-Aldrich Co., USA, or Polish Chemical Reagents, Poland) and used without further purification. IR spectra (600–4000 cm<sup>-1</sup>) were recorded on a Nicolet 6700 FT-IR spectrophotometer (in the ATR mode, ZnSe crystal). Elemental analyses (Table S1, Supporting Information) were performed on a CHN PerkinElmer 2400 analyzer.

The considered hydrazones were prepared by condensation of 2pyridinecarboxaldehyde with the corresponding acid hydrazides in methanolic solution (Scheme 2) following the procedure described in the literature.<sup>5,9</sup> Single crystals suitable for X-ray diffraction studies were grown from the mother liquor by slow evaporation at room temperature. Alternatively, they were obtained by recrystallization from dry methanol or DMF solutions.

2.2. X-ray Crystallography. 2.2.1. X-ray Data Collection. Singlecrystal X-ray measurements of 1, 1·H<sub>2</sub>O, 2, 4·H<sub>2</sub>O, 4·2H<sub>2</sub>O, 5, and 5· H<sub>2</sub>O were carried out on an Agilent Technologies Xcalibur CCD diffractometer equipped with a molybdenum sealed X-ray tube (Mo  $K_{\alpha}$  radiation,  $\lambda = 0.71073$  Å), graphite monochromator, and Oxford Cryosystems nitrogen gas-flow device (Cobra Plus). The measurement of 3·H<sub>2</sub>O was performed on a Bruker AXS Kappa APEX II Ultra diffractometer equipped with a TXS rotating anode, multilayer optics, and Oxford Cryosystems nitrogen gas-flow device (700 Series Cryostream). In all the cases, single crystals of suitable sizes were mounted on a goniometer head using Paratone N oil and cooled to 100 or 90 K. Data collection strategies, based solely on  $\omega$  scans, were optimized and monitored applying the appropriate algorithms implemented within the *CRYSALIS*<sup>10</sup> or *APEX2*<sup>11</sup> program suites, respectively. Unit cell parameter determination, raw diffraction image integration, Lorentz and polarization corrections, oblique incidence effects, multiscan absorption corrections, and frame-to-frame scaling were performed with the diffractometer software (CRYSALIS or APEX2). Merging of reflections was carried out with the SORTAV program.<sup>12</sup> Final data collection parameters are summarized in Table

2.2.2. Structure Solution and Refinement. All structures were solved using direct methods implemented in the SHELXS program<sup>1</sup> and refined with the SHELXL program<sup>13</sup> within the independent atom model (IAM) approximation. In all cases, the positions of hydrogen atoms and orientations of methyl groups were determined from Fourier residual maps. Subsequently, transferred aspherical atom model (TAAM)<sup>14</sup> refinements were performed in the MOPRO package<sup>15</sup> with the aid of the new version of the University at Buffalo Databank (UBDB)<sup>16</sup> and the LSDB program,<sup>16,17</sup> based on the Hansen-Coppens multipole model.<sup>18</sup> During TAAM refinements, all electron density parameters are kept fixed at the databank values, whereas the scale factor, atomic positions, and atomic displacement parameters (ADPs) are iteratively varied. Additionally, for the purpose of this work the UBDB databank was extended with the atom types specific for hydrazone molecules (Table S2, Supporting Information), according to the literature procedure.<sup>19</sup> The final refinement statistics for all compounds are summarized in Table 1. The CIF files for each refinement are available from the Supporting Information or can be retrieved from the Cambridge Crystallographic Data Centre (CCDC)<sup>20</sup> (deposition numbers CCDC 974829–974836).

## Table 1. Crystal Data and TAAM Refinement Details Characterizing All Studied Hydrazone Crystals

cruet structure	1	1.4 0	2	3.H O
chemical formula	CHNO	CHNO	2 C H N O	$5 H_2 O$
formula weight	149.14	167.16	163 17	243.25
	149.14	122	103.17	124
rmet evet	monoclinic	triclinic	monoclinic	127
cryst syst	$P_2 / c$	$\overline{D1}$	$\frac{P2}{c}$	Phea
	$12_1/t$	$\frac{1}{6}$	52692(2)	6078(1)
μ, Α Ι. Ι.	9.3229(9)	7.0214(7)	8.0654(2)	0.970(1)
<i>b</i> , A	4.0938(3)	/.9214(/)	8.0034(2)	11.921(2)
c, A	18.170(2)	8.0/45(7)	18.5394(5)	29.198(6)
$\alpha$ , deg	90	/2.412(8)	90	90
p, deg	95.509(9)	80.110(/)	92.938(3)	90
$\gamma$ , deg	90	69.625(8)	90	90
V, A <sup>3</sup>	/19./(1)	397.04(6)	801.64(4)	2429.0(8)
Z	4	2	4	8
F(000)	312	176	344	1024
$d_{\rm calc},  {\rm g} \cdot {\rm cm}^{-3}$	1.377	1.399	1.352	1.331
completeness	97.5%	98.5%	96.7%	98.9%
$(\sin \theta/\lambda)_{\rm max}, {\rm A}^{-1}$	0.70	0.66	0.85	1.13
$\theta$ range, deg	3.47-29.82	2.87-27.97	3.35-37.16	2.79-53.23
absorp coeff, $\mu$ ,mm <sup>-1</sup>	0.098	0.106	0.094	0.093
cryst size, mm <sup>3</sup>	$0.54 \times 0.15 \times 0.12$	$0.42 \times 0.18 \times 0.06$	$0.65 \times 0.38 \times 0.10$	$0.25 \times 0.22 \times 0.17$
cryst color and form	colorless needle	colorless plate	colorless plate	colorless needle
Т, К	100	100	90	90
R <sub>int</sub>	2.75%	1.71%	2.24%	5.88%
reflns collected/unique	5730/2021	2760/1883	15459/3984	119023/14445
reflns with $I \ge 3\sigma(I)$	1446	1250	2873	10 443
params/restraints	128/14	145/18	145/18	215/26
R[F]	3.15% <sup>a</sup> /4.73% <sup>b</sup>	$2.65\%^{a}/4.56\%^{b}$	2.76% <sup>a</sup> /4.34% <sup>b</sup>	$2.48\%^{a}/3.50\%^{b}$
$R[F^2]$	$6.67\%^{a}/6.91\%^{b}$	$3.96\%^{a}/4.28\%^{b}$	$6.38\%^{a}/6.61\%^{b}$	$4.42\%^{a}/4.51\%^{b}$
wR[F]	$3.60\%^{a}/3.81\%^{b}$	$2.81\%^{a}/3.09\%^{b}$	$3.00\%^{a}/3.17\%^{b}$	3.05% <sup>a</sup> /3.22% <sup>b</sup>
S	$1.57^{a}/1.39^{b}$	$1.22^{a}/1.08^{b}$	$1.57^{a}/1.40^{b}$	$1.36^{a}/1.25^{b}$
$Q_{\rm res}^{\rm min/max}$ , e·Å <sup>-3</sup>	-0.19/+0.22	-0.17/+0.15	-0.27/+0.34	-0.34/+0.19
cryst structure	4·H <sub>2</sub> O	$4 \cdot 2H_2O$	5	5 · H₂O
chemical formula	$C_{13}H_{12}N_3O_2Cl$	$C_{13}H_{14}N_3O_3Cl$	$C_{13}H_{12}N_4O$	$C_{13}H_{14}N_4O_2$
formula weight	277.69	295.71	240.25	258.26
T <sub>m</sub> , °C	131	118	155	128
cryst syst	orthorhombic	hexagonal	monoclinic	monoclinic
space group	Pbca	R3	$P2_1/n$	$P2_1/c$
<i>a,</i> Å	7.0180(2)	26.0229(3)	12.497(4)	15.191(1)
<i>b,</i> Å	11.8624(4)	26.0229(3)	5.8221(9)	6.8256(5)
c, Å	31.332(1)	11.2044(2)	16.191(2)	12.215(1)
$\alpha$ , deg	90	90	90	90
$\beta$ , deg	90	90	99.42(2)	98.478(6)
γ, deg	90	120	90	90
V, Å <sup>3</sup>	2608.4(2)	6571.0(2)	1162.1(4)	1252.8(2)
Z	8	18	4	4
E(000)	1152	2.772.	504	544
$d = g \cdot cm^{-3}$	1 415	1 346	1 374	1 370
completeness	98.0%	99.3%	98.1%	99.1%
$(\sin \theta/\lambda)  \Lambda^{-1}$	0.86	1 13	0.66	0.66
$(\sin \theta/\pi)_{\rm max}$ A	3 43-37 61	2.71 - 53.20	3 30-27 97	3.28_27.96
o range, deg	0.204	0.272	0.002	0.006
absorp coeff, $\mu$ , find	0.274	0.272	0.092	0.090
cryst size, min				vollow poodlo
			100	
1, K D	7U 4 920/	70 4 400/	2 150/	7U 1.510/
K <sub>int</sub>	4.83%	4.40%	3.15%	1.51%
refins collected/unique	48334/6809	206261/17456	4849/2/49	5208/29/1
refins with $I \ge 3\sigma(I)$	4399	11 /04	1599	2329
params/restraints	220/24	237/28	211/24	228/28
<i>K</i> [ <i>F</i> ]	3.17%"/6.32%"	2.87%"/4.58%"	4.69%"/7.84% <sup>b</sup>	2.96%"/3.96%"
$R[F^2]$	5.97%"/6.68% <sup>6</sup>	3.64%"/3.87% <sup>b</sup>	8.74% <sup><i>a</i></sup> /9.86% <sup><i>b</i></sup>	$6.56\%^{a}/6.78\%^{b}$

2.3. NMR Studies. <sup>13</sup>C and <sup>15</sup>N spectra were recorded at room temperature with a Bruker Avance 400 WB spectrometer at 9.4 T, using 100.61 and 40.50 MHz resonance frequencies, respectively. A Bruker 4.0 mm HX double-resonance magic-angle spinning (MAS) probe was applied. The <sup>13</sup>C and <sup>15</sup>N experiments were performed using cross-polarization (CP),<sup>21</sup> high power decoupling, and MAS<sup>23</sup> with 4 mm zirconia rotors driven by dry air. The MAS rates were 7.5 kHz and 3.5–5.0 kHz for <sup>13</sup>C and <sup>15</sup>N, respectively. The Hartmann–Hahn conditions<sup>22</sup> for <sup>13</sup>C and <sup>15</sup>N were matched with the aid of adamantane and glycine-<sup>15</sup>N. Typical <sup>13</sup>C acquisition parameters, including a  $(\pi/2)$  pulse of 2.7  $\mu$ s and a recycle delay of all hydrazones, were optimized (30-250 s). Chemical shifts were referenced to TMS using adamantane as an external secondary standard ( $\delta = 38.3$  ppm from TMS for the high-frequency peak). The <sup>15</sup>N CP/MAS spectra were acquired under the following conditions: a  $(\pi/2)$  pulse of 4.1  $\mu$ s and a contact time of 5 ms. They have been referenced to liquid nitromethane by setting the -345 ppm value to the peak of crystalline glycine-15N. The NMR spectra were processed, and peaks were deconvoluted with the ACD/SpecManager NMR program.<sup>23</sup> In order to verify the signal assignment, GIPAW calculations of shielding constants based on X-ray structures of NAHs were performed using the Cambridge Serial Total Energy Package (CASTEP) program<sup>2</sup> implemented in the Materials Studio 6.1 software.<sup>25</sup> The computation details can be find in the Supporting Information.

**Crystal Growth & Design** 

**2.4. Thermal Analysis.** The thermal stabilities of the studied hydrazones were examined using a Setsys 16/18 (Setaram) thermal analyzer, recording the TG/DTG/DSC curves. Crystals obtained from the crystallization batches had been air-dried before they were subjected to DSC or TGA analysis. The samples (4–7 mg) were heated in a ceramic crucible between 30-900 °C in a flowing air atmosphere with a heating rate of 10 °C min<sup>-1</sup>. Loss of solvent from the crystals was characterized by TG, and mass loss was calculated based on the mass of the original sample. The temperatures of the dehydration processes and temperatures and enthalpies of fusion (Table S1, Supporting Information) were established on the basis of the DSC curves.

**2.5. Computational Studies.** *2.5.1. Isolated Molecule Calculations.* All isolated molecule computations were performed using the *GAUSSIAN* program package (*GAUSSIAN09* version).<sup>26</sup> Constrained energy scans of the N2–C2–C3–N3 and, separately, the O1–C1–C8–C9 dihedral angles were performed for selected model hydrazone molecules at the DFT(B3LYP)/6-31G\*\* level of theory.<sup>27,28</sup> During the scan procedure, solely the mentioned dihedral angle was constrained in each case, and all the other parameters were fully optimized. No symmetry constraints were applied during the calculations. In the cases where discontinuous features were observed in the trajectories (Figure S1, Supporting Information), only the minimum energy conformations were optimized. These were done both at the DFT(B3LYP)/ 6-31G\*\* and at the MP2/aug-cc-pVDZ level of theory.<sup>29,30</sup>

2.5.2. Periodic Calculations. All energy computations within the *CRYSTAL* program package (*CRYSTAL09* version)<sup>31</sup> were performed at the DFT(B3LYP) level of theory. The 6-31G\*\* molecular allelectron basis set was utilized for the purpose of the conducted calculations. Both the Grimme dispersion correction<sup>32</sup> and correction for basis set superposition error (BSSE)<sup>33</sup> were applied. Ghost atoms were selected up to 5 Å distant from the studied molecule in a crystal lattice and were used for the basis set superposition error estimation. The evaluation of Coulomb and exchange series was controlled by five thresholds, set to values of  $10^{-7}$ ,  $10^{-7}$ ,  $10^{-7}$ ,  $10^{-25}$ . The condition for the SCF convergence was set to  $10^{-7}$  on the energy difference between two subsequent cycles. The TAAM refined crystal geometries, which have previously been proven to be appropriate for sensible computational analyses of the solid state,<sup>34</sup> were used for the purposes of the *CRYSTAL* calculations. The cohesive energy  $(E_{\rm coh})$  was calculated following the procedure described in the literature:<sup>35</sup>

$$E_{\rm coh} = \frac{1}{Z} E_{\rm bulk} - E_{\rm mol}$$

where  $E_{\text{bulk}}$  is the total energy of a system (calculated per unit cell) and  $E_{\text{mol}}$  is the energy of an isolated molecule extracted from the bulk (with the same geometry as in the crystal phase). Z stands for the number of molecules in the unit cell.

The *CRYSTAL* package was additionally used for the dimer interaction energy estimation at the  $DFT(B3LYP)/6-31G^{**}$  level of theory. The supermolecular approach was applied with both Grimme dispersion and BSSE corrections.

All CRYSTAL input files were prepared using the CLUSTERGEN program.  $^{36}$ 

#### 3. RESULTS AND DISCUSSION

3.1. Crystal Syntheses and Introductive Remarks. A common feature of the studied compounds is their tendency to crystallize as hydrates. The same propensity was previously observed for some other N-aroylhydrazone derivatives.<sup>3</sup> Among the compounds reported in this paper (Scheme 2), crystallization only as an anhydrous form is restricted to 2, whereas the remaining hydrazones form stoichiometric hydrates  $(3 \cdot H_2O, 4 \cdot H_2O, 4 \cdot 2H_2O)$ , or exist both in the hydrated and solvent-free forms  $(1, 1 \cdot H_2O, 5, 5 \cdot H_2O)$ . Most of the studied compounds form well-shaped single crystals as a result of solvent evaporation directly from the stock solution (1, 2,  $3 \cdot H_2O$ ,  $4 \cdot 2H_2O$ ,  $5 \cdot H_2O$ ). In turn, the crystals of  $1 \cdot H_2O$ ,  $4 \cdot$ H<sub>2</sub>O, and 5 can be obtained by recrystallization from DMF or dry methanol. It is worth noting that both forms of 5 actually grow simultaneously from the latter solution. Crystallization from other common organic solvents (e.g., ethanol, propan-1ol, propan-2-ol, acetone, acetonitrile, chloroform, tetrahydrofuran, DMSO) leads most often to stoichiometric hydrates or solvent-free powder solids but never to other solvated crystal structures. Such observations suggest that the specific intermolecular interactions between either hydrazones, or more importantly hydrazones and water molecules, are crucial in the aggregation and crystallization processes and, in consequence, determine the structures and compositions of the final products. Furthermore, the water incorporated into crystal networks can be either associated with the solvent or absorbed from the air. The size and hydrogen bond donor and acceptor properties of water molecules seem to satisfy best hydrazone-based crystal networks. Nevertheless, it should be stressed that no systematic study dedicated either to solvatomorphism or polymorphism screening has yet been undertaken.

The majority of the compounds under consideration crystallize in centrosymmetric space groups ( $P\overline{I}$ ,  $P2_1/c$ , or Pbca) with one hydrazone molecule in the asymmetric part of the unit cell. The highest crystallographic symmetry was observed for the 2-chlorophenyl derivative dihydrate,  $4 \cdot 2H_2O$  ( $R\overline{3}$  space group), which is isostructural with the previously reported 2-pyridinecarbaldehyde-2'-bromobenzoyl hydrazone dihydrate<sup>38</sup> (CSD refcode: HIGCOQ). Furthermore, a detailed

Table	2. Sel	ected (	Jeometric	Parameters	tor	Studied	Hydrazones	after	TAAM	Refinement"
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<i>d,</i> Å	1	1.H₂O	2	3·H <sub>2</sub> O	$4 \cdot H_2O$	4·2H₂O	5	5 · H₂O
C1-O1	1.225(1)	1.226(1)	1.2365(6)	1.2285(5)	1.225(1)	1.2257(4)	1.223(3)	1.237(1)
C1-N1	1.355(1)	1.344(1)	1.3595(6)	1.3624(5)	1.364(1)	1.3527(4)	1.377(3)	1.369(1)
N1-N2	1.371(1)	1.368(1)	1.3698(6)	1.3677(5)	1.371(1)	1.3718(4)	1.373(3)	1.374(1)
N2-C2	1.288(1)	1.279(1)	1.2866(6)	1.2834(5)	1.281(1)	1.2817(4)	1.278(3)	1.287(1)
C2-C3	1.468(1)	1.467(2)	1.4682(7)	1.4669(6)	1.470(1)	1.4645(4)	1.470(4)	1.475(1)
C1-C8			1.4984(7)	1.4952(6)	1.500(1)	1.5008(4)	1.491(4)	1.493(1)
$\theta$ , deg	1	$1 \cdot H_2O$	2	3·H <sub>2</sub> O	$4 \cdot H_2O$	$4 \cdot 2H_2O$	5	$5 \cdot H_2O$
O1-C1-N1	123.2(1)	123.6(1)	119.06(5)	122.96(3)	123.6(1)	124.45(4)	122.5(3)	121.7(1)
O1-C1-C8			122.40(6)	121.60(3)	122.5(1)	122.31(4)	122.8(2)	122.6(1)
N1-C1-C8			118.54(4)	115.42(2)	113.9(1)	113.23(3)	114.7(3)	115.8(1)
C1-N1-N2	119.1(1)	118.0(1)	121.26(4)	118.24(1)	117.9(1)	118.99(3)	119.4(2)	118.3(1)
N1-N2-C2	114.9(1)	116.0(1)	115.33(5)	115.29(2)	115.7(1)	114.58(3)	115.5(2)	115.4(1)
N2-C2-C3	122.5(1)	121.1(1)	120.99(6)	120.50(2)	120.0(1)	120.42(3)	121.8(3)	120.8(1)
C2-C3-N3	113.8(1)	114.7(1)	115.22(4)	114.34(2)	114.6(1)	114.75(3)	114.5(3)	114.5(1)
au, deg	1	$1 \cdot H_2O$	2	3·H <sub>2</sub> O	$4 \cdot H_2O$	$4 \cdot 2H_2O$	5	5 · H₂O
01-C1-N1-N2	-176.8(1)	178.9(1)	179.13(5)	-1.70(2)	3.2(1)	0.65(3)	-8.0(2)	2.2(1)
C1-N1-N2-C2	175.8(1)	-176.5(1)	-175.29(4)	-176.88(2)	-179.7(1)	-172.84(3)	172.6(2)	176.1(1)
N1-N2-C2-C3	-179.0(1)	-178.8(1)	-179.37(4)	178.89(2)	-176.9(1)	-178.65(3)	176.5(2)	-178.4(1)
N2-C2-C3-N3	173.8(1)	176.7(1)	-178.40(4)	-175.08(2)	173.0(1)	-177.47(3)	178.8(2)	176.2(1)
01-C1-C8-C9				22.48(2)	-42.7(1)	68.18(3)	-32.5(2)	-23.4(1)
<sup><i>a</i></sup> <i>d</i> , bond distance;	$\theta$ , bond angle; $\tau$	, torsion angle.						

comparison of the studied structures with the closely related hydrazone derivatives deposited in CSD indicated significant similarity of the unit cell parameters, corresponding atom coordinates, and hydrogen-bonding patterns of 2-pyridinecarboxaldehyde acetylhydrazone **2** with benzaldehyde<sup>39a</sup> and 2fluorobenzaldehyde<sup>39b</sup> acetylhydrazones (CSD refcodes: VUH-MUG and KUTWEC).

In turn, the crystal structure of  $3{\cdot}H_2O$  has been reported previously by two groups, 5d,e each time determined from diffraction data collected at ambient temperature and refined using the standard spherical atom model. In the course of the present study, we have redetermined this structure from the data measured at 90 K and refined using the transferable aspherical atom model (TAAM) approach.<sup>14</sup> In order to fully characterize the crystal structure motifs and understand the structural and energetic factors that control the packing of molecules with a given functional group, it is essential to have a wider overview of the solid-state arrangement of molecules bearing that group. Therefore, comprehensive structural, energetic, and Hirshfeld surface analyses of 3·H<sub>2</sub>O were carried out and are included in our study. However, because the molecular and crystal structure of this compound has been described previously and the 3·H<sub>2</sub>O crystal is isostructural to 4· H<sub>2</sub>O, only the latter structure is discussed in detail.

**3.2. Molecular Structure and Cohesive Energy.** The relevant geometric parameters for all studied structures are given in Table 2, whereas the molecular plots with the atom-labeling schemes are presented in Figure 1. As indicated by the X-ray data, all of the studied compounds appear in their keto– imino tautomeric forms in the solid state with the *trans* configuration around the C2=N2 double bond of the hydrazone bridge and *s*-*trans* junction between imine and amide functions (Scheme 1).

The central C3–C2–N2–N1–C1–C8 spacer unit (Figure 1) in benzoyl derivatives, 3–5, as well as the C3–C2–N2–N1–C1 moiety in the acyl hydrazones, 1 and 2, are effectively planar with the all-*trans* extended-chain conformation, which is supported by the appropriate torsion angles being close to  $180^{\circ}$ 

(Table 2). The overall geometry of 2 is very similar to that observed in some other closely related N-acetylhydrazones (CSD refcodes: EYAQIF, KABHEC, KUTWEC, VABZOP, XOZDIA). A common conformational feature for all compounds is the trans arrangement of the pyridine N3 atom with respect to the imine N2 atom as defined by the N2-C2-C3–N3 torsion angles, deviating by no more than  $\pm 7^{\circ}$  from 180°. Such a conformation prevents potential repulsion between the H atoms attached to the C2 and C4 carbon atoms. In order to check the rotational freedom of the C2-C3 bond, an energy scan was also performed (Figure 2a). In the case of model system 1, two minima, which correspond to trans and *cis* conformations, differ energetically by about 22 kJ $\cdot$ mol<sup>-1</sup>. In addition, the rotation barrier is rather high (system needs to be activated by about 40 kJ mol<sup>-1</sup> to rotate along the C2–C3 bond from trans to cis arrangement. Therefore, due to the hampered rotation and significant conformational energy difference, the more advantageous trans conformation is observed in all the crystal structures of the studied hydrazones. A small twist of the 2-pyridyl ring from the approximate plane of the spacer unit, observed in the solid state, is naturally a result of the crystal field effects.

In general, the most visible geometric difference between the N-acyl- (1 and 2) and N-aroylhydrazones (3-5) is the conformation of the hydrazide function, which adopts the trans and cis arrangement, respectively. The energetic effects accompanying rotation of the N1-C1 bond were examined computationally. In the case of the model systems 1 and 3, two local minima were found regarding the fixed O1-C1-N1-N2 torsion angle. In the case of 1, the more stable conformation is the one where the O1 and N2 atoms are at the opposite sides of molecule (EE' conformation in Scheme 1; Table S3, Supporting Information). This conformation is energetically favored by about 12-16 kJ·mol<sup>-1</sup>, depending on the level of theory used. In the compound 3, the bulky phenyl group leads to diminishing of the energy differences, making the *trans* (*EE*' conformation) orientation more energetically preferable by only about 5-9 kJ·mol<sup>-1</sup>. It is worth mentioning that the



Figure 1. Labeling of atoms and estimation of their thermal motion parameters as ADPs (50% probability level) after the final TAAM refinements. Hydrogen and other selected atom labels are omitted for clarity.

molecule of 1 is flat in both of the most favorable conformations, whereas in the case of 3, it deviates from planarity (ca.  $3^{\circ}$  and  $15^{\circ}$ , for more and less stable minimum, respectively). Interestingly, in the  $3 \cdot H_2O$  crystal structure, the

hydrazone molecule adopts the less stable conformation (EZ') with the O1-C1-N1-N2 torsion angle being equal to  $-1.70(2)^{\circ}$ , which seems to result from intermolecular interactions in the crystal lattice.



Figure 2. Torsion-angle-( $\tau$ )-constrained scans for (a) N2–C2–C3–N3 angle in compound 1 and O1–C1–C8–C9 angles in compounds (b) 3 and (c) 4 (bold font denotes rotation along the respective bond).

In the solid state, a significant rotation of the phenyl ring is also observed in the benzovl derivatives 3-5 (Figure 1). The degree of rotation depends on the substituent in the orthoposition. The ortho-substituents in the hydrated and solventfree forms of the 5 compound exhibit the cis configuration with respect to the amide O1 atom, and so does the chlorine atom in both crystals of 4. Whereas in the former case an intramolecular hydrogen bond is formed, in the latter one there is not much interaction between the carbonyl oxygen atom and the chlorine substituent (more details are provided in section 3.3.2). Thus, in 4, due to the steric effects and electrostatic forces, the rotation degree is obviously greater. To support the observed features, C1-C8 bond rotation energy scans were also performed (Figure 2b,c). In the model compound 3, the minima indicate slight rotation of the phenyl ring (about  $30^{\circ}$ ) in the optimal structure. This is very well reflected in the 3·H<sub>2</sub>O crystal structure. Compound 4 constitutes a more interesting case, where two types of minima are observed. At both minima, the phenyl ring is rotated by about 30°; however, in the more advantageous conformation, the chlorine substituent is placed on the opposite side of the molecule to the amide O1 atom ("trans" conformation). Interestingly, in both hydrous crystal structures of 4, the less stable conformation is observed

(compared with the computational results). In this case, such a result can come from not taking into account dispersion interactions while doing the scan but also from the intermolecular interactions present in a crystal. Naturally, the rotation barrier is highest for 5 (Figure S1, Supporting Information), where the intramolecular hydrogen bond is preferentially formed. Compound 5 adopts the close-to-optimal conformation in its crystal structures.

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Having a closer look at the geometrical parameters, bond lengths and angles characterizing 1-5 (Table 2) are among typical values for this class of compounds,<sup>5,37</sup> with a clear distinction between single and double bonds in the central functional spacer. The C1–O1 (1.223(3)–1.237(1) Å) and N2–C2 (1.278(3)–1.288(1) Å) interatomic distances can be classified as double bonds, whereas the C1–N1 (1.344(1)–1.377(3) Å) distances agree well with the mean values reported for the amide  $C_{sp}^2$ –N (about 1.34 Å) bonds.<sup>40</sup> In turn, the N1–N2 (1.368(1)–1.374(1) Å) distances are slightly shorter than typical azine  $N_{sp}^2$ – $N_{sp}^2$ (about 1.40 Å) single bonds;<sup>40</sup> however, they are in good agreement with those observed in some other, closely related NAHs.<sup>37</sup> Small deviations in the corresponding bond lengths in different crystal forms result most probably from different intermolecular interaction patterns. A common

phenomenon for the 3-5 benzoyl derivatives is a significant widening of the O1-C1-N1 and O1-C1-C8 angles (Table 2), accompanied by narrowing of the N1-C1-C8 angle. This is caused by the repulsion between lone electron pairs at the O1 and N2 atoms and/or steric hindrance between carbonyl and phenyl functional groups.

As mentioned previously, the largest geometrical deviations are observed in the relative arrangement of the terminal units, especially pronounced for the benzoyl derivatives, 4 and 5. In the case of compound 1, the molecule is almost completely planar in  $1 \cdot H_2O$  (Table 2), whereas in its anhydrous crystal a small rotation (to within 6°) around N1-N2 and C2-C3 bonds is visible. The differences in the overall geometry of the aroyl derivatives, 4 and 5, are mostly caused by rotation around the C1-C8 bond. The displacement of the terminal phenyl ring in the 2-chloro and 2-aminophenyl derivatives (compounds 4 and 5) is more significant than that of the nonsubstituted phenyl derivative in 3·H<sub>2</sub>O (Table 2). This is driven by the steric hindrance and the nature of interactions between C9-substituents and carbonyl O1-atoms. In the case of 5, the phenyl group is oriented in a way that assures a reasonable geometry of the hydrogen bond, either intermolecular (5) or inter- and intramolecular  $(5 \cdot H_2 O)$ , formed between the C9 amino group and the respective acceptor atoms. What is more, the involvement of the water molecules in intermolecular interactions with surrounding host molecules forces further conformational changes in the hydrated hydrazones. This is evidenced by the dihedral angle values between the least-squares-fitted planes to the 2-pyridine and phenyl rings. The angles equal  $47.42(1)^{\circ}$  and  $80.05(1)^{\circ}$  in 4.  $H_2O$  and  $4.2H_2O$ , whereas they are  $51.00(1)^\circ$  and  $30.80(2)^\circ$  in 5 and  $5 \cdot H_2O_1$ , respectively.

A careful examination of the molecular geometries of the studied hydrazones in their hydrous and solvent-free forms certainly reveals their ability to exist as different conformers in the solid state. It seems that the imbalance in the total number of hydrogen-bond donor and acceptor atoms in the systems, spatial molecular flexibility and affinity for water make hydrazones prone to inclusion of water molecules into their crystal networks. Water molecules ensure the hydrogen bond saturation of the host compounds. There is a visible gain in energy per asymmetric part of the unit cell (ASU) content (around 50 kJ·mol<sup>-1</sup>) when water molecules are incorporated into the crystal (Table 3). Nevertheless, the whole crystal-lization process also involves entropy changes and other factors. Table 3 shows the differences in the hydrazone framework

Table 3. Cohesive Energy Values of the Studied Crystals in Their Hydrous and Anhydrous Forms"

structure	ASU content	$E_{\rm coh}$ , kJ·mol <sup>-1</sup>	$E_{\rm coh}^{\rm anh}$ , kJ·mol <sup>-1</sup>
1	1H	-110.6	
$1 \cdot H_2O$	1H + 1W	-175.6	-75.0
2	1H	-115.4	
$3 \cdot H_2O$	1H + 1W	-207.7	-107.1
$4 \cdot H_2O$	1H + 1W	-218.1	-115.6
$4 \cdot 2H_2O$	1H + 2W	-287.0	-103.1
5	1H	-168.7	
5 · H₂O	1H + 1W	-216.8	-116.1

<sup>*a*</sup>Abbreviations: H, hydrazone molecule; W, water molecule;  $E_{coh}$ , cohesive energy,  $E_{coh}^{anh}$ , cohesive energy of structure with artificially removed water.

stabilization energies for the anhydrous crystal structures, hydrated crystal structures, and those with the excluded water content (for an example of a similar analysis, see ref 41).

The final structure is a balance between the hydrazone conformational stability, intermolecular interactions, entropy, and kinetics. Among the anhydrous structures, **1** is characterized by the least advantageous cohesive energy. When more bulky phenyl substituents are introduced, the cohesive energy becomes more beneficial.

**3.3. Supramolecular Structures and Intermolecular Interactions.** To obtain an overall picture of the studied structures, a Hirshfeld surface approach<sup>42</sup> was employed. Hirshfeld surfaces are a useful tool in crystal engineering because they allow for crystal packing investigations and some quantification of contributions coming from different intermolecular contact types existing in a crystal lattice. Thus, here we present the Hirshfeld surface fingerprint plots in Figure 3. The percentage contributions of important intermolecular interactions for each structure are given in Figure S2 in the Supporting Information.

Although it is hard to distinguish sets of similar structures, observations of a general nature can be easily drawn from the analysis of fingerprint plots. The important feature of all the plots is that they are rather asymmetric. This is clearly the result of conformational flexibility of the molecules and the anisotropic environment in the solid state, especially in the case of hydrates. The asymmetry is most visible in the 1·H<sub>2</sub>O crystal structure, where the double-spike feature is most pronounced. The upper and middle spikes are associated with the O…H contacts, whereas the bottom one is related to the N…H interactions. This separation is also observed, though to a lesser extent, for the  $4 \cdot H_2O$ ,  $4 \cdot 2H_2O$ , 5, and  $5 \cdot H_2O$  crystal structures. Generally, the sharp spike features result from hydrogen bonds present in the studied structures and show their importance for structural stability. Another observation that can be made on the basis of Figure 3 concerns more efficient packing of the hydrated structures in comparison to their anhydrous equivalents, as reflected in the plotted interatomic distances.

On the other hand, the plot of percentage contributions of selected interatomic contacts to the Hirshfeld surfaces of the hydrazone molecules in the studied crystals (Figure S2, Supporting Information) gives us an idea of the most common interactions in the crystal lattices. Most important here are both O…H (10-22%) and N…H (7-18%) contacts, which reflect the hydrogen bond impact, and C…H (8-29%) interactions or less emphasized C...C, C...N, etc., responsible for contacts more dispersive in nature. In the case of anhydrous structures, the percentage contributions of O...H and N...H contacts are very comparable. Naturally N···H interactions are outnumbered by O…H contacts in the hydrated structures. It is also worth noting that the C···H contacts contribution is very substantial, being most pronounced for 5 (29%) and least for  $1 \cdot H_2O(8\%)$ . In the case of compound 4, a significant contribution from Cl---H contacts, being around 14-15%, is also observed.

3.3.1. Anhydrous Hydrazone Crystal Structures. Among the intermolecular interactions involved in stabilization of solvent-free crystals, hydrogen bonds of the N-H…O and/or N-H…N type play the dominant role, as is evident from the Hirshfeld surface analysis. In all the studied cases, the amide N1-H group acts as a donor, while the amide O1 atom or pyridine N3 atoms function as hydrogen bond acceptors. Geometrical parameters of the shortest intermolecular



Figure 3. Hirshfeld surface fingerprint plots for all the studied hydrazone crystal structures (only hydrazone molecules are considered in the case of hydrates). Characteristic features of fingerprint plots are depicted as red triangles (O…H interactions), blue squares (N…H), green circles (C…H), and stars (Cl…H).

interactions found in all the studied systems are listed in Table 4.

In the crystal of 1, the strongest interaction is formed by the adjacent 21 axis related molecules, which are connected together by relatively short N1-H1N...N3<sup>#1</sup> (symmetry codes as in Table 4) hydrogen bonds reinforced by weak C2-H2...N3<sup>#1</sup> interactions (the interaction energy of the corresponding dimer is  $-37.8 \text{ kJ} \cdot \text{mol}^{-1}$ , Table 4, Figure 4a). This leads to the formation of helical chains (Figure 4b) running down the Y axis. Additional stabilization of the motifs is provided by weak C7-H7...O1<sup>#3</sup> contacts of about -5.7 kJ· mol<sup>-1</sup> in strength (Figure 4c, Table S4, Supporting Information). The neighboring chains, related one to another by inversion and hence running antiparallel, are connected by the combination of weak C4–H4…O1<sup>#2</sup> and C1–H1…N2<sup>#2</sup> hydrogen-bond type contacts (Table 4, Figure 4a). The headto-head oriented molecules, linked by those interactions, create centrosymmetric dimers, characterized by an interaction energy of  $-28.5 \text{ kJ} \cdot \text{mol}^{-1}$ . The crystal packing is further supported by relatively strong  $\pi$ -stacking interactions (Table S4, Supporting Information, and Figure 4b), involving the amide, hydrazone, and pyridyl ring fragments. Supplementary stabilization of the 3D structure is achieved by weak C5-H5...O1<sup>#4</sup> interactions (-6.7 kJ·mol<sup>-1</sup> in total) and C7-H7… $\pi$  contacts, present between complex and significantly puckered (100) sheets (Figure 4d).

In turn, the main motif in the crystal of 2 is based on N-H… O hydrogen-bonding involving just amide groups. The energetically favorable *E* configuration of the hydrazide moiety enables the N1 and O1 atoms from the adjacent molecules to interact via strong N1-H1N···O1<sup>#9</sup> hydrogen bonds (Table 4, Figure 5a). As a result, the cyclic amide-amide homosynthon A (Scheme 3) involving an  $R_2^2(8)^{43}$  hydrogen-bonded ring motif with interaction energy equal to  $-65.5 \text{ kJ} \cdot \text{mol}^{-1}$  is formed. It is worth noting that **2** is the only structure in the group where this motif is observed and, what is more, it is the strongest stabilized synthon among the studied structures. The centrosymmetric dimers are linked further into the [210] molecular chains via H…H<sup>44</sup> interactions (Figures 5a,b). The H4…H5<sup>#33</sup> and H8b… H5<sup>#33</sup> (symmetry code: (#33) -x + 2, -y + 1, -z + 1) contacts are particularly interesting, because they are characterized by interhydrogen distances smaller than the sum of VdW radii (2.137 and 2.359 Å, respectively). It is, however, difficult to estimate their actual contribution to the interaction energy of the corresponding dimer (total interaction energy -8.8 kJ. mol<sup>-1</sup>), where electrostatic interactions are also involved (C5-H5…N2<sup>#33</sup>). The 3D framework in 2 can be analyzed in terms of two 2D substructures. The first one utilizes weak C7-H7... O1<sup>#10</sup>, C6–H6…N3<sup>#11</sup>, and C8–H8b… $\pi$  ( $d_{C8\dots\pi_{cent}(N3-C7)}$  = 3.550(3) Å,  $d_{\text{H8B}\cdots\pi_{\text{cent}}} = 2.623$  Å,  $\theta_{\text{C8}-\text{H8B}\cdots\pi_{\text{cent}}} = 144^{\circ}$ ; symmetry code: -x + 1, -y + 1, -z + 1) hydrogen bonds (Figure 5d),

Table 4. Geometries of Hydrogen Bonds and Selected Short Contacts for All Studied Hydrazone Structures after TAAM Refinement Together with Interaction Energy Values of Selected Hydrazone Dimers and Hydrazone–Water Contacts<sup>a</sup>

compound	interaction <sup>b</sup>	$d_{\mathrm{D-H}\prime}$ Å	$d_{\mathrm{H}\cdots\mathrm{A}}$ , Å	d <sub>D…A</sub> , Å	$d_{\mathrm{D-H}\cdots\mathrm{A}}$ , deg	$E_{\rm intr} \ \rm kJ \cdot mol^{-1}$
1	N1-H1N…N3 <sup>#1</sup>	1.027(1)	1.940(3)	2.957(2)	169.9(3)	27.9
	C2-H2···N3 <sup>#1</sup>	1.027(1)	2.701(4)	3.568(2)	136.8(3)	-3/.8
	$C1-H1\cdots N2^{\#2}$	1.082(2)	2.520(4)	3.582(2)	166.7(3)	-28.5
	C4-H4····O1 <sup>#2</sup>	1.083(2)	2.427(5)	3.447(2)	156.4(5)	20.0
	C7–H7…O1 <sup>#3</sup>	1.083(2)	2.706(4)	3.644(2)	144.8(5)	-5.7
	C5-H5…O1 <sup>#4</sup>	1.083(2)	2.701(4)	3.257(2)	111.5(5)	-6.7
1·H <sub>2</sub> O	N1-H1N…O1W	1.027(1)	1.877(4)	2.869(5)	161.4(4)	-27.2
	C2-H2···O1W	1.082(1)	2.63(1)	3.417(8)	129(1)	
	$OIW-HIWOI^{**}$	0.958(1)	1.900(5)	2.835(4)	164.5(5)	-20.5
	$O1W - H2W \cdots N3^{n-1}$	0.958(1)	1.919(4)	2.863(2)	167.9(4)	-20.1
	$C_1 - H_1 \cdots N_3$	1.082(1)	2.035(8)	3.403(5)	132.9(0) 141.2(4)	-13.8
	$C_{4} = H_{5} \dots O_{1}^{\#8}$	1.083(1)	2.023(0)	3.333(4)	141.2(4) 125.0(7)	-23.9
	C6-H6O1W <sup>#8</sup>	1.083(1)	2.40(1) 2.71(1)	3.219(7) 3.696(7)	123.9(7) 152.2(7)	-7.9
2	$N1 - H1NO1^{#9}$	1.005(1) 1.026(2)	1.842(2)	2.864(1)	132.2(7) 173.4(2)	-69.5
-	$C7-H7O1^{\#10}$	1.020(2) 1.082(2)	2.356(4)	3.363(1)	154.1(3)	-10.6
	C8-H8C···O1 <sup>#5</sup>	1.077(2)	2.543(2)	3.590(1)	163.9(2)	-19.2
	C6-H6…N3 <sup>#11</sup>	1.082(2)	2.628(4)	3.599(1)	149.1(3)	-9.2
3·H <sub>2</sub> O	N1-H1N…O1W	1.025(1)	1.830(2)	2.827(1)	163.2(3)	
	C2-H2O1W	1.082(1)	2.392(4)	3.249(1)	135.0(3)	-21.3
	C13-H13O1W	1.083(1)	2.356(4)	3.277(1)	141.9(3)	
	O1W-H2W…N3 <sup>#12</sup>	0.956(1)	1.920(2)	2.848(1)	162.9(3)	-25.5
	O1W-H1W…O1 <sup>#13</sup>	0.956(1)	2.195(5)	3.000(1)	141.1(4)	
	O1W-H1W…N2 <sup>#13</sup>	0.956(1)	2.314(5)	3.047(1)	133.0(4)	-25.7
	C4-H4…O1W <sup>#14</sup>	1.082(1)	2.558(4)	3.450(1)	145.0(3)	
	C13-H13O1 <sup>#13</sup>	1.083(1)	2.464(4)	3.283(1)	131.5(3)	-27.6
	C5-H5…O1 <sup>#31</sup>	1.083(1)	2.545(4)	3.170(1)	115.9(3)	-21.5
$4 \cdot H_2O$	N1-H1N···O1W	1.027(2)	1.867(2)	2.828(1)	154.3(7)	
	C2-H2···O1W	1.082(2)	2.464(9)	3.269(1)	130.3(8)	-22.0
	C13-H13O1W	1.082(2)	2.627(9)	3.328(1)	121.9(8)	
	$O1W - H2W - N3^{+10}$	0.958(2)	1.935(4)	2.862(1)	162.1(5)	-25.6
	$01W - H1W N2^{#16}$	0.957(2)	2.060(7)	2.924(1) 2.127(1)	149.1(7) 126.2(8)	_28.5
	$C_{4} = H_{4} = 0.1 M_{18}^{+18}$	1.082(2)	2.470(9)	3.137(1) 3.560(1)	120.2(8) 140.3(5)	-28.3
	$C_{13} - H_{13} - O_{1}^{\#16}$	1.082(2) 1.082(2)	2.393(0) 2.454(9)	3.309(1) 3.249(1)	129.2(6)	
	$C_{5}$ H5N3 <sup>#17</sup>	1.082(2)	2.725(6)	3.695(1)	129.2(6) 1491(5)	-30.9
	C7-H7Cl1 <sup>#19</sup>	1.082(2)	2.83(1)	3.596(1)	127.6(7)	-29.8
	C11-H11Cl1 <sup>#1</sup>	1.082(2)	2.79(1)	3.647(1)	135.3(7)	-5.5
$4 \cdot 2H_2O$	O1W-H1W···N3	0.957(2)	1.794(2)	2.737(4)	167.6(3)	-19.0
	O1W-H2W···O2W	0.958(2)	1.763(2)	2.721(1)	177.5(2)	-15.8
	O2W-H4WO1W <sup>#20</sup>	0.957(2)	1.840(2)	2.789(1)	171.2(2)	-15.1
	N1-H1N…O1W <sup>#20</sup>	1.027(2)	1.819(2)	2.836(1)	169.9(2)	20 /
	C2-H2····O1W <sup>#20</sup>	1.082(2)	2.531(5)	3.352(1)	132.0(4)	-28.4
	O2W-H3W…O1 <sup>#21</sup>	0.957(2)	1.973(3)	2.908(1)	164.6(3)	_32.4
	C4-H4····O2W <sup>#25</sup>	1.082(2)	2.68(2)	3.733(1)	161.7(2)	-32.4
	C5-H5…O1 <sup>#22</sup>	1.082(2)	2.178(2)	3.248(1)	169.1(2)	-14.2
	C13-H13···O2W <sup>#23</sup>	1.082(2)	2.452(5)	3.282(1)	132.5(4)	-7.3
_	C6–H6…Cl1 <sup>#24</sup>	1.082(2)	2.909(5)	3.742(1)	133.8(4)	-32.6
5	N4-H4A····O1	1.024(2)	2.23(3)	2.821(3)	115(1)	
	$N4 - H4A \cdots O1^{2}$	1.024(2)	2.21(1)	3.058(7)	139(1)	-39.0
	$N4 - H4B \cdots O1^{-2}$	1.024(2)	2.22(1)	3.219(3)	163(1)	-50.2
	$N1 - H1N \cdots N3$	1.02/(2)	2.0/(1)	3.044(5)	13/(1) 128(1)	24.2
	$C_{13}$ H13N3 <sup>#27</sup>	1.083(2) 1.083(2)	2.30(1)	3.531(3) 3.512(5)	123(1)	-34.3
	C4-H4O1 <sup>#7</sup>	1.003(2) 1.083(2)	2.09(1) 2.57(1)	3,578(8)	155(1)	
	C5-H5N4 <sup>#7</sup>	1.083(2)	2.49(1)	3,450(7)	147(1)	-23.1
5·H₂O	N4-H4A…O1	1.010(2)	1.929(8)	2.712(1)	132(1)	
2-	N1-H1N···O1W	1.027(2)	1.873(4)	2.867(1)	161.8(5)	
	C13-H13-01W	1.083(2)	2.392(7)	3.278(2)	138.0(6)	-22.6
	C2-H2-O1W	1.082(2)	2.414(7)	3.268(2)	134.8(6)	

#### Table 4. continued

compound	interaction <sup>b</sup>	d <sub>D-H</sub> , Å	d <sub>H…A</sub> , Å	d <sub>D…A</sub> , Å	$d_{\mathrm{D-H}\cdots\mathrm{A}}$ deg	E <sub>int</sub> , kJ⋅mol <sup>-1</sup>
	O1W-H2W…N3 <sup>#7</sup>	0.958(2)	1.960(4)	2.889(1)	162.9(4)	-25.7
	O1W-H1W-01#28	0.958(2)	2.143(7)	2.965(1)	143.1(7)	
	O1W-H1WN2 <sup>#28</sup>	0.958(2)	2.388(9)	3.088(1)	129.6(7)	-27.9
	C4-H4…O1W <sup>#30</sup>	1.083(2)	2.622(7)	3.563(2)	145.0(5)	
	C13-H13-01#28	1.083(2)	2.532(7)	3.324(2)	129.2(5)	-26.4
	N4-H4B…N4 <sup>#32</sup>	1.009(2)	2.67(1)	3.278(3)	118.5(7)	-15.6
	C5-H5…O1 <sup>#29</sup>	1.082(2)	2.54(1)	3.257(2)	122.7(6)	-18.0

<sup>*a*</sup>Calculated at the DFT(B3LYP-D)/6-31G\*\* level of theory with BSSE and Grimme corrections applied. <sup>*b*</sup>Symmetry transformations: (#1) -x + 1, y + 1/2, -z + 1/2; (#2) -x + 1, -y + 2, -z + 1; (#3) -x + 1, y + 3/2, -z + 1/2; (#4) x - 1, y - 1, z; (#5) x + 1, y, z; (#6) x - 1, y, z; (#7) -x, -y + 1, -z + 1; (#8) x + 1, y - 1, z + 1; (#9) -x, -y, -z + 1; (#10) x + 1, -y + 1/2, z + 1/2; (#11) -x + 2, y + 1/2, -z + 3/2; (#12) -x, 1 - y, -z; (#13) -x + 1/2, y + 1/2, z; (#14) -x + 1/2, y - 1/2, z; (#15) -x + 1, -y + 1, -z; (#16) -x + 3/2, y + 1/2, z; (#17) -x + 1/2, y - 3/2, z; (#18) -x + 3/2, y - 1/2, z; (19) x + 1/2, -y + 1/2, -z; (#20) -y + 2/3, x - y + 1/3, z + 1/3; (#21) y, -x + y, -z + 1; (#22) -y + 1/3, x - y + 2/3, z - 1/3; (#23) -x + y + 1/3, -x + 2/3, z + 2/3; (#24) -x + 1/3, -y + 2/3, -z + 2/3; (#25) x - y, x, -z + 1; (#26) x, y - 1, z; (#27) -x - 1/2, y - 1/2, -z + 3/2; (#28) x, -y + 1/2, z - 1/2; (#29) -x, -y + 1, -z + 2; (#30) x, -y + 1/2, z + 1/2; (#31) -x, -y, -z; (#32) -x + 1, -y + 1, -z + 2.



**Figure 4.** (a) Hydrogen-bonding motifs, (b)  $\pi$ -stacked dimers and molecular chain helically extended along the 2<sub>1</sub> screw axis (green solid line), (c) weak C-H···O and C-H··· $\pi$  interactions, and (d) (100) molecular layers in crystal **1**, viewed down the *Y* axis. Dashed lines indicate hydrogen bonds or  $\pi$ -stacking interactions.

which link the adjacent molecules into ( $\overline{102}$ ) layers. The second one is based on  $\pi \cdots \pi$  interactions between planar molecular units (Figures 5b,c) and formed due to stacking of the [210] molecular chains. As indicated by the interaction energy values, the dispersive  $\pi$ -stacking interactions are generally quite significant (e.g.,  $-29.0 \text{ kJ} \cdot \text{mol}^{-1}$  for the dimer created by the -x + 1, -y + 1, -z + 1 related molecules, Table 4, Table S4, Supporting Information). Nevertheless, the overall crystal cohesive energy is comparable to that of **1** (Table 4).

The crystal packing of **5** is dominated by strong N–H···O/N hydrogen bonds involving amide, amine, or pyridine functional groups and reveals a molecular chain arrangement typical for this class of compounds, which further associates into layer motifs. As in **1**, the adjacent  $2_1$  screw-axis related molecules are connected here by relatively short N1–H1n···N3<sup>#27</sup> hydrogen bonds, which together with the C2–H2···N3<sup>#27</sup> contacts give rise to molecular chains along the [010] crystallographic direction with the cyclic hydrazone–pyridine  $R_2^1(6)$  homosynthon **B** (Scheme 3, Figure 6a). The interaction energy of



**Figure 5.** Part of the crystal structure of **2** showing (a) formation of [210] molecular ribbon via strong N–H···O hydrogen bonds (the total energy of the dimer =  $-65.5 \text{ kJ}\cdot\text{mol}^{-1}$ ) and weak H···H contacts ( $-8.8 \text{ kJ}\cdot\text{mol}^{-1}$ ), (b) crystal packing viewed along the X axis, (c) molecular dimers stabilized by C–H···O and  $\pi$ -stacking interactions, and (d) weak C–H···O/N and C–H··· $\pi$  intermolecular interactions.

Scheme 3. Supramolecular Synthons Observed in the Hydrazone Crystals





C: hydrazone-water-pyridine heterosynthon



B: hydrazone-pyridine homosynthon



D: hydrazone-water-hydrazone heterosynthon

Article



**Figure 6.** Selected parts of the crystal structure of **5** showing (a, b) hydrogen-bonding motifs (dashed lines) and (c) crystal packing viewed along the *Y* axis.

this motif is similar to that of the **B** synthon in **1** and is equal to  $-34.3 \text{ kJ}\cdot\text{mol}^{-1}$ . The assembly is reinforced by weak C13–H13…N3<sup>#27</sup> and C7–H7… $\pi_{\text{phen}}$  (-x - 1/2, y + 3/2, -z + 3/2) interactions involving pyridine and phenyl rings (Figure 6b). The most advantageous dimer, for which the interaction energy amounts to about  $-50 \text{ kJ}\cdot\text{mol}^{-1}$ , is created however with the assistance of both N4–H4B…O1<sup>#26</sup> hydrogen bond and the  $\pi$ -stacking interactions (Figure 6b). Additionally, relatively strong hydrogen bonds are formed between the head-to-head oriented molecules from the adjacent chains, that is, N4–H4A…O1<sup>#9</sup> (Figure 6a).

These interactions are characterized by an overall dimer interaction energy of  $-39.0 \text{ kJ} \cdot \text{mol}^{-1}$ . The mentioned contacts are further accompanied by weak C4–H4…O1<sup>#7</sup> and C5–H5… N4<sup>#7</sup> interactions (total energy of the corresponding dimer:  $-23 \text{ kJ} \cdot \text{mol}^{-1}$ ; Table S4, Supporting Information), which results in a 2D (101) layered network formation (Figure 6c). The molecules are arranged in such a way that the hydrophilic and hydrophobic parts are separated in the crystal lattice. The neighboring layers are held together by C–H… $\pi$  contacts ( $d_{C10\dots\pi_{cent}(C8-C13)} = 3.374(3)$  Å,  $d_{H10\dots\pi_{cent}} = 2.594$  Å,  $\theta_{C10-H10\dots\pi_{cent}} = 128^{\circ}$ ). The richness of the electrostatic interactions, reinforced by the additional NH<sub>2</sub> group in contrast to the other studied molecules, and dispersive interactions makes this crystal structure significantly more

energetically favored than the remaining anhydrous crystal structures of 1 and 2 (Table 4). This is surely due to the additional  $\pi$ -electron-rich center, the phenyl substituent, which at the same time contains an amino group eager to form hydrogen bonds.

3.3.2. Hydrazone Hydrates. The incorporation of water molecules into the crystal structure framework of the studied compounds leads to quite different supramolecular arrangements and hydrogen-bonding patterns. In general, in the structures of  $1 \cdot H_2O - 5 \cdot H_2O$ , water molecules span the adjacent units into the complex architectures. The energetic results gathered in Table 3 clearly indicate a significant increase in crystal cohesive energy per ASU when water molecules are incorporated into the crystal structure. Water molecule size and properties ensure saturation of the hydrogen bond donor and acceptor centers, as well as much more favorable hydrogen bond geometries, making the overall packing more energetically advantageous. Also, comparing the fingerprint plots generated for the water containing and anhydrous pairs of crystals, one may notice that average interatomic contacts are becoming shorter in the case of hydrated structures. This means that the structure is more efficiently packed.

In the  $1 \cdot H_2O$  crystal structure, the two adjacent inversionrelated host units are connected by two water molecules, acting as hydrogen-bonding acceptors for hydrazone N1 and C2 centers and as donors to pyridine N3 atoms (Figure 7a). As a



Figure 7. (a) Hydrogen-bonding pattern in crystal of  $1 \cdot H_2O$ ; (b) single ( $\overline{1}12$ ) sheet motifs viewed along the Z axis; (c) weak C-H···O/N and  $\pi \cdot \cdot \pi$  interlayer interactions; (d) crystal packing viewed along the  $[1\overline{1}1]$  direction.

result, a cyclic hydrazone-water-pyridine heterosynthon C (Scheme 3) is formed. The water-hydrazone interactions related to this motif are characterized by interaction energy close to -27.2 kJ·mol<sup>-1</sup> for the first kind of interactions, whereas for the water-pyridine hydrogen bond, this is -20.1 kJ·mol<sup>-1</sup> (Table 4, Table S4, Supporting Information). The overall stabilization energy of this molecular arrangement reaches  $-128.1 \text{ kJ} \cdot \text{mol}^{-1}$  (i.e.,  $-64.0 \text{ kJ} \cdot \text{mol}^{-1}$  per each hydrazone-water pair). These units are then linked by a combination of weak C4-H4…O1<sup>#7</sup> (corresponding dimer interaction energy -23.9 kJ·mol<sup>-1</sup>) and C5-H5…O1<sup>#8</sup> (-8.7 kJ·mol<sup>-1</sup>) interactions, which, in turn, lead to the centrosymmetric hydrazone tetramers (Figure 7b). The tetramers associate further into the  $(\overline{1}12)$  molecular sheets via the C6-H6…O1W<sup>#8</sup> ( $-7.9 \text{ kJ} \cdot \text{mol}^{-1}$ ) interactions. The layers are stabilized by strong water-carbonyl O1W-H1W-01#5 and weak formyl-pyridyl C1-H1...N3<sup>#6</sup> (Figure 7c) hydrogen bonds (corresponding dimer interaction energies -20.5 and -13.8 kJ·mol<sup>-1</sup>, respectively). Water molecules appear in the crystal structure so as to fasten together hydrazone species, leading to a complex 3D network (Figure 7d). It is also worth mentioning that  $\pi$ -stacking interactions cannot be neglected in the case of  $1 \cdot H_2O$  since, as in the anhydrous structures, they contribute noticeably to the overall cohesive energy (e.g., -27.5kJ·mol<sup>-1</sup> for the -x + 1, -y + 1, -z + 1 dimer, Figure 7c).

Despite the differences in molecular compositions and internal symmetries of the studied crystals, the supramolecular patterns in  $3 \cdot H_2O - 5 \cdot H_2O$  are very similar. While the isostructural hydrates 3·H2O and 4·H2O crystallize in the orthorhombic *Pbca* space group, the 2-aminophenyl  $(5 \cdot H_2 O)$ derivative adopts monoclinic  $P2_1/c$  symmetry. However, similarly to  $1 \cdot H_2O$ , in all the remaining crystal structures, water species fill in the gaps between the adjacent inversionrelated hydrazone molecules and serve as hydrogen-bonding supramolecular mediators. In general, the hydrazone-water interaction energy is in the range from -20 to -30 kJ·mol<sup>-1</sup> (Table 4). Within the selected asymmetric units, the two independent molecular components are linked by short, almost linear N1-H1N…O1W hydrogen bonds, enhanced by two weak C2-H2···O1W and C13-H13···O1W contacts (Figure 8a, Table 4). These bimolecular units are further connected via strong bifurcated O1W-H1W...(O1,N2)<sup>#13/16/28</sup> hydrogen bonds (heterosynthon D) and weak C4–H4…O1W  $^{\#14/18/30}$ contacts into molecular chains, propagating along the [010] (3.  $H_2O_1$ ,  $4 \cdot H_2O$ ) or [001] ( $5 \cdot H_2O$ ) crystallographic directions (Figure 8b). At the same time, each water molecule is engaged in an additional strong O-H...N hydrogen bond to the pyridine N3<sup>#12/15/7</sup> atom from the adjacent inversion-related molecule leading to a cyclic hydrazone-water-pyridine heterosynthon C. The combination of both chain and ring motifs is sufficient to create a 2D layered architecture. Interlayer stabilization is provided by  $C_{Ar}$ -H··· $\pi_{Ar}$  contacts  $(3 \cdot H_2O)$  or C11-H11...Cl1<sup>#1</sup>  $(4 \cdot H_2O)$ , -5.5 kJ·mol<sup>-1</sup>, Figures





**Figure 8.** (a) Hydrogen-bonding pattern in a crystal of  $4 \cdot H_2O$ ; (b) [010] molecular chains in view along the X axis; (c) short  $Cl \cdots \pi$  contacts in  $4 \cdot H_2O$ ; (d) crystal packing in view along the Y axis. The supramolecular arrangements of  $3 \cdot H_2O$  and  $5 \cdot H_2O$  are very similar.

8b,d) and N4–H4B…N4<sup>#32</sup> ( $5 \cdot H_2O$ ,-15.6 kJ·mol<sup>-1</sup>) hydrogen bonds.

It is noteworthy that the Cl atoms in crystal 4·H<sub>2</sub>O are additionally engaged in short Cl1…C11<sup>#14</sup> contacts (Figure 8c). Given the geometry of these contacts ( $d_{Cl1...C11} = 3.415(2)$  Å,  $\theta_{C9-Cl1...C11} = 155^{\circ}$ ; -5.9 kJ·mol<sup>-1</sup>), they can be classified as "edge-on" Cl… $\pi$  interactions.<sup>45</sup>

In turn, incorporation of one additional water molecule, as in the lattice network of 4.2H2O, induces considerable changes in the lattice symmetry and the supramolecular pattern compared with the orthorhombic monohydrate structure,  $4 \cdot H_2O$ . Interestingly, the dihydrate of 4 crystallizes in the trigonal  $R\overline{3}$ space group, with a stoichiometric content of water molecules occupying general positions. As indicated by Figure 9b,e, the crystal structure is characterized by two types of channels along the Z axis, the primary hydrophilic and secondary hydrophobic ones in the ratio of 2:1, respectively. In general, the structure of 4.2H<sub>2</sub>O is governed by an extensive net of strong interactions around the well-ordered guest water molecules, filling the hydrophilic 1D channels (water constitutes over 50% of the volume of free space  $(V_v)$  in the "anhydrous" 4.2H<sub>2</sub>O crystal structure, Figure 9e), and consequently a second type of channel with chlorophenyl ring walls is formed. The hydrogenbonded water polymeric structure created around the 31 axis is characterized by about  $-65.8 \text{ kJ} \cdot \text{mol}^{-1}$  of stabilization energy (per two symmetry-independent water molecules). This energy value is equivalent to one strong hydrogen bond per water molecule in such a water chain. The 1D water substructure is created via O1W-H2W…O2W and then O2W-H4W…  $\text{O1W}^{\#20}$  directional hydrogen bonds. Clearly, the hydrogen

bonding potential of a single water molecule is greater than that, just to mention our latest studies of water clusters in the ortho-boronic acid solvatomorphs and ice crystals.<sup>46</sup> Therefore, water should strongly interact with the neighboring hydrazone molecules so as to saturate their remaining hydrogen bond centers. Indeed, it seems that water chains constitute a kind of "template" around which the hydrazone molecules are arranged spirally. As mentioned above, one hydrogen atom of each water molecule is involved in hydrogen bonding with the oxygen atom of an adjacent symmetry-independent water molecule, while its own oxygen atom is simultaneously hydrogen bonded to another molecule of water to complete the motif (Figure 9a). At the same time, the second hydrogen atom of O1W donates to pyridyl N3 from the host molecule whereas the oxygen atom serves as an acceptor in the three-center N1-H1N/C2-H2...  $\text{O1W}^{\#20}$  hydrogen bond. Then, each O2W water molecule participates as a donor in the strong O2W-H3…O1#21 hydrogen bond with the host unit.

On the other hand, two different trigonal motifs (TA and TB motifs; Figure 9c,d) created by host molecules can be distinguished in the structure. The overall arrangement of the motifs down the 3-fold screw axis is …TATBTATB…. Regarding the interactions between the host hydrazone molecules, the C5–H5…O1<sup>#22</sup> contact (-14.2 kJ·mol<sup>-1</sup>; Figure 9d) between the adjacent molecules forming the spiral TB motif seems to be noticeable, as well as relatively strong C6–H6…Cl1<sup>#24</sup> and  $\pi \dots \pi$  stacking interactions between the overlapping pyridyl–pyridyl (-32.6 kJ·mol<sup>-1</sup>, Figure 9a) and pyridyl–phenyl rings (-20.5 kJ·mol<sup>-1</sup>), which hold the molecules from TA and TB motifs together.



Figure 9. (a) Hydrogen-bonding patterns in a crystal of  $4 \cdot 2H_2O$ . (b) Crystal packing viewed along the Z axis. Two spiral host motifs viewed along the Z axis, formed around the guest hydrogen-bonded chains: (c) motif TA; (d) motif TB. (e) Voids in real (left) and artificial "anhydrous" (right) structures of  $4 \cdot 2H_2O$  (viewed along the Z axis).<sup>47</sup>

**3.4. NMR Studies.** The <sup>13</sup>C CP/MAS NMR spectra of the studied crystalline *N*-acylhydrazone derivatives are shown in Figure 10, whereas Table S5 (Supporting Information) presents <sup>13</sup>C NMR chemical shifts of these compounds. The <sup>13</sup>C CP/MAS NMR experimental shifts are in good agreement with the CASTEP calculated isotropic shielding (Supporting Information). The number of signals in the <sup>13</sup>C CP/MAS NMR spectra

of  $1 \cdot H_2O$ , 2,  $4 \cdot 2H_2O$ , and 5 is in agreement with the number of carbon atoms in the molecules, in contrast to the spectra of 1,  $3 \cdot H_2O$ , and  $5 \cdot H_2O$ . In the case of 1 an additional signal at 156.84 ppm can be observed. This signal comes from the carbonyl group and proves that compound 1 was contaminated by formic hydrazide. All attempts to purify 1 led to the formation of the crystal structure of  $1 \cdot H_2O$ . In the cases of 3.





 $H_2O$  and  $5 \cdot H_2O$ , the partial overlap of the signals hampers their correct assignment. In the spectra of the studied hydrazones, there is no signal splitting because each crystal form contains a single molecule in the asymmetric part of the unit cell.

Furthermore, in the NMR spectra of most NAHs, no significant differences in the chemical shifts of the individual carbon atoms are observed. Only in the case of compound 2, the signal of carbon atom C1 is shifted toward higher-frequency ( $\Delta \delta = 8-12.23$  ppm). This effect results from the crystal packing of 2 (Figure 5), mainly determined by the strong N–H…O hydrogen-bonding leading to the cyclic amide–amide homosynthon **A**.

In turn, the <sup>15</sup>N CP/MAS NMR spectra were used to characterize substituent effects and hydrogen bonds in the studied derivatives. The <sup>15</sup>N chemical shifts are given in Table S6 (Supporting Information). Particular attention should be paid to differences in chemical shift values of the nitrogen atom N1. Its chemical shift in the case of 1,  $1 \cdot H_2O$ , and 2 is in all cases less than 200 ppm, whereas for  $3 \cdot H_2O$ ,  $4 \cdot 2H_2O$ , 5, and 5.  $H_2O$ , it is always above this value. This effect is caused by the substitution of carbon atom C1 with the phenyl ring. The N2 nitrogen atom in the structure 5 does not participate in the hydrogen bond formation but is involved in the  $\pi$ -stacking interactions described previously. These interactions lead to a significant difference in the observed chemical shift of N2

(approximately 13 ppm). Moreover, the chemical shifts of the N3 nitrogen atom in the structures 2 and 4.2H2O differ significantly from the ones in the remaining N-acylhydrazone derivatives. In the structure 2, the signals coming from nitrogen atoms N2 and N3 overlap and form one broadened peak at -56 ppm. In this case, the two discussed nitrogen atoms are involved in weak interactions, namely, C6-H6...N3<sup>#11</sup> and C8-H8b/c···N2. In 4·2H<sub>2</sub>O, the position of the signal of nitrogen atom N3 is shifted toward higher frequency ( $\delta = -107$ ppm). In this crystal structure, N3 is involved in a short linear hydrogen bond, O1W-H1W...N3. Moreover, due to the short distance between O1W and N3 (2.737(4) Å) and the higher thermal motion during the solid-state NMR measurements, proton transfer from the water molecule to the nitrogen atom N3 is possible. In this case, the discussed shifting of the nitrogen N3 signal would be a combination of two effects: a very strong hydrogen bond and the N3-H<sup>+</sup>...OH<sup>-</sup> interaction.

As previously shown,<sup>48,49</sup> solid-state NMR, combined with quantum mechanical computations of NMR shielding, can be successfully applied to characterize crystal structures. The solidstate NMR method is also very useful in monitoring the stability and purity of the studied compounds. Based on perfect correlation between shielding constants calculated for the XRD structure of 1 and the appropriate chemical shifts in the NMR spectra, it can be concluded that the hydrazide form is only an impurity (is not incorporated in the crystal lattice), and the discussed spectrum is a superposition of two independent components (Figure S3, Supporting Information). Moreover, the results obtained for  $4 \cdot H_2O$  and  $4 \cdot 2H_2O$  indicate that the stable compound used for NMR experiments is the latter one, because a better fit was obtained for the dihydrate structure ( $R^2$ value of 0.992 vs 0.953).

**3.5. Thermal Stability.** The thermal stabilities were assessed by both DSC and TGA. The melting point values for the studied crystals and enthalpies of fusion for anhydrous hydrazone crystals were determined from the DSC curves (Figure 11 and Figure S4, Supporting Information).

The results of TGA/DSC studies of hydrazone hydrates suggest significant differences in their behavior. The thermal desolvation of  $1 \cdot H_2O$  and  $3 \cdot H_2O$  takes place via two stages and is accompanied by two broad endotherms with the peak maxima at 92 and 110 °C ( $1 \cdot H_2O$ ) and at 95 and 111 °C ( $3 \cdot H_2O$ ). The total TGA weight loss of 10.89% ( $1 \cdot H_2O$ ) and 7.32% ( $3 \cdot H_2O$ ) is in accordance with the 1:1 host–guest ratio



Figure 11. DSC (red solid line), TG (blue solid line), and DTG (green solid line) plots showing mass loss of the studied crystals of (a) 5 and (b) 5. H<sub>2</sub>O.

as determined from the X-ray data. The weight loss of 5.52% for  $1 \cdot H_2O$  and 3.79% in the case of  $3 \cdot H_2O$ , which corresponds to the first stage of the dehydration process, may suggest formation of semihydrates as intermediate forms. The final melting of the desolvated products was observed at 132° and 124°, respectively. In contrast, the DSC thermograms of 4· $H_2O$ , 4· $2H_2O$ , and 5· $H_2O$  show single, very broad desolvation peaks starting at 49, 51 and 46 °C, respectively, overlapped by a sharp endotherm of fusion. The corresponding TGAs indicate a mass loss of 11.87% (calculated 12.17%) for 4· $2H_2O$ , 6.66% (calculated 6.48%) for 4· $H_2O$ , and 6.72% (calculated 6.97%) for 5· $H_2O$ , which confirms that they are 1:2, 1:1, and 1:1 hydrates, respectively.

The thermal behavior of the anhydrous hydrazones is quite different compared with their hydrated forms. The single sharp endothermic peaks at 122 °C (heat of fusion,  $\Delta H_{\rm f} = 107.7 \ {\rm J} \cdot {\rm g}^{-1} = 16.1 \ {\rm kJ} \cdot {\rm mol}^{-1}$ ) for the formylhydrazine derivative 1, at 123 °C ( $\Delta H_{\rm f} = 113.5 \ {\rm J} \cdot {\rm g}^{-1} = 18.5 \ {\rm kJ} \cdot {\rm mol}^{-1}$ ) for 2, and at 155 °C ( $\Delta H_{\rm f} = 93.9 \ {\rm J} \cdot {\rm g}^{-1} = 22.6 \ {\rm kJ} \cdot {\rm mol}^{-1}$ ) for 5 (Table S1, Supporting Information), corresponding to the melting points of these compounds, were observed in the DSC experiment. At the same time, no evidence indicating thermal decomposition of 1, 2, and 5 was found in their TG curves up to the melting temperature.

In general, there is a clear correlation between the enthalpy of fusion values and the melting point temperatures for anhydrous hydrazones. Interestingly, one can also find some correlation of the above-mentioned quantities with the cohesive energies described earlier (Table 3). It is, however, important to stress that generally there is no straightforward relation between cohesive energy values and the two other physical quantities, and due to the few data points, no significant conclusions can be drawn.

#### 4. SUMMARY AND CONCLUSIONS

In this contribution, we have reported a detailed structural characterization of a series of simple *N*-acyl- and *N*-aroylhydrazones, compounds that are widely used in chemical synthesis. This study constitutes the first extensive investigation of energetic features of the hydrazone crystal structures.

The studied hydrazones have been crystallized in their solvent-free forms or as hydrates or both. In general, the performed crystallization experiments confirmed the previously reported<sup>37</sup> hydrazone affinity for water and its inclusion into their crystal networks. The crystallization conditions seem to have minor influence on the phase that is formed. The water molecules incorporated into the crystal can be derived either from the crystallization solution or from the air. What is more, in some cases both solvated and solvent-free forms can be obtained simultaneously. This suggests that the crystallization outcomes are driven by specific intermolecular interactions in solution rather than the preparation regime.

The most striking conformational differences between *N*-acyl- and *N*-aroylhydrazones concern their hydrazide moiety, which adopts the *trans* and *cis* arrangement, respectively. The less stable *cis* configuration observed in the latter group seems to be imposed by intermolecular interactions involving the amide function.

In turn, a common structural feature of all studied hydrazones is the deficiency of proton-donor groups. The imbalance between the hydrogen-bond donor/acceptor atoms can be saturated via incorporation of a water molecule into the crystal, which satisfies the host's hydrogen-bond acceptor capacity without significant changes in its molecular geometry. Incorporation of water molecules to the crystals leads to visibly shorter hydrogen bonds. In each case, water molecules play the role of hydrogen-bonding linkages between the amide and pyridine N or amide O atoms. The significant contribution of water molecules to the total crystal lattice energy has been confirmed by the theoretical calculations similarly to our previous studies for hydrated boronic acid crystals.<sup>50</sup> A single water molecule incorporated into the hydrazone crystal leads to a significant cohesive energy gain of over 50 kJ $\cdot$ mol<sup>-1</sup> per ASU. Small water molecules are effectively packed in the crystal lattice and create well-directed hydrogen bonds with the host molecules, which are characterized by energy ranging from about -20 to -30 kJ·mol<sup>-1</sup>. The water-hydrazone interactions are among the strongest ones in the analyzed crystals. Apart from strong hydrogen bonding, there is an extensive net of weak C-H···O, C-H···N, and C-H··· $\pi$  interactions and  $\pi$ ··· $\pi$ stacking contacts in all studied crystals. Significant contribution of the latter ones to the total crystal lattice energy was supported by the computational results.

#### ASSOCIATED CONTENT

#### **S** Supporting Information

Theoretical calculations of NMR shielding constants in CASTEP, synthetic, physicochemical and spectral characteristics of all studied crystals, multipolar parameters of the new UBDB-like atom types utilized for TAAM refinement, relative energies between two optimized minima for isolated molecules, at two levels of theory, molecular motifs, symmetry codes and interaction energy values, <sup>13</sup>C NMR and <sup>15</sup>N chemical shifts of the studied hydrazones, torsion-angle-constrained scan for the O1-C1-C8-C9 angle in compound 5, percentage contributions of selected interatomic contacts to the Hirshfeld surfaces of hydrazone molecules, <sup>13</sup>C CP/MAS NMR spectra of the compound 1 and formic hydrazide, DSC, TG, and DTG plots for  $1 \cdot H_2O$ , 1, 2,  $3 \cdot H_2O$ ,  $4 \cdot 2H_2O$ , and  $4 \cdot H_2O$  crystals, and crystallographic information in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

#### AUTHOR INFORMATION

#### **Corresponding Author**

\*Liliana Mazur. E-mail: lmazur2@op.pl.

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#### Notes

The authors declare no competing financial interest.

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