Chemistry of Amidines. Part 3.[1] Analysis of Conformation about the *N*'-Pyridyl Bond in *N*'-(2-Pyridyl)formamidines

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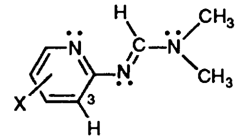
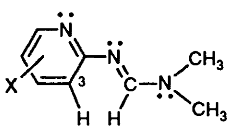
A conformational analysis of a series of *N*,*N*-dimethyl-*N*'-(2-pyridyl)formamidines and their conjugate acids using the ^1H NMR nuclear Overhauser effect shows that they exist preferentially in the conformation in which the pyridine and the imino nitrogen lone pairs are *anti*. For compounds having electron-donating substituents the *syn* conformation becomes important on protonation.

There has been considerable interest in recent years in the conformational analysis of amidines. Most studies[2] have concentrated on rotations about the partial double bond between the amino nitrogen and the carbon, while some[3] have examined conformations about the imino nitrogen to carbon bond. Few have directly addressed the problem of conformation about the imino nitrogen to substituent bond. One paper[4] reports a crystal structure of *N*,*N*-morpholino-*N*'-(4-nitrophenyl)formamidine showing the aromatic ring and the amidine system to be coplanar. Conformational preferences about this bond are of particular relevance for the *N*'-(2-pyridyl)formamidines **1**. In earlier work we have suggested, on the basis of the correlations of pK_a[5] and $\Delta G^\ddagger$ (for dimethylamino group rotation)[1] with σ° and σ^-, respectively, that the pyridyl ring and the amidine system are coplanar in D_2O and $[^2H_6]$DMSO, but we were unable to say whether the *syn* (**1s**)‡ or *anti* (**1a**) form is preferred. We have undertaken therefore, a conformational analysis of compounds **1** (X = 5-Me, 4-Me, H, 5-Cl, 5-Br, 5-NO_2) by ^1H NMR using the nuclear Overhauser effect. While NOE is widely used for structural elucidation of more rigid systems, it has been much less widely used for conformational analysis in flexible systems.[6] We are unaware of any other studies where this effect has been used to probe conformations of amidines, particularly where, as in the present case, the conformers are not separable, or where a preferred conformer is not assignable on the basis of NMR chemical shifts.

Molecular mechanics for the coplanar aromatic ring–amidine *syn* conformation (**1s**) calculate the distance between H_f and H_3 (or between H_f and H_2 of **2a** or between H_f and H_6 of **2s**) to be of the order of 0.21 nm, well within the distance over which an NOE should be observable, and for the phenylamidine **2** irradiation of the H_f signal gave enhancements of 6% (H_2) and 4% (H_6) in $[^2H_6]$DMSO; similar enhancements in H_f were observed on separate irradiations at H_2 and H_6. For the conjugate acid of **2** mutual enhancements of 7% (H_f–H_2) and 4% (H_f–H_6) were observed. These observations allow a semi-quantitative assessment of the magnitude of such NOE enhancements for this type of system, and show that both *syn* and *anti* conformations, **2s** and **2a**, respectively, are appreciably populated.


1a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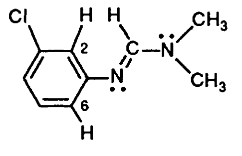
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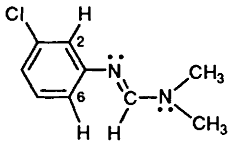
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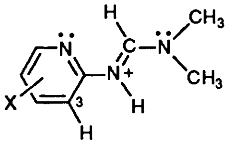
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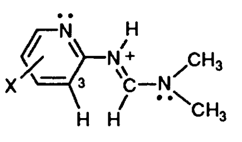
3s

In contrast no enhancements were observed for the H_f/H_3 pair for any of the pyridylformamidines (**1**) in $CDCl_3$ or $[^2H_6]$DMSO. The lack of an NOE must be interpreted cautiously, but H_f is certainly capable of receiving enhancement; several per cent upon irradiation of the dimethylamino signals. By analogy with **2**, enhancements of the order of several per cent would be expected for the *syn* conformation **1s**, and the lack of enhancement shows that the *anti* conformation **1a** is the more stable, although rotation about the nitrogen–pyridyl group bond is probably fast.

It has been shown that these amidines protonate preferentially on the imino nitrogen to give the conjugate acids **3**.[5] For the conjugate acids **3** (obtained by addition of a small excess of trifluoroacetic acid) in $CDCl_3$ no enhancements were observed for the H_f/H_3 pair. The spectrum showed a fairly sharp signal for the 'acidic' proton (in rapid exchange with that of the trifluoroacetic acid), and irradiation at this position led to enhancements of 4–5% for the H_3 signal; clearly conformation **3a** is preferred in $CDCl_3$. In $[^2H_6]$DMSO no sharp signal due to the 'acidic' proton of **3** was detected, but enhancements for the H_f/H_3 pair were negligible for all compounds except for the conjugate acid of the 4-methyl-substituted pyridylformamidine (**3**, X = 4-Me) where mutual enhancements of 3% were observed. Thus, the *anti* conformation **3a** is preferred for all the conjugate acids in $CDCl_3$, but the *syn* conformation **3s** becomes significant in $[^2H_6]$DMSO when the microscopic basicity of the (unprotonated) pyridyl nitrogen is increased by a suitably

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‡ We have defined the *syn* conformation as that in which the imino and pyridyl lone pairs are on the same side of the molecule. For the prononated form the *syn* conformation is that derived from the *syn* conjugate base. For the phenylformamidine we have defined the *syn* conformation as that in which the substituent to the ring and the imino lone pair are *syn*.

positioned electron-donating group.* The preference of the unprotonated pyridylamidines for the *anti* conformer **1a** can be rationalised qualitatively in terms of the repulsion between the imino and pyridyl nitrogen lone pairs and steric repulsion between H_3 and H_f. Factors influencing conformational preferences of the protonated amidines are more finely balanced since the ratio of conformers is influenced by relatively small changes in solvent and structure. We suggest that the steric interaction between H_3 and H_f is the dominant factor until the microscopic basicity of the pyridyl nitrogen is increased sufficiently to make a loose association between its lone pair and the electron-deficient 'acidic' proton significant.

We are continuing our studies of the NOE in amidines and have commenced molecular mechanical and semi-empirical modelling to determine the factors which influence conformational preferences.

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* In no case did irradiation of the acidic proton or H_f result in any significant enhancement of signals due to other aromatic protons, although enhancements of the signals due to the dimethylamino protons were observed for both and *vice versa*.