JOC Note
pubs.acs.org/joc

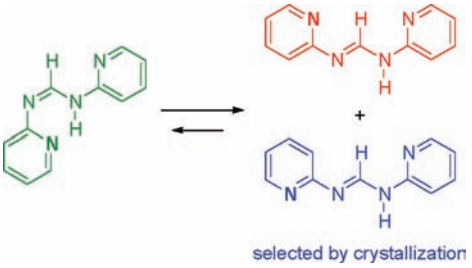
Stereochemical and Conformational Exchanges in *N*,*N*′-Di(2-pyridyl)formamidines: An X-ray and ^{1}H NMR Study

Liyan Xing, Charline Wiegert, and Anne Petitjean*

Department of Chemistry, Queen's University, 90 Bader Lane, Kingston ON K7L3N6, Canada

anne.petitjean@chem.queensu.ca

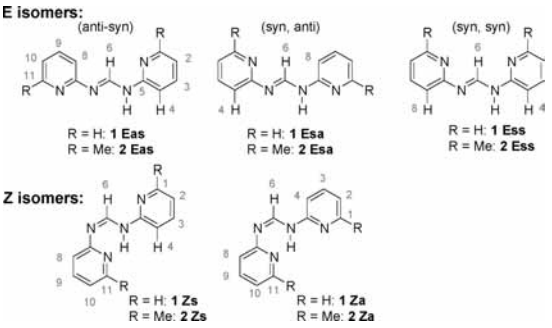
Received September 22, 2009



The solid state structure of *N*,*N*′-di(2-pyridyl)formamidine displays a four-hydrogen-bonded dimer. In solution, two isomers are observed, one of which is selected and amplified either by crystallization or by adding protons. Solution state analysis of *N*,*N*′-di(2-pyridyl)formamidines reveals the presence of the uncommon *Z* formamidine isomer, which equilibrates with the *E*-isomer with an activation energy of 90 kJ mol^{-1} in $CDCl_3$.

N-containing heterocycles (e.g., pyridines, pyrimidines, pyridazine)[1] and derivatives (e.g., hydrazones[2]) have received much attention as building blocks for well-defined secondary structures of artificial sequences (e.g., foldamers[1d,3] and macrocycle precursors[3]). Most of the rationale behind their use comes from their close resemblance to the 2,2′-dipyridyl motif, which prefers a transoid conformation.[4] Amidines are also nitrogen-containing functions that have been recently elegantly used to control the self-assembly of complex architectures.[5] Combining both pyridine heterocycles and an amidine function, we report herein the first crystal structure of *N*,*N*′-di(2-pyridyl)formamidine (**1**) and, for the first time, a detailed ^{1}H NMR solution study of **1** and of *N*,*N*′-di(6-methyl-2-pyridyl)formamidine (**2**). In addition, isomer distribution and amplification are reported in the solid and solution states.

SCHEME 1. Isomers and Conformers Relative to This Study



The stereochemistry of coordination complexes based on pyridine-containing formamidines has been the subject of many studies;[6] yet, to our knowledge, no crystal structure of free **1** has been reported. Similarly, the solution behavior of free **1** has never been thoroughly investigated. Structurally speaking, **1** is a very rich substrate; many of its geometrical isomers (cis and trans CN double bond) and rotational isomers (pyridine N syn or anti to the formamidine hydrogen) and tautomers (location of the C=N bond) may be selected via coordination chemistry.[6] The conformational preference of the 2-pyridylformamidine fragment is also of importance for the synthesis of larger systems. While investigating formamidine-based polymers, Böhme et al. realized that 2,6-diaminopyridine condenses with triethylorthoformate to form cyclic formamidine trimers as predominant products.[7] Those were rationalized through weak interactions, where the basic pyridyl nitrogen may hydrogen bond with the formamidine hydrogen (**1 Ess** state; see Scheme 1 for nomenclature). Furthermore, interesting tautomeric equilibria take place within the trimeric macrocycle.[7] Cuccia et al. have then extended the concept of hydrogen bond directed synthesis of macrocycles to naphthyridine-based trimers of a very similar nature, based on the rationale of a major **1 Ess** species.[8]

(1) (a) Hanan, G.; Lehn, J.-M.; Kyritsakas, N.; Fischer, J. *J. Chem. Soc. Chem. Commun.* **1995**, 757–766. (b) Ohkita, M.; Lehn, J.-M.; Baum, G.; Fenske, D. *Chem.—Eur. J.* **1999**, *5*, 3471–3481. (c) Cuccia, L. A.; Lehn, J.-M.; Homo, J.-C.; Schmutz, M. *Chem.—Eur. J.* **2002**, *8*, 3448–3457. (d) Petitjean, A.; Cuccia, L. A.; Schmutz, M.; Lehn, J.-M. *J. Org. Chem.* **2008**, *73*, 2481–2495.

(2) (a) Gardinier, K. M.; Khoury, R. G.; Lehn, J.-M. *Chem.—Eur. J.* **2000**, *6*, 4124–4131. (b) Schmitt, J.-L.; Stadler, A.-M.; Kyritsakas, N.; Lehn, J.-M. *Helv. Chim. Acta* **2003**, *86*, 1598–1624.

(3) (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173–180. (b) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893–4011. (c) Sanford, A.; Gong, B. *Curr. Org. Chem.* **2003**, *7*, 1649–1659.

(4) Howard, S. T. *J. Am. Chem. Soc.* **1996**, *18*, 10269–10274.

(5) (a) Tanaka, Y.; Katagiri, H.; Furusho, Y.; Yashima, E. *Angew. Chem., Int. Ed.* **2005**, *44*, 3867–3870. (b) Katagiri, H.; Tanaka, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 2435–2439.

(6) (a) van Albada, G. A.; Mutikainen, I.; Turpeinen, U.; Reedijk, J. *Eur. J. Inorg. Chem.* **1998**, 547–549. (b) Yang, P.-Y.; Chang, F.-C.; Suen, M.-C.; Chen, J.-D.; Keng, T.-C.; Wang, J.-C. *J. Organomet. Chem.* **2000**, *596*, 226–231. (c) Lee, C.-W.; Chan, Z.-K.; Chen, T.-R.; Chen, J.-D. *Inorg. Chim. Acta* **2003**, *348*, 135–142. (d) Liang, H.-C.; Wu, Y.-Y.; Chang, F.-C.; Yang, P.-Y.; Chen, J.-D.; Wang, J.-C. *J. Organomet. Chem.* **2003**, *669*, 182–188. (e) Yeh, C.-W.; Yen, Y.-S.; Lin, W. B.; Su, C.-W.; Chen, J.-D.; Wang, J.-C. *Struct. Chem.* **2005**, *16*, 141–148. (f) Chen, C.; Su, C.-W.; Yeh, C.-W.; Hu, H.-L.; Chen, J.-D.; Wang, J.-C. *J. Chin. Chem. Soc.* **2006**, *53*, 299–303.

(7) (a) Böhme, F.; Rillich, M.; Komer, H. *Macromol. Chem. Phys.* **1995**, *196*, 3209–3216. (b) Böhme, F.; Kunert, C.; Klinger, C.; Komber, H. *Macromol. Symp.* **1998**, *128*, 183–193. (c) Kunert, C.; Voigt, D.; Friedel, P.; Komber, H.; Böhme, F. *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *39*, 1280–1287. (d) Komber, H.; Limbach, H.-H.; Böhme, F.; Kuner, C. *J. Am. Chem. Soc.* **2002**, *124*, 11955–11963.

(8) Xing, L.; Ziener, U.; Sutherland, T. C.; Cuccia, L. A. *Chem. Commun.* **2005**, 5751–5753.

DOI: 10.1021/jo9020453 Published on Web 11/13/2009

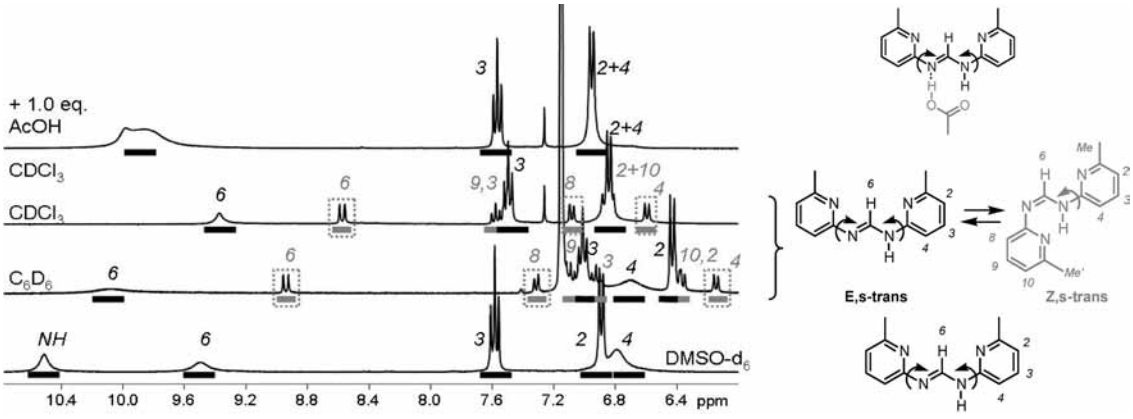


FIGURE 1. Left: Comparative ^{1}H NMR spectra (aromatic portion, 300 MHz) of **2** in DMSO-d_6, C_6D_6, $CDCl_3$, and $CDCl_3$ + 1.0 equiv of acetic acid (from bottom to top); critical protons are highlighted in gray dotted lines. Right: Structure(s) present in each solution ("s-trans" refers to the formamidine C(H)−N single bond).

However, the solid and solution state studies reported herein reveal a much richer stereochemical and conformational diversity of the *N*,*N*′-di(2-pyridyl)formamidine motif than just the previously assumed **1 Ess** isomer and conformer.

Solution Studies of 1 and 2. The conformation and stereochemistry of **1** have been very poorly characterized in solution. As a matter of fact, only ^{1}H NMR in DMSO-d_6 is found in the literature,[7d] despite the fact that this molecule is very soluble in many different solvents, and has been extensively utilized in coordination studies. It seems as though the complexity of the ^{1}H NMR spectra in solvents other than DMSO-d_6 has long been ignored. As for **2**, there is simply no NMR data reported in the literature to our knowledge.

Figure 1 exemplifies the solution state NMR behavior of **2** (**1** shows a similar behavior; **2** will only be discussed here as the presence of the 6-methyl group facilitates the analysis; see the Supporting Information for related data on **1**). In DMSO-d_6 (Figure 1 bottom), the simple spectrum shows a symmetrical species, consistent with literature findings.[7d] More specifically, the formamidine (H6) proton's high chemical shift reflects the proximity of the pyridine lone pair involved in weak hydrogen bonding. Its broad signal, however, is indicative of an exchange process that probably involves the rotation of the N−C_{py} single bond on both sides of the formamidine N=CH−N fragment (represented by curved arrows in Figure 1), whereby the formamidine proton experiences fairly polar (pyridine N) and less polar (pyridine H4) environments.

Consistent with the exchange between rotamers around the C_{py}−N bond is the breadth of the pyridine H4 signal (around 6.8 ppm in DMSO-d_6), as its local environment changes from an electron-rich (imine-type N) to a less electron-rich (proton H6) nature (note that the additional tautomeric equilibrium itself does not lead to such broadening in most other *N*,*N*′-bisarylformamidines). Overall, in DMSO-d_6, *N*,*N*′-di(2-pyridyl)formamidines **1** and **2** therefore exist as exchanging conformers with an *E* configuration (first line in Scheme 1). [Consistent with an exclusive *E* isomer in DMSO-d_6 is the similarity of the chemical shifts of **1** and that of protons of the related macrocycle in ref 7d, which is locked in an all-*E* configuration (δ(NH) = 10.7 ppm, δ(H4) = 6.6 ppm). As a result, the presence of both the *E* and *Z* isomers for **1** (and for **2**) in fast exchange in DMSO-d_6 is highly unlikely.]

In $CDCl_3$ and C_6D_6, the same molecules show a different behavior. In addition to the symmetrical signals reminiscent of the DMSO-d_6 spectrum (black bars, Figure 1), a dissymmetrical species is present (gray bars and boxes in Figure 1 for **2**; see the Supporting Information for similar signals for **1**). These additional signals have been assigned to the uncommon *Z* formamidine C=N isomer (Figure 1 right, middle line, in gray) based on 2D COSY and NOESY experiments (Supporting Information). Indeed, in C_6D_6 where signals are best resolved, through-bond coupling (COSY) allows the identification of signals belonging to each pyridine ring.

Through-space couplings in those additional signals (NOESY, C_6D_6, 25 °C) point to **Zs** and **Za** isomers coexisting with the **E** isomers discussed above: in those additional signals, (i) the methyl groups on C11 and NH are in proximity (H6 and H8 are far enough apart that no NOE signal is observed between them; this confirms a *Z* (cis) C=N species) and (ii) H4 and H6 may be found close together (unhindered rotation of the (H)N−C_{py} bond), consistent with an s-trans (H)C−N species. The observed chemical shifts agree with such an assignment (gray boxes, Figure 1): the relatively high chemical shift of H8 reflects the proximity of the imine-type electron-rich nitrogen, while the low chemical shift of H4 reflects that of a more "amine-like" environment.

So, overall, in non-hydrogen-bonding solvents, **2** and **1** exist as two slowly exchanging geometrical isomers: **E,s-trans** ("s-trans" referring to the formamidine C(H)−N single bond, which encompasses conformers **Esa**, **Eas**, and **Ess**; in black, Figure 1) and **Z,s-trans** (which encompasses conformers **Zs** and **Za**; in gray, Figure 1). The percentage of **Z-s-trans** form for **2** (respectively **1**) is 35% (respectively 38%) in $CDCl_3$ and 22% (respectively 20%) in C_6D_6 at 40 mM. Such a stable **Z,s-trans** form has, to our knowledge, never been reported among neutral *N*,*N*′-disubstituted formamidines.[9] The

(9) One example of a thermodynamically stable *Z* amidine in the context of *N*,*N*,*N*′-trisubstituted species may be found in: Raczyńska, E. D. *J. Chem. Res.* (*S*) **1987**, 410−411, in which Z HC(=NAr)NMe_2 is reported to be stabilized when Ar = *o*-hydroxyphenyl, through a hydrogen bond between the hydroxyl function on the aryl group and the lone pair of the imino nitrogen covalently bound to the aryl ring. *Kinetically* produced *Z N*,*N*,*N*′-trisubstituted amidines and their isomerization to the stable *E* form are reported in: (a) Hegarthy, A. F.; Chandler, A. *J. Chem. Soc., Chem. Commun.* **1980**, 131–132. (b) Hegarthy, A. F.; Chandler A. *Tetrahedron Lett.* **1980**, *21*, 885−888 and (c) Hegarthy, A.; Cunningham, I. D. *J. Chem. Soc., Perkin Trans. II* **1986**, 537–541.

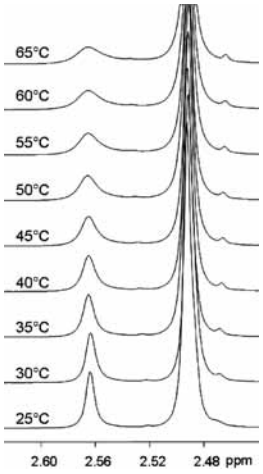


FIGURE 2. Methyl region of the variable temperature ^{1}H NMR spectra of **2** in $CDCl_3$ (400 MHz).

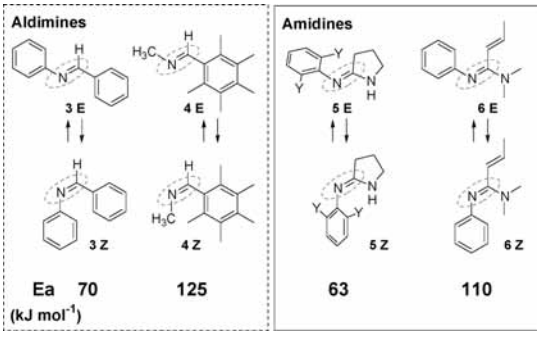
intramolecular pyridine N---H−N hydrogen bond indeed stabilizes the otherwise unstable **Z,s-trans** state through the formation of a six-membered hydrogen-bonded ring. Evidence of such a hydrogen bond driven folding comes from (i) the **Z,s-trans** NH broad doublet (δ 13.2 ppm in $CDCl_3$, 13.4 ppm in C_6D_6; see the Supporting Information) and (ii) its coupling to H6 (doublet at 8.94 ppm in C_6D_6, 8.57 ppm in $CDCl_3$; ^3J = 10.3 Hz). Such strong coupling confirms the **s-trans** conformation and suggests that the labile NH proton has a fairly long residence time within the **Z,s-trans** form, compared to the more labile **E,s-trans** NH (broad singlet for H6).

Consistent with the justification of an intramolecular bond in the **Z,s-trans** isomer, the introduction of a disruptive, hydrogen-bonding, solvent (e.g., CD_3OD) to the $CDCl_3$ and C_6D_6 solutions leads to the disappearance of the **Z,s-trans** form in favor of the **E,s-trans** isomer (proposed isomerization mechanisms in the Supporting Information). Competition for hydrogen bonding to the acidic NH probably also explains the absence of the **Z,s-trans** isomer in DMSO-d_6.

Similarly, the equilibrium between the **Z,s-trans** and the **E,s-trans** isomers of **2** (and of **1**) may be biased toward the **E,s-trans** isomer by addition of a carboxylic acid partner (Figure 1 top), leading to the exclusive formation of a carboxylic acid/**E,s-trans** complex. Interestingly, the same mixture may also be biased to form the **E,s-cis** isomer via coordination to Mo,[6b] Cu^I,[6c] Re,[6d] or Mn.[6f]

As the *Z* isomer for neutral *N*,*N*′-disubstituted formamidine had not been reported previously, preliminary studies on the activation energy of *E*/*Z* isomerization in this context were undertaken by ^{1}H NMR at variable temperatures. Figure 2 illustrates the changes in line width for the methyl protons of the exchanging species, as a function of temperature,[10] in $CDCl_3$ (note that, in $CDCl_3$, one of the two methyl groups of the *Z* form overlaps with the six methyl protons of the *E* form; see the Supporting Information for full spectra). Although no coalescence was observed up to 65 °C, line broadening analysis[10] of the methyl group signals was used to estimate an activation energy of 90 ± 2 kJ mol^{-1} (21.5 ± 0.5 kcal mol^{-1}; see the Supporting Information for the line broadening analysis).

SCHEME 2. Imines and Amidines with Reported Activation Energies for the *Z*/*E* Isomerization of C=N Double Bonds (see ref 11b for 3Z/3E, ref 11c for 4Z/4E, ref 11d for 5Z/5E with Y = Me or Cl, and ref 11e for 6Z/6E)



Although there is no precedent to compare with among *N*,*N*′-disubstituted formamidines, the kinetics of C=N isomerization of **2** may be compared with that of other C=N containing functions (Scheme 2).

The activation energy for *Z*/*E* isomerization of **2** falls in the range of activation energies for C=N isomerization of aldimines:[11a] it is larger than that of *N*-aryl aldimines such as **3** (61−79 kJ mol^{-1}, 14.6−18.8 kcal mol^{-1}, in methanol and acetonitrile)[11b] and smaller than that of *N*-alkyl aldimines such as **4** (125 kJ mol^{-1}, 30 kcal mol^{-1}, in *tert*-butyl alcohol).[11c] In the context of amidines, the value reported herein is significantly higher than that for cyclic amidines where the N(=C) is substituted with aryl groups bearing ortho and ortho′ substituents (63 kJ mol^{-1}, 15 kcal mol^{-1}, in $CDCl_3$),[11d] and lower than for *N*,*N*-dimethyl-*N*′-phenylamidines (∼110 kJ mol^{-1}, ∼26 kcal mol^{-1}, in $CDCl_3$).[11e] Overall, the presence of the pyridine substituents seems to have a significant effect stabilizing the unusual *Z*-isomer, but probably similarly stabilizes the transition states in the course of isomerization (possible mechanisms in the Supporting Information), resulting in no dramatic effect on the activation energy of isomerization of the N=C double bond ($CDCl_3$).

Solid State Structure of 1. The solid state structure of **1** reported herein shows the selection of only one specific isomer with a defined conformation in the crystal state (Figure 3). Only the **E,s-trans** form crystallizes; the limited rotation around the single bonds is actually worth mentioning (see anti/syn discussion below). As expected from the several structures available in the literature for formamidines bearing simple hydrocarbon-based aromatic substituents,[12]

(10) Günter, H., *NMR Spectroscopy*; Wiley: New York, 1998; Chapter 9.

(11) (a) Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 219–235. (b) Geibel, K.; Grellmann, K.; Staudinger, B.; Wendt, H. *Ber. Bunsen. Ges. Phys. Chem.* **1972**, *76*, 1246–1251. (c) Jennings, W. B.; Al-Showiman, S.; Boyd, D. R.; Campbell, R. M. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1501–1506. (d) Jackman, L. M.; Jen, T. *J. Am. Chem. Soc.* **1975**, *97*, 2811–2818. (e) Naulet, N.; Filleux, M. L.; Martin, G. J.; Pornet, J. *Org. Magn. Reson.* **1975**, *7*, 326–330.

(12) (a) Anulewicz, R.; Krygowski, T. M.; Pniewska, B. *Acta Crystallogr., Sect. C: Cryst. Struct.* **1990**, *C46*, 2121–2132. (b) Anulewicz, R.; Krygowski, T. M.; Jaroszewska-Manaj, J.; Pniewska, B. *Pol. J. Chem.* **1991**, *65*, 465–471. (c) Anulewicz, R.; Wawer, I.; Krygowski, T. M.; Männle, F.; Limbach, H.-H. *J. Am. Chem. Soc.* **1997**, *119*, 12223–12230. (d) Ren, T.; Radak, S.; Ni, Y.; Xu, G.; Lin, C.; Shaffer, K. L.; DeSilva, V. *J. Chem. Crystallogr.* **2002**, *32*, 197–203. (e) Abdou, H. E.; Mohamed, A. A.; López-de-Luzuriaga, J. M.; Fackler, J. P. Jr., *J. Cluster Sci.* **2004**, *15*, 397–411. (f) Masuda, J. D. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2008**, *E64*, o1447.

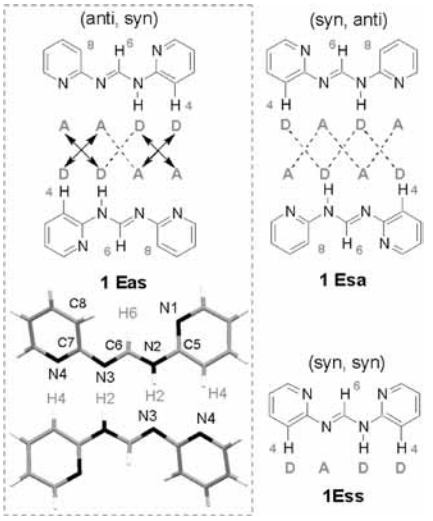


FIGURE 3. Pyridine orientations in **1** and dimers, with trans C=N and s-trans C−N bonds ("D" and "A" are H-bond donors and acceptors, respectively). Crystal structure of **1** selected bond distances (Å): N4−H4 2.475(14), N3−H2 2.173(15), N1−H6 2.358(10). Dihedral angles (deg): C6−N3−C7−C8 38.79(15), C6−N2−C5−N1 2.64(16).

the formamidine function of **1** dimerizes through a double H-bond between the N−H of one formamidine and the imine-type N of the other. In addition to this common motif, the presence of the nitrogen atom of the pyridine brings an additional feature: the pyridine rings strengthen the dimer through two additional hydrogen bonds involving the basic nitrogen of one pyridine ring and the weakly acidic pyridine proton H4 (Figure 3) of the other, although the pyridine N and H−C bonds are not fully aligned due to the twist generated by the H8/H6 steric repulsion. Two conformers may form such a quadruply H-bonded assembly (**1 Eas** and **1 Esa,** Figure 3), yet only the **1 Eas** conformer is selected in the solid state as it leads to more attractive secondary electrostatic interactions (four versus none; full arrows) and fewer repulsive secondary electrostatic interactions (two versus six; dotted lines), consistent with the model developed by Jorgensen et al.[13]

In conclusion, *N*,*N*′-dipyridylformamidines derived from 2-aminopyridines show a rich stereochemical and conformational diversity, combined with selection features, in the solid state as well as in solution. Although the *N*,*N*′-dipyridylformamidine motif has been extensively used in coordination chemistry[6] (and, to a lesser extent, in macrocyclic synthesis[7,8]), to the best of our knowledge, its solid state structure, stereochemistry and conformations in non-hydrogen-bonding solvents had never been reported previously.

Considering the recent interest in amidines as building blocks in the self-assembly of complex systems,[5] the solved crystal structure of **1** may be informative to design more complex architectures to be used in crystal engineering. Indeed, the well-defined orientation of the pyridyl substituents may be used to construct porous materials for polar substrates (see the Supporting Information for a view of the crystal packing). In addition, although the pyridyl proton based H-bonds observed in the solid state of **1** are too weak to provide significant stabilization in dilute solutions (we did not observed any significant concentration effects in $CDCl_3$ and C_6D_6), extensions of the H-bonding capabilities along the pyridines may be considered in order to enhance the hydrogen-bonding strength with more than four D/A sites. Finally, the observation of a stable *Z* isomer for *N*,*N*′-dipyridylformamidines may be used to derive more elaborate, trigger responsive, foldamers.

Experimental Section

Synthesis. 1 and **2** were synthesized according to a published procedure;[7d] their identity was confirmed by melting temperatures (measured mp (**1**) 105−106 °C, lit.[7d] mp 104−106 °C; measured mp (**2**) 106−108 °C, lit.[14] mp 110.5−112.5 °C).

Crystal Data. 1 was crystallized by slow evaporation from an acetone solution at room temperature. $C_{11}H_{10}N_4$, M = 198.23, monoclinic, a = 10.9881(19) Å, b = 4.3351(7) Å, c = 20.561(4) Å, U = 968.5(3) Å^3, T = 180(2) K, space group $P2/n$, Z = 4, 5802 reflections measured, 1191 unique (R_{int} = 0.0399). The final $wR(F^2)$ was 0.0893 (all data). Hydrogen atoms were refined freely.

NMR Analysis. Solutions in $CDCl_3$ were prepared by dissolving a known amount of the compound of interest in $CDCl_3$ that had been freshly filtered through a short column of activated basic alumina in order to eliminate any trace of residual HCl/DCl. Other solvents (DMSO-d_6, C_6D_6, $(CD_3)_2CO$, CD_3OD) were used as received. 2D spectra (COSY, NOESY) were measured on a 500 MHz spectrometer. Mixing time for the NOESY analysis of **2** was set to 1.4 s.

Acknowledgment. The authors are grateful to Dr. Ruiyao Wang for his assistance with X-ray crystallography and Professor Gang Wu for helpful discussions regarding NMR data and chemical exchange analysis. The authors would also like to thank two of the referees for constructive comments and suggestions on solution state studies. Finally, Queen's University, the Canadian Foundation for Innovation, the Ministry of Research and Innovation (Ontario), and Natural Sciences and Engineering Research Council of Canada (NSERC) are acknowledged for financial support.

Supporting Information Available: Additional CPK and ortep views of **1** in the solid state; crystal packing; crystal data and structure refinement; table of bond lengths, angles, and torsion angles; table of H-bond related distances and angles; full ^{1}H NMR spectra of **2** in various solvents; aromatic portion of the ^{1}H NMR spectra of **1** in various solvents; selected portions of the NOESY spectrum of **2**; full variable temperature spectra of **2** in $CDCl_3$; line broadening analysis of **2** ($CDCl_3$, variable temperatures on methyl region); proposed *Z*/*E* isomerization mechanisms for neutral *N*,*N*′-di(2-pyridyl)formamidines. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) (a) Jorgensen, W. L.; Pranata, J. *J. Am. Chem. Soc.* **1990**, *112*, 2008–2010. (b) Jorgensen, W. L.; Pranata, J. *J. Am. Chem. Soc.* **1991**, *113*, 2810–2819.

(14) Seidel, M. C.; van Tuyle, G. C.; Weir, W. D. *J. Org. Chem.* **1970**, *35*, 1662–1664.