

Acid-Induced Molecular Folding and Unfolding of *N*-Methyl Aromatic Amide Bearing 2,6-Disubstituted PyridinesIwao Okamoto,<sup>\*,†</sup> Mayumi Nabeta,<sup>†</sup> Yasuko Hayakawa,<sup>†</sup> Nobuyoshi Morita,<sup>†</sup> Tetsuya Takeya,<sup>†</sup> Hyuma Masu,<sup>‡</sup> Isao Azumaya,<sup>‡</sup> and Osamu Tamura<sup>†</sup>

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Conformational transformation of a molecule or supramolecule can greatly influence its function.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3,4</sup> However, there are only a few examples such a drastic conformational change of the amide skeleton induced by environmental change without functional transformation.<sup>5</sup>

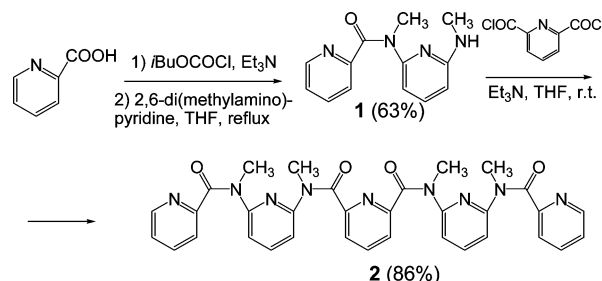
We designed pyridine-containing *N*-methyl aromatic amides as candidate protonation-responsive units. As many groups have reported, the pyridine ring serves as a ligand for metals or as a hydrogen bond acceptor in many functionalized molecules or supramolecules.<sup>6</sup> Recently we reported that some pyridine-containing *N*-methyl amides switch their conformation in response to environmental factors such as solvent acceptor ability or acidity.<sup>7</sup> 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 <sup>1</sup>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.<sup>8</sup> 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 hy-

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

drogen 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).

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

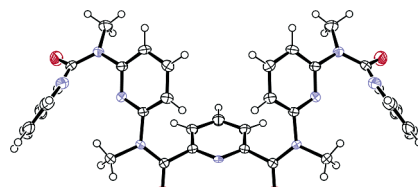
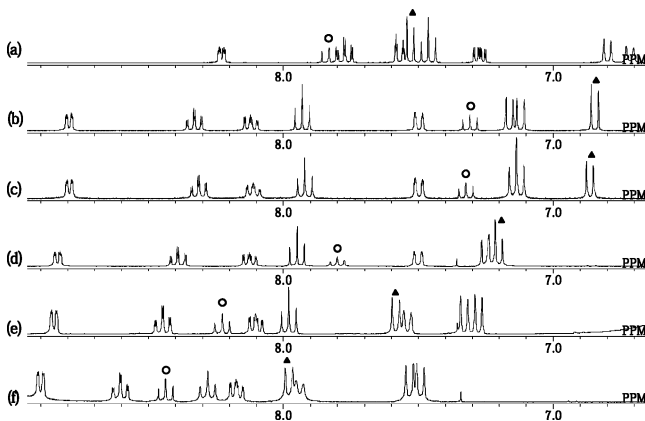
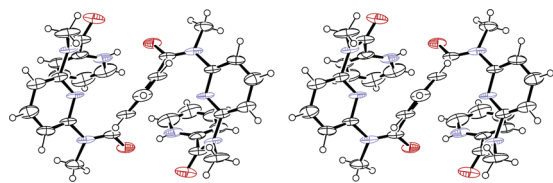
Figure 1. Crystal structure of the amide **2**.

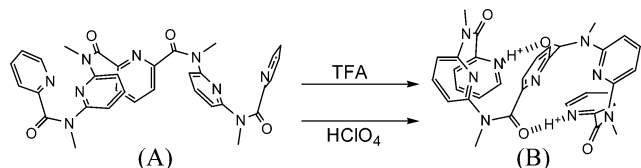
Figure 2. <sup>1</sup>H NMR spectra of **2** and **2H** in CD<sub>3</sub>CN. (a) **2**; (b) **2** with TFA-*d* (50 equiv); (c) **2H**; (d) **2** with DClO<sub>4</sub> (4 equiv); (e) **2** with DClO<sub>4</sub> (8 equiv); (f) **2** with DClO<sub>4</sub> (40 equiv). The triplet marked with a circle is 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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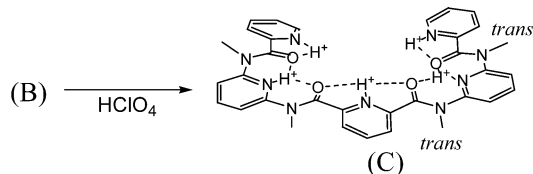
**Figure 3.** Crystal structure of salt **2H** (stereoview). Counteranions are omitted for clarity.

**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*.<sup>7b</sup> This generates a *flat* molecular conformation owing to three-center intramolecular hydrogen bonding (Scheme 3, C),<sup>9</sup> 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,<sup>6e</sup> the dynamic change to *flat* form (C) requires our *cis*–*trans* switching system of *N*-methyl amides.

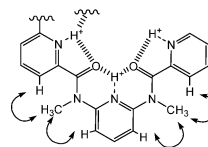
**Scheme 3.** Conformational Flattening of **2** in the Presence of Perchloric Acid



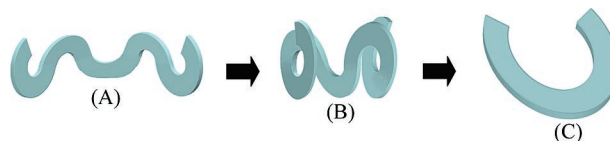
The *flat* conformation of **2** was also confirmed by NOESY measurement of **2** in the presence of perchloric acid. The correlations between *N*-methyl protons and pyridine protons indicate that all the *N*-methyl amide bonds take the *trans* conformation (Scheme 4).

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 conforma-

**Scheme 4.** NOESY Correlations of **2** with DClO<sub>4</sub> (40 equiv) in CD<sub>3</sub>CN



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



tional control has considerable potential for controlling the shape of large molecules or supramolecules.

**Supporting Information Available:** Synthesis, <sup>1</sup>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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