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## Self-Organization of 2-Acylaminopyridines in the Solid State and in Solution

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Aggregation of 2-acylaminopyridines and their 6-methyl derivatives in chloroform solution was studied by  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{15}\text{N}$  NMR spectroscopies. The results were compared with  $^{13}\text{C}$  and  $^{15}\text{N}$  CPMAS NMR and IR spectral as well as with X-ray structural data. Intermolecular interactions in solution and in solid state were found to have a similar nature. Relatively strong  $\text{N}_{\text{amide}}-\text{H}\cdots\text{N}_{\text{pyridine}}$  intermolecular hydrogen bonds enable dimerization to take place. Steric interactions in *N*-pivaloyl- and *N*-1-adamantylcarbonyl as well as that caused by the 6-methyl group hinder formation of the dimeric aggregates stabilized by the  $\text{N}_{\text{amide}}-\text{H}\cdots\text{N}_{\text{pyridine}}$  intermolecular hydrogen bonds. In general, the DFT optimized geometries of the aggregates in chloroform solution are in agreement with the X-ray crystal structures. Wavenumbers of the stretching vibration band of the  $\text{C}=\text{O}$  group were also found indicative of the type of hydrogen bond present in the solid state.

## Introduction

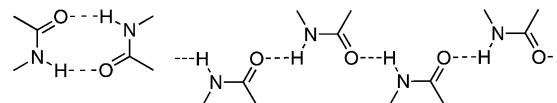
Hydrogen bonding is a reversible and directional noncovalent interaction.<sup>1</sup> Although it is much weaker than the covalent bond, large number of acidic and/or basic centers present in the molecules enables formation of the quite stable aggregates.<sup>2–5</sup> Several biologically important systems are stabilized by the multiple hydrogen bonds.<sup>2–5</sup> Multiple hydrogen bonds are an important factor that governs organization of the extended structures.<sup>6</sup> Such interactions are very important in crystal engineering, a branch of the supramolecular chemistry concerned with design and synthesis of these systems in the crystalline state.<sup>6</sup>

Secondary structure of peptides<sup>7–9</sup> is stabilized by the net of  $\text{N}-\text{H}\cdots\text{O}=\text{C}$  hydrogen bonds.<sup>10–13</sup> Amides can have the cyclic or catenary (ribbon) hydrogen bonded structures (Chart 1).<sup>14</sup> Strong hydrogen bonds in these compounds,  $\text{N}^+-\text{H}\cdots\text{O}=\text{C}$ ,  $\text{N}^+-\text{H}\cdots\text{O}=\text{C}^-$ , and  $\text{N}-\text{H}\cdots\text{O}=\text{C}^-$  are called the “salt bridges”.<sup>13</sup>

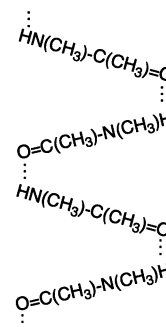
Molecules of the ordinary amides may also interact with each other in a similar way. Experimental studies show *N*-methylacetamide to be the most simple secondary amide involved in a net of the intermolecular hydrogen bonds; chains of the peptide hydrogen bonds were detected in its crystals (Chart 2).<sup>15,16</sup> Similar intermolecular interactions take place in solid benzanilide,  $\text{PhCONHPh}$ .<sup>17</sup>

Among different secondary amides, *N*-(pyridin-2-yl) derivatives seem especially interesting from a point of view of self-association. This structural fragment is present in many compounds designed to aggregate in a predictable way.<sup>18–29</sup> Although 2-(*N*-nitramino)pyridine is the tautomer of minor importance,<sup>30,31</sup> 2-acetylaminopyridine seems to be the preferred tautomeric form.<sup>32</sup> *N*-(Pyridin-2-yl) secondary amides contain one acidic (NH) and two basic (ring nitrogen and carbonyl oxygen) centers. This enables formation of the intermolecular hydrogen bonds of both  $\text{N}-\text{H}\cdots\text{N}$  and  $\text{N}-\text{H}\cdots\text{O}=\text{C}$  type.

## CHART 1: Hydrogen Bonding Patterns in Amides



## CHART 2: Chains of the Peptide Hydrogen Bonds



Such interactions are expected to be present in solid 2-acylaminopyridines and even in their solutions in solvents of moderate polarity. The influence of structural factors on the aggregation of 2-acylaminopyridines has been studied occasionally. Only the  $\text{N}_{\text{amide}}-\text{H}\cdots\text{N}_{\text{pyridine}}$  intermolecular interactions were detected by X-ray analysis to be present in solid 2-benzoylaminopyridines<sup>33</sup> and 2-(pentafluorobenzoylamino)pyridine.<sup>34</sup>

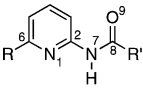
It is known from its NMR spectra that 2-cyclohexylcarbonylaminopyridine in chloroform solution at 298 K is predominantly monomeric ( $K_{\text{dimer}} = 2 \text{ M}^{-1}$ ).<sup>35</sup> On the other hand, IR spectra (Nujol mulls) show that 2-acetylaminopyridine in a condensed phase forms stable dimers by strong  $\text{N}_{\text{amide}}-\text{H}\cdots\text{N}_{\text{pyridine}}$  intermolecular hydrogen bonds.<sup>36</sup> Its 6-methyl derivative can also be dimeric: two monomeric subunits in its crystal<sup>37</sup> are surprisingly bound to each other not by the  $\text{NH}\cdots\text{N}$  but by  $\text{NH}\cdots\text{O}=\text{C}$  hydrogen bonds.<sup>38,39</sup> Although we found these results very interesting, no other compounds of this type were studied. Lacking data for the steric influence of the alkyl groups in 2-acylaminopyridines on their self-association in the solid state and in solution prompted us to prepare and

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## CHART 3: The Compounds Studied

	R/R'	No	R/R'	No
	H/Me	<b>1a</b>	Me/Me	<b>1b</b>
	H/Et	<b>2a</b>	Me/Et	<b>2b</b>
	H/ <i>i</i> -Pr	<b>3a</b>	Me/ <i>i</i> -Pr	<b>3b</b>
	H/ <i>t</i> -Bu	<b>4a</b>	Me/ <i>t</i> -Bu	<b>4b</b>
	H/1-Ad <sup>a</sup>	<b>5a</b>	Me/1-Ad <sup>a</sup>	<b>5b</b>

<sup>a</sup> 1-Adamantyl

study the respective derivatives carrying sterically varying acyl groups (Chart 3). The steric influence of the 6-methyl group in the molecules seemed also worthy to be considered. Moreover, 2-acylaminopyridines have not been earlier studied by the single crystal X-ray diffractometry.

## Experimental Methods

**X-ray Experiments.** Suitable single crystals for X-ray experiments were these synthesized (no further crystallization was necessary). Unfortunately, crystals of **5b** were of too poor quality for the data collection. The obtained single crystals were mounted on a Nylon loop sample holder with perfluoro polyether oil and data were collected at 123(2) K using Bruker-Nonius KappaCCD diffractometer with APEX-II detector and graphite monochromatized Mo K $\alpha$  ( $\lambda = 0.71073$  Å) radiation. COLLECT<sup>40</sup> software was used for the data collection ( $\theta$  and  $\omega$  scans) and DENZO-SMN<sup>41</sup> for the processing. The structures were solved by direct methods with SIR2004<sup>42</sup> and refined by full-matrix least-squares methods with WinGX-software,<sup>43</sup> which utilizes the SHELXL-97 module.<sup>44</sup> Lorentzian polarization correction was applied on all data, and absorption correction was not used. All C–H hydrogen positions were calculated and refined as the riding atom model with 1.2 and 1.5 times the thermal parameter of the C atoms, respectively. The N–H hydrogen positions were found from the electron density map and fixed (by DFIX) to a distance of 0.91 Å from N atom with the thermal parameter set to 1.2 times that of the N atom parameter. The disorder of acylamino side chain in **3b** was found from the electron density map as secondary positions for non-hydrogen atoms and refined with standard disorder refinement with two partitions (occupation factor ratio = major/minor 65:35). The disordered 6-methyl H atoms in **2b** were refined with AFIX 123 instruction, constraining each hydrogen to two positions with occupation factors of 0.5 and rotated from each other by angle of 60°. Crystal data and parameters as well as the ORTEP plots for the compounds studied can be found in the Supporting Information.

**Spectroscopy.** The <sup>13</sup>C CP/MAS NMR spectra were recorded on a Bruker Avance 400 NMR spectrometer equipped with a 4 mm standard bore CP/MAS probehead, whose X channel was tuned to 100.62 MHz for <sup>13</sup>C and 40.55 MHz for <sup>15</sup>N, respectively. The other channel was tuned to 400.13 MHz for the broad band <sup>1</sup>H decoupling. Approximately 100 mg of finely powdered sample was packed into the ZrO<sub>2</sub> rotor, which was closed with a Kel-F cap. The spinning rate was 10 kHz except in the case of **2b** where it was 9 kHz (at 10 kHz spin rate no quaternary carbons were visible). The <sup>13</sup>C CP/MAS NMR experiment for all samples was carried out under Hartmann–Hahn conditions with Spinal-64 decoupling. A 2 ms contact time was used to obtain efficient polarization transfer. A short 50  $\mu$ s contact time was used to suppress the signals of quaternary carbons and to help in spectral assignment. A number of 100–200 scans were recorded with a 4 s recycle delay for each sample. All FIDs were processed by an exponential apodization function with line broadening of 10 Hz prior to FT. Originally, the <sup>13</sup>C CP/MAS NMR spectra were referenced to the glycine

carbonyl signal at 176.03 ppm, after which the chemical shifts were recalculated to tetramethylsilane  $\delta(^{13}\text{C}) = 0.00$  ppm. The <sup>15</sup>N CP/MAS NMR experiments were carried out for all samples at a 10 kHz spinning rate (except of **2b** where it was 5 kHz) under Hartmann–Hahn condition. A contact time of 4 ms was used for efficient polarization transfer with a 5 s recycle delay to acquire the CP/MAS spectra. A number of 1000–15000 (overnight) scans were acquired to obtain the <sup>15</sup>N CP/MAS NMR spectra for each sample. All FIDs were processed by exponential apodization function with line broadening of 10 Hz prior to FT. Originally, the <sup>15</sup>N CP/MAS NMR spectra were referenced to the signal of glycine nitrogen at –345.25 ppm, after which the chemical shifts were recalculated to nitromethane  $\delta(^{15}\text{N}) = 0.0$  ppm.

Liquid state NMR acquisition and processing parameters are the same as those in our other publication.<sup>45</sup> <sup>1</sup>H NMR spectra in the dilution experiments were recorded at various concentrations of the compounds studied.  $\delta(\text{H7})$  was used as a probe. Dimerization constants were calculated according to the previously reported procedures.<sup>46</sup> IR spectra of KBr pellets of the compounds studied were recorded on a Bruker Vector 22 IR spectrophotometer.

**Calculations.** Calculations at the M05/6-31+G(d,p) level for geometry optimizations of all structures studied have been performed in Gaussian.<sup>47</sup> The PCM<sup>48</sup> model of solvation was used. The energy minimum was confirmed by the frequency calculations (all positive frequencies were obtained).

**Syntheses.** Solution of acid chloride (10.6 mmol) in dry methylene chloride (10 mL) was added dropwise to the magnetically stirred solution of 2-aminopyridine or its 6-methyl derivative (10.6 mmol) and triethylamine (10.6 mmol) in dry methylene chloride (20 mL) at 5 °C. The reaction mixture was allowed to reach room temperature and stirred for an additional 2 h. Water (20 mL) was then added, the organic layer separated and dried (Na<sub>2</sub>SO<sub>4</sub>), the solvent evaporated, and the residue recrystallized from hexane/ethyl acetate (10:1).

**1a.** Yield 1.24 g (86%). Mp 73–74 °C (lit. mp 68–68.5 °C,<sup>49</sup> 71 °C<sup>50</sup>). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 9.43 (br s, 1H, H7), 8.23–8.24 (m, 2H, H3 and H6), 7.69 (t, <sup>3</sup>J<sub>H,H</sub> = 8.5 Hz, 1H, H4), 7.02 (m, 1H, H5), 2.19 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR: 168.98 (C8), 151.84 (C2), 147.21 (C6), 138.64 (C5), 119.53 (C4), 114.46 (C3), 24.48 (CH<sub>3</sub>).

**2a.** Yield 1.43 (90%). Mp 66–67 °C (lit. mp 62 °C,<sup>51</sup> 66–67 °C<sup>52</sup>). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 8.75 (br s, 1H, H7), 8.24–8.25 (m, 2H, H3 and H6), 7.69 (t, <sup>3</sup>J<sub>H,H</sub> = 8.5 Hz, 1H, H4), 7.02 (m, 1H, H5), 2.41 (q, 2H, CH<sub>2</sub>), 1.23 (t, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR: 172.49 (C8), 151.71 (C2), 147.45 (C6), 138.44 (C5), 119.53 (C4), 114.23 (C3), 30.67 (CH<sub>2</sub>), 9.32 (CH<sub>3</sub>).

**3a.** Yield 1.45 g (83%). Mp 60–61 °C (lit. mp 51–53 °C<sup>53</sup>). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 8.53 (br s, 1H, H7), 8.24–8.25 (m, 2H, H3, and H6), 7.68 (t, <sup>3</sup>J<sub>H,H</sub> = 8.5 Hz, 1H, H4), 7.01 (m, 1H, H5), 2.54 (m, 1H, CH), 1.23 (s, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR: 175.73 (C8), 151.75 (C2), 147.54 (C6), 138.36 (C5), 119.58 (C4), 114.21 (C3), 36.57 (CH), 19.38 (CH<sub>3</sub>).

**4a.** Yield 1.68 g (89%). Mp 76–77 °C (lit. mp 71–73 °C<sup>54</sup>). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 8.22–8.24 (m, 2H, H3, and H6), 8.00 (br s, 1H, H7), 7.67 (t, <sup>3</sup>J<sub>H,H</sub> = 7.5 Hz, 1H, H4), 7.00 (m, 1H, H5), 1.34 (s, 9H, CH<sub>3</sub>). <sup>13</sup>C NMR: 176.95 (C8), 151.55 (C2), 147.63 (C6), 138.28 (C5), 119.60 (C4), 113.87 (C3), 39.72 (quaternary C), 27.42 (CH<sub>3</sub>).

**5a.** Yield 2.07 g (76%). Mp 124–125 °C (white crystals). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 8.23–8.24 (m, 2H, H3, and H6), 7.95 (br s, 1H, H7), 7.66 (t, <sup>3</sup>J<sub>H,H</sub> = 8 Hz, 1H, H4), 6.99 (m, 1H, H5), 2.08–1.70 (15H, 1-adamantyl). <sup>13</sup>C NMR: 176.42 (C8), 151.61

**TABLE 1: Selected  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{15}\text{N}$  Chemical Shifts (ppm) for 0.1–0.2 M Solutions of (6-Methyl)-2-acylaminopyridines in  $\text{CDCl}_3$  at 303 K**

compound	H7	C2	C6	C8	N1	N7
<b>1a</b>	9.43	151.84	147.21	168.98	−105.4	−238.2 <sup>a</sup>
<b>2a</b>	8.75	151.71	147.45	172.49	−103.7	−240.4
<b>3a</b>	8.53	151.75	147.54	175.73	−102.5	−242.1
<b>4a</b>	8.00	151.55	147.63	176.95	−101.4	−246.7 <sup>b</sup>
<b>5a</b>	7.95	151.62	147.69	176.42	−100.8	−247.0
<b>1b</b>	8.16	150.63	156.62	168.51	−101.7	−242.0
<b>2b</b>	7.91	150.63	156.66	172.16	−103.4	−240.2
<b>3b</b>	7.94	150.75	156.61	175.43	−102.6	−242.1
<b>4b</b>	7.91	150.90	156.63	176.92	−102.2	−246.5
<b>5b</b>	7.88	150.93	156.63	176.39	−102.3	−246.9

<sup>a</sup>  $^1J_{\text{N,H}} = 89$  Hz. <sup>b</sup>  $^1J_{\text{N,H}} = 88$  Hz.

**TABLE 2: Dimerization Constants for (6-Methyl)-2-acylaminopyridines (solutions in  $\text{CDCl}_3$ )**

compound	$K_{\text{dimer}}$
<b>1a</b>	13.0
<b>2a</b>	17.0
<b>3a</b>	4.5
<b>1b</b>	2.5
<b>2b</b>	1.5

(C2), 147.69 (C6), 138.20 (C5), 119.53 (C4), 113.95 (C3), adamantyl 41.62, 39.10, 36.37, 28.06. Anal. Calcd: C, 74.97; H, 7.86; N, 10.93. Found: C, 74.90; H, 7.83; N, 10.90.

**1b.** Yield 1.42 g (89%). Mp 91–92 °C (lit. mp 85–88 °C<sup>55</sup>).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 8.16 (br s, 1H, H7), 7.97 (d,  $^3J_{\text{H,H}} = 8$  Hz, 1H, H3), 7.57 (t,  $^3J_{\text{H,H}} = 8$  Hz, 1H, H4), 6.87 (d,  $^3J_{\text{H,H}} = 7.5$  Hz, 1H, H5), 2.43 (s, 3H, 6-CH<sub>3</sub>), 2.16 (s, 3H, CH<sub>3</sub>).  $^{13}\text{C}$  NMR: 168.51 (C8), 156.62 (C6), 150.63 (C2), 138.66 (C5), 119.13 (C4), 110.78 (C3), 23.89 (6-CH<sub>3</sub>), 24.58 (CH<sub>3</sub>).

**2b.** Yield 1.33 g (76%). Mp 34–35 °C (yellow crystals).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 7.91 (br s, 1H, H7), 8.00 (d,  $^3J_{\text{H,H}} = 8$  Hz, 1H, H3), 7.57 (t,  $^3J_{\text{H,H}} = 8$  Hz, 1H, H4), 6.87 (d,  $^3J_{\text{H,H}} = 7.5$  Hz, 1H, H5), 2.43 (s, 3H, 6-CH<sub>3</sub>), 2.39 (q, 2H, CH<sub>2</sub>), 1.23 (t, 3H, CH<sub>3</sub>).  $^{13}\text{C}$  NMR: 172.16 (C8), 156.66 (C6), 150.63 (C2), 138.61 (C5), 119.03 (C4), 110.66 (C3), 23.93 (6-CH<sub>3</sub>), 30.76 (CH<sub>2</sub>), 9.35 (CH<sub>3</sub>). Anal. Calcd: C, 65.81; H, 7.37; N, 17.06. Found: C, 65.73; H, 7.33; N, 17.01.

**3b.** Yield 1.61 g (85%). Mp 79–80 °C (pale yellow crystals).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 8.00 (d,  $^3J_{\text{H,H}} = 8.5$  Hz, 1H, H3), 7.94 (br

s, 1H, H7), 7.56 (t,  $^3J_{\text{H,H}} = 8$  Hz, 1H, H4), 6.86 (d,  $^3J_{\text{H,H}} = 7.5$  Hz, 1H, H5), 2.50 (m, 1H, CH), 2.42 (s, 3H, 6-CH<sub>3</sub>), 1.23 and 1.24 (s, 3H + 3H, two nonequivalent CH<sub>3</sub> groups).  $^{13}\text{C}$  NMR: 175.43 (C8), 156.61 (C6), 150.75 (C2), 138.58 (C5), 119.02 (C4), 110.72 (C3), 36.72 (CH), 23.90 (6-CH<sub>3</sub>), 19.37 (CH<sub>3</sub>). Anal. Calcd: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.34; H, 7.87; N, 15.70.

**4b.** Yield 1.78 g (87%). Mp 68–69 °C (lit. mp 66–68 °C<sup>54</sup>).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 8.03 (d,  $^3J_{\text{H,H}} = 8$  Hz, 1H, H3), 7.91 (br s, 1H, H7), 7.56 (t,  $^3J_{\text{H,H}} = 7.5$  Hz, 1H, H4), 6.86 (d,  $^3J_{\text{H,H}} = 7.5$  Hz, 1H, H5), 2.43 (s, 3H, 6-CH<sub>3</sub>), 1.31 (s, 9H, CH<sub>3</sub>).  $^{13}\text{C}$  NMR: 176.92 (C8), 156.63 (C6), 150.90 (C2), 138.56 (C5), 119.05 (C4), 110.63 (C3), 39.74 (quaternary C), 27.48 (CH<sub>3</sub>), 23.93 (6-CH<sub>3</sub>).

**5b.** Yield 2.36 g (82%). Mp 127–128 °C (pale yellow crystals).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 8.04 (d,  $^3J_{\text{H,H}} = 8$  Hz, 1H, H3), 7.88 (br s, 1H, H7), 7.55 (t,  $^3J_{\text{H,H}} = 8$  Hz, 1H, H4), 6.85 (d,  $^3J_{\text{H,H}} = 7.5$  Hz, 1H, H5), 2.09–1.71 (15H, 1-adamantyl).  $^{13}\text{C}$  NMR: 176.39 (C8), 156.63 (C6), 150.93 (C2), 138.50 (C5), 118.97 (C4), 110.72 (C3), 1-adamantyl 41.63, 39.12, 36.40, 28.10, 23.96 (6-CH<sub>3</sub>). Anal. Calcd: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.47; H, 8.16, N, 10.32.

## Results and Discussion

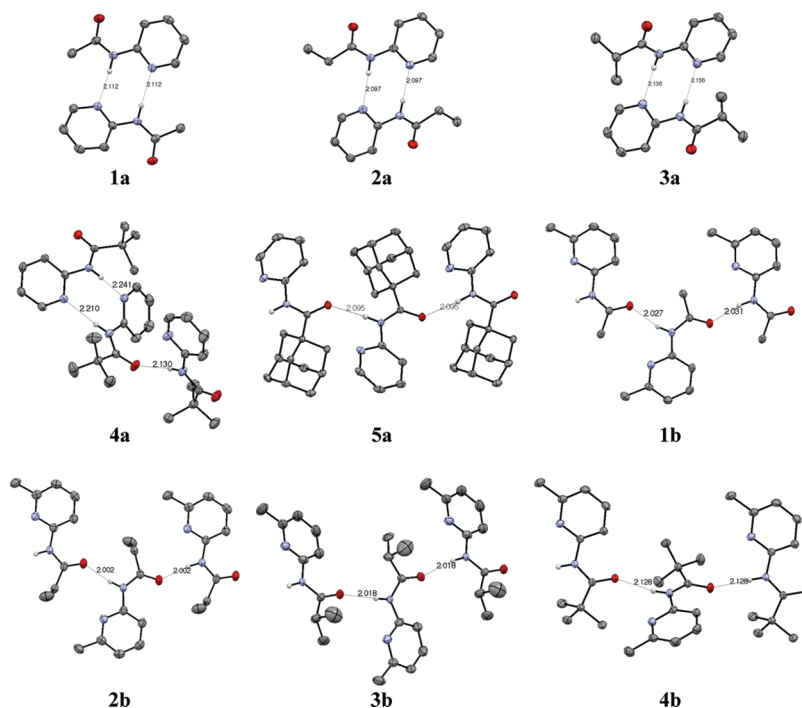
NMR spectral data seemed very promising when used in evaluation of the association susceptibility of the compounds studied both in solution and in solid state. The  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{15}\text{N}$  chemical shifts in chloroform solutions are collected in Table 1 as well as in Experimental Methods and in Supporting Information.

Analysis of the chemical shifts shows that H7 is most and least shielded in **5** and in **1**, respectively, both in series **a** and **b**. This proves that H7 is the most deshielded in **1a**. There is a significant difference in the chemical shifts of H7 in **1a** and other compounds within the series. Although the changes of  $\delta\text{H7}$  show the same tendency in series **b**, the respective differences are less distinct. The presence of the 6-methyl group was found to have a vanishing effect on sequence of changes in  $\delta\text{C8}$  ( $\delta\text{C8}$ : **4** > **5** > **3** > **2** > **1**). It is similar for  $\delta\text{N1}$  in series **a** ( $\delta\text{N1}$ : **5** > **4** > **3** > **2** > **1**). Thus, N1 is the most and least basic in **1a** and **5a**, respectively. On the other hand, N1 is more deshielded in compounds of series **b**, which shows that basicity

**TABLE 3: Solid State  $^{13}\text{C}$  and  $^{15}\text{N}$  CPMAS Chemical Shifts (ppm) for (6-Methyl)-2-acylaminopyridines at 298 K**

compound	C2	C3	C4	C5	C6	C8	N1	N7
<b>1a</b> <sup>a</sup>	152.78	114.07	118.85	139.05	147.15 149.89	168.75	−107.0	−235.5
<b>2a</b>	152.74	114.82	117.56	138.89	147.78	172.91	−108.0	−237.4
<b>3a</b>	152.40	114.64	120.79	141.04	147.43	177.23	−103.1	−238.2
<b>4a</b>	152.24 153.64	113.34 116.17	118.91 119.68 120.79 121.57	137.76 139.88	147.84 149.06	176.97 177.80 179.00	−100.4 −94.0 −90.7	−244.0 −242.1
<b>5a</b>	152.21	114.6	121.80	136.80	147.06	178.00	−90.6	−242.1
<b>1b</b>	150.93	109.39 108.37	117.10	137.78 137.18	156.47	171.47	−91.2	−232.2
<b>2b</b>	151.51	108.78	117.61	137.40	156.04	175.67	−93.8	−235.4
<b>3b</b>	151.20 150.83	111.27	118.84	136.27	156.61	178.14 177.73	−86.3	−234.4
<b>4b</b>	151.80	110.17	118.24	136.70	157.42	178.47	−87.9 −95.0	−243.3
<b>5b</b>	151.18	110.39	117.71	136.98	156.18	176.67	−88.9	−242.8

<sup>a</sup> Two signals at 23.92 and 23.01 ppm suggest that two conformationally different molecules are present in the unsymmetric unit. Other substituent chemical shifts are available in the Supporting Information.

**CHART 4: ORTEP Diagrams<sup>56</sup> of Different Self-Associations in Some (6-Methyl)-2-acylaminopyridines (thermal ellipsoids drawn at 50% probability level)<sup>a</sup>**<sup>a</sup> Most hydrogen atoms were omitted for clarity.**TABLE 4: Selected X-ray Determined (first row) and Optimized<sup>a</sup> (second row) Interatomic Distances (Å) as Well as Valence and Dihedral Angles (deg) in 1a–4a<sup>b,c</sup>**

	1a		2a		3a		4a	
H7...N1'	2.11		2.10		2.14		2.21, 2.24	
N7...N1'	2.99	2.07	3.00	2.08	3.02	2.09	3.06, 3.08	2.17
N1...N1'	3.61	3.09	3.60	3.10	3.60	3.11	3.37	3.16
N7...N7'	3.85	3.60	3.62	3.62	3.48	3.59	3.75	3.41
N1C2N7	113.4	3.78	113.3	3.79	112.9	3.72	113.0, 114.1	3.72
C2N7C8	127.1	113.6	127.5	113.7	128.3	113.8	126.8, 124.4	114.04
N7C8O9	123.9	128.6	123.7	128.7	123.3	128.3	122.3, 121.8	127.2
N1C2N7C8	163.7	123.8	162.6	123.6	166.6	123.4	156.1, 139.2	122.2
C2N7C8O9	0.0	166.8	4.29	167.9	1.9	160.0	0.1, 4.3	153.3
C2N7N1'C2'	25.2, 24.3	−0.1	55.7	0.9	67.2	4.1	62.7, 69.6	1.4
C8N7N1'C6'	28.7, 37.4	55.2	42.5	54.1	43.8	61.7	63.5, 74.1	76.5
		39.6		38.7		50.1		68.0

<sup>a</sup> M05/6-31+G(d,p), solution in chloroform, PCM. <sup>b</sup> Unprimed and primed atoms are these in two different interacting molecules. <sup>c</sup> Double experimental parameters show that some dimers are not symmetric.

of this atom in 6-methyl-2-acylaminopyridines is of quite different character. The sequence of changes in  $\delta N7$  is also almost independent of 6-methyl group ( $\delta N7$ : **1** > **2** > **3** > **4** > **5**).

The <sup>1</sup>H NMR dilution experiments (see Experimental Methods) have been performed to calculate dimerization constants for the compounds studied. The extremely insignificant effect of the dilution precludes evaluation of self-association for some of them. The data presented in Table 2 show that although susceptibility of **1a** to dimerize is relatively high,  $K_{\text{dimer}}$  is the

**TABLE 5: Selected X-ray Determined Interatomic Distances (Å) and Valence Angles (deg) in 4a, 5a, and 1b–4b**

parameter	4a	5a	1b <sup>a</sup>	2b <sup>a</sup>	3b	4b
H7...O9'	2.13	2.10	2.03	2.00	2.02	2.13
O9...N7'	3.01	2.99	2.90, 2.91	2.90	2.87	2.99
C8O9N7'	130.8	137.2	134.7, 134.4	139.1, 138.8	160.4	85.3

<sup>a</sup> Double experimental parameters show that there are two different intermolecular interactions in the asymmetric unit.



**TABLE 6: Selected X-ray Dihedral Angles between the O9C8N7 and O9'C8'N7' Planes (DH1) and between Planes of the Pyridine Rings (DH2) (deg) as Well as Distances (*d*) between Centroids of the Pyridine Rings (Å) in Aggregates of 1a–5a and 1b–4b<sup>a</sup>**

parameter	1a	2a	3a	4a	5a	1b	2b <sup>b</sup>	3b	4b
DH1	49.0	72.1	84.3	86.3					
				66.9	63.1	34.0	10.1, 1.3	38.4	74.1
DH2	35.1	43.3	60.0	75.6					
				79.3	51.6	32.6	4.7, 1.2	21.6	62.9
D	6.06	6.13	6.13	5.52					
				6.77	7.80	8.65	8.84, 8.83	8.33	7.68

<sup>a</sup> First and second rows refer to the N<sub>amide</sub>–H···N<sub>pyridine</sub> and N<sub>amide</sub>–H···O=C hydrogen bonded aggregates, respectively. <sup>b</sup> Double experimental parameters show that there are two different interactions of the hydrogen bond character in the asymmetric unit.

highest for the ethyl derivative **2a** (dimerization constants determined for **1a** and **2a** are comparable with that observed earlier for 2-cyclohexylaminopyridine in chloroform solution).<sup>35</sup> As this can be also seen, the respective compounds in series **b** are less susceptible to dimerization. The steric effect of the 6-methyl group is probably responsible for this behavior.

Separate NMR signals are often observed in the CPMAS spectrum of the solid sample that contains different crystal forms (polymorphs), which are averaged in the liquid sample. <sup>13</sup>C and <sup>15</sup>N NMR CPMAS spectral data (Table 3) **1a,b–5a,b** are comparable with those of their chloroform solution (Table 1). This gives extra evidence that similar self-aggregation takes place both in solution and in crystalline state. Since values of  $\delta(\text{N1})$  for **1a** and **5a** are significantly different, one can suppose that the hydrogen bonding network in their crystals is also different. X-ray data show this to be the case.

To get a reliable insight into crystal structure of the aggregates, single crystal X-ray diffraction studies were performed (except for **5b**). Their crystal parameters are presented in Supporting Information. Different intermolecular hydrogen bonding interactions between the molecules of **1a–5a** and **1b–4b** (Chart 4) are responsible for formation of the aggregates. One can see there that the type of intermolecular interactions depends on steric effect of the alkyl group attached to C8 and that of 6-methyl. The N<sub>amide</sub>–H···N<sub>pyridine</sub> hydrogen bonds stabilize dimers in crystals of **1a–3a**. Both N<sub>amide</sub>–H···N<sub>pyridine</sub> and N<sub>amide</sub>–H···O=C interactions are present in the crystal of **4a**. Only the later type of hydrogen bond was detected for **5a**. Similar intermolecular hydrogen bonds are also preferred in crystals of 6-methyl derivatives **1b–4b**. It is noteworthy that among the compounds presented in Chart 4 only **1a–3a** form typical dimers in the solid state.

Some important X-ray geometrical parameters of the aggregates stabilized by the NH···N hydrogen bonds are presented in Table 4. It is noteworthy that experimental geometries (see, e.g., C8N7N1'C6' dihedral angles, H7···N1' lengths of hydrogen bonds and N1···N1' interatomic distances) of the species present in crystal are very much comparable with these optimized (Table 4). This coincidence also shows that self-aggregation of the compounds studied is influenced by steric interactions. Double experimental parameters in Table 4 show that some aggregates are not symmetric (two slightly different molecules are present in the asymmetric unit). One can see that monomeric units in the dimers are not coplanar and that intermolecular hydrogen bonds present there are relatively strong.

Important X-ray geometrical parameters of the aggregates stabilized by the NH···O hydrogen bonds are presented in Table 5. One can see that these interactions are also relatively strong. It seems noteworthy that the 6-methyl group precludes formation of the dimer of **1b**. Its steric effect is comparable with that of bulky 1-adamantyl group in **5a**.

**TABLE 7: C=O Stretching Vibrations in the IR Spectra (KBr pellets) of 1a,b–5a,b**

compound	$\nu_{\text{C=O}}$ (cm <sup>−1</sup> )
<b>1a</b>	1697, 1690
<b>2a</b>	1690
<b>3a</b>	1693
<b>4a</b>	1684, 1676
<b>5a</b>	1666
<b>1b</b>	1661
<b>2b</b>	<sup>a</sup>
<b>3b</b>	1666
<b>4b</b>	1667
<b>5b</b>	1658

<sup>a</sup> A broad band at 1683 cm<sup>−1</sup> was observed. The compound is highly hygroscopic.

Dihedral angles between the O9C8N7 and O9'C8'N7' planes and between centroids of the pyridine rings in the aggregate are shown in Table 6. These data show that bulky R' groups are responsible for twisting of the subunits in the aggregate with respect to each other. This, in turn, results in shortening of the distance between the pyridine rings in the **1b,3b**, and **4b** associates stabilized by the N<sub>amide</sub>–H···O=C hydrogen bonds. As this can be seen in Table 6, **2b** does not follow the observed changes in geometrical parameters. This behavior results probably in its unusual properties such as exceptionally low melting point (see Experimental Methods) and hydroscopicity.

C=O stretching vibrations can also show the type of molecular aggregation for the compounds studied. Positions of the amide I band collected in Table 7 prove that arrangement of the molecules in the solid state depends on the substituent(s). Two bands in the IR spectra of **1a** and **4a** show their aggregates to be unsymmetric. In solid state compounds **1a–3a** form dimers stabilized by NH···N hydrogen bonds. Observed stretching vibration shows that C=O groups in their molecules are not involved in similar interactions. Two C=O stretching bands seen in the spectrum of **4a** show its solid-state aggregate to have two different carbonyl groups but only one of them is involved in the intermolecular N<sub>amide</sub>–H···O=C hydrogen bond (Chart 4). Red shift of the C=O vibration band in the spectra of compounds **5a**, **1b**, **3b–5b** confirms their molecules to participate in formation of a network of NH···O hydrogen bonds. X-ray geometrical parameters prove that N<sub>amide</sub>–H···O=C interactions are the only hydrogen bonds used by the molecules of these compounds to attract each other (Chart 4).

## Conclusions

The presence of acidic and basic centers in the molecules of 2-acylaminopyridines forces them to form aggregates. Liquid state <sup>1</sup>H, <sup>13</sup>C, and <sup>15</sup>N NMR and solid state <sup>13</sup>C and <sup>15</sup>N NMR CPMAS as well as IR spectral and X-ray data prove the

comparable intermolecular interactions to take place both in their chloroform solution and in the solid state. Unless R is not too bulky, relatively strong  $N_{\text{amide}}\cdots H\cdots N_{\text{pyridine}}$  intermolecular hydrogen bonds enable dimerization to take place. Steric interactions in *N*-pivaloyl- and *N*-1-adamantylcarbonyl derivatives preclude formation of the dimers. Instead, aggregates formed in such a case are stabilized by both the  $N_{\text{amide}}\cdots H\cdots N_{\text{pyridine}}$  and  $N_{\text{amide}}\cdots H\cdots O=C$ , e.g., for  $R = t\text{-Bu}$ , or exclusively by  $N_{\text{amide}}\cdots H\cdots O=C$  intermolecular hydrogen bonds, e.g., for  $R = 1\text{-Ad}$ . Effectiveness of dimerization in solution is lowered by steric effect of the 6-methyl group. Moreover, aggregates of 6-methyl-2-acylaminopyridines are not dimers.

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**Supporting Information Available:** NMR spectra, dilution experiment curves, IR spectra, X-ray data, and geometries of the optimized structures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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