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Acid-Induced Molecular Folding and Unfolding of *N*-Methyl Aromatic Amide Bearing 2,6-Disubstituted Pyridines

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Conformational transformation of a molecule or supramolecule can greatly influence its function.[1] Although predicting the conformation of a large molecule or supramolecule is not simple, sometimes a major structural change of a large molecule or supramolecule is based upon conformational switching of a small structural unit.[2] Therefore, understanding, predicting, and controlling the conformation of small structural units is of great interest.

The amide bond is very important structural unit which can form two conformations, cis and trans. Most secondary aromatic amides, such as benzanilide or acetanilide, favor trans conformation, but N-methylation of these amides causes an almost complete change to cis conformation.[3,4] However, there are only a few examples such a drastic conformational change of the amide skeleton induced by environmental change without functional transformation.[5]

We designed pyridine-containing *N*-methyl aromatic amides as candidate protonation-responsive units. As many groups have reported, the pyridine ring serves as a ligand for metals or as a hydrogen bond acceptor in many functionalized molecules or supramolecules.[6] Recently we reported that some pyridine-containing *N*-methyl amides switch their conformation in response to environmental factors such as solvent acceptor ability or acidity.[7] In this work, we have investigated the structural features of the *N*-methyl pyridyl amide **2** and its dynamic protonation-associated conformational conversion from *layered* to *spiral* and then *flat*.

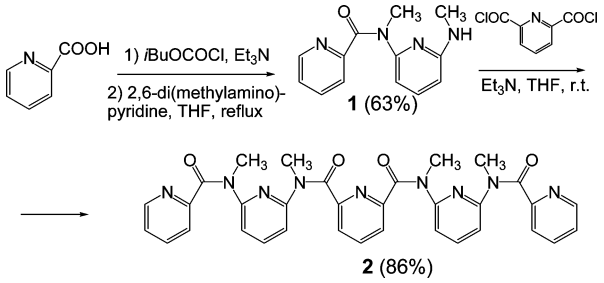
The *N*-methyl pyridyl amide **2** was synthesized in a simple manner from the corresponding acid anhydride, chloride, and *N*-methyl amine (Scheme 1). X-ray crystallography revealed the characteristic structure of *N*-methyl aromatic amides (Figure 1), that is, all the amide bonds take cis conformation. The pyridine rings are in a syn arrangement about the central pyridine, forming an almost *layered* shape.

In order to study the effect of addition of acid, the ^{1}H NMR spectra of **2** in the presence of trifluoroacetic acid-*d* (TFA-*d*) and perchloric acid-*d* were investigated (Figure 2). Most of the signals were shifted toward lower field. This is reasonable, because lower-field shift is a general trend for protonated pyridine rings.[8] However, addition of TFA-*d* caused significant higher-field shifts of protons of the central pyridine ring (spectrum b). These unusual shifts suggest a conformational change, such as folding or wrapping of the molecule; the resulting anisotropic effect of the surrounding pyridine rings would be the origin of the shifts.

The crystal structure of **2H**, the perchlorate salt obtained from the amide **2** and two equivalents of perchloric acid, revealed the steric features of doubly protonated amide **2** (Figure 3).

All the amide bonds in **2H** retained cis conformation, and *spiral*-shaped folding of the whole molecule occurred. Protonation at the two terminal pyridine nitrogen atoms caused intramolecular hydrogen bonding with the oxygen atom of the amide group (Scheme 2, B). The crystal structure of **2H** can be considered as representative of the structure of **2** in solution in the presence of TFA, because the spectrum of the salt **2H** showed good accordance with that of **2** in TFA (Figure 2, spectra b and c).

Scheme 1. Synthesis of the Amide **2**



This folding of the doubly protonated amide **2** was released by further protonation. Figure 2 also shows that a further change of the signals accompanies addition of perchloric acid. The higher-field shift of the central pyridine protons disappeared, and the signals moved to lower field with the addition of perchloric acid (Figure

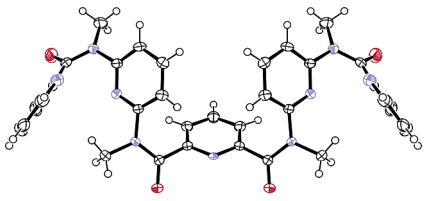


Figure 1. Crystal structure of the amide **2**.

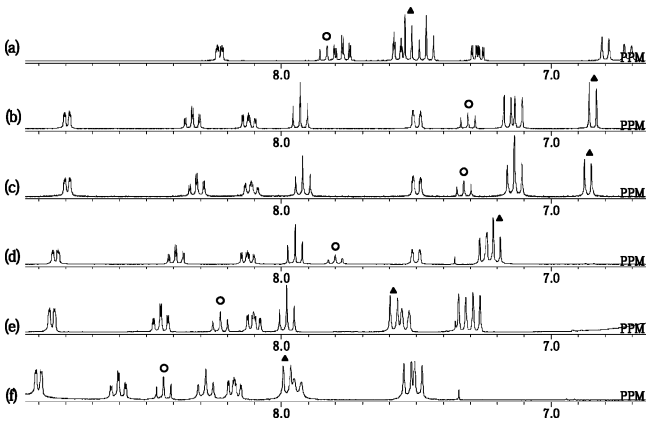


Figure 2. ^{1}H NMR spectra of **2** and **2H** in CD_3CN. (a) **2**; (b) **2** with TFA-*d* (50 equiv); (c) **2H**; (d) **2** with $DClO_4$ (4 equiv); (e) **2** with $DClO_4$ (8 equiv); (f) **2** with $DClO_4$ (40 equiv). The triplet marked with a circle is the signal of H-4 of the central pyridine ring, and a triangle shows H-3 and H-5 of the central pyridine ring.

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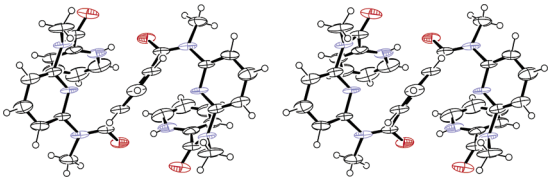
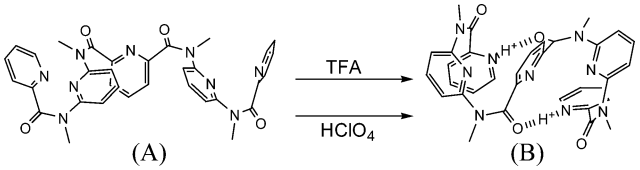


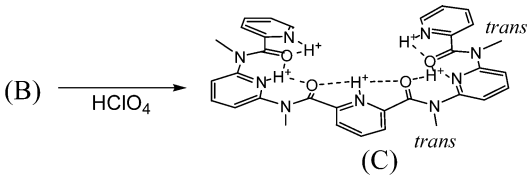
Figure 3. Crystal structure of salt **2H** (stereoview). Counteranions are omitted for clarity.

Scheme 2. Conformational Change of **2** in the Presence of Perchloric Acid or TFA



2, spectra c−f). These lower-field shifts can be considered the result of protonation at the inner pyridine nitrogen atoms and consequent conformational change. As we reported before, protonation of the 2-methylaminopyridine moiety causes amide bond switching from cis to trans.[7b] This generates a *flat* molecular conformation owing to three-center intramolecular hydrogen bonding (Scheme 3, C),[9] and abrogates the anisotropic higher-field shift. Whereas the conformational change from the *layered* form (A) to the *spiral* form (B) is based upon the rigid cis-amide building blocks and a strategy similar to the transition reported by Huc,[6e] the dynamic change to *flat* form (C) requires our cis−trans switching system of *N*-methyl amides.

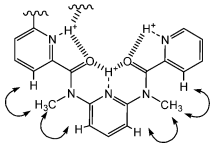
Scheme 3. Conformational Flattening of **2** in the Presence of Perchloric Acid



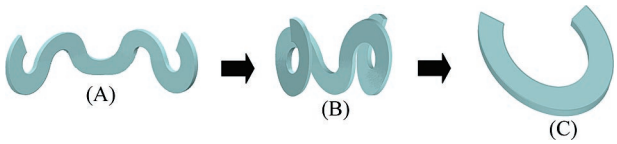
The *flat* conformation of **2** was also confirmed by NOESY measurement of **2** in the presence of perchloric acid. The correlations between *N*-methyl protons and pyridine protons indicate that all the *N*-methyl amide bonds take the trans conformation (Scheme 4).

In conclusion, the shape of the amide **2** can be adjusted from the *layered* form (Scheme 5, A) to the *spiral* folded form (B) (by addition of TFA or stepwise addition of perchloric acid) and further adjusted to the *flat* conformation (C) by further addition of perchloric acid. The dynamic conformational conversion is caused by amide bond switching together with intramolecular hydrogen-bonding effects. This environment-responsive type of conformational control has considerable potential for controlling the shape of large molecules or supramolecules.

Scheme 4. NOESY Correlations of **2** with $DClO_4$ (40 equiv) in CD_3CN



Scheme 5. Stepwise Conformational Change of **2** in the Presence of Perchloric Acid



Supporting Information Available: Synthesis, ^{1}H NMR spectra, and X-ray crystallographic data for **2** and **2H** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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