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Acid-induced conformational switching of aromatic *N*-methyl-*N*-(2-pyridyl)amides

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Abstract—Aromatic *N*-methyl amides containing *N*-(2-pyridyl) and 2-pyridinecarboxamide or 2,6-pyridinedicarboxamide moieties switch their conformation from cis to trans depending upon the addition of acid.
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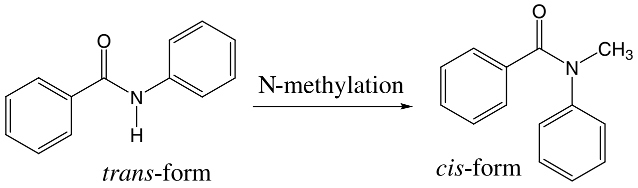
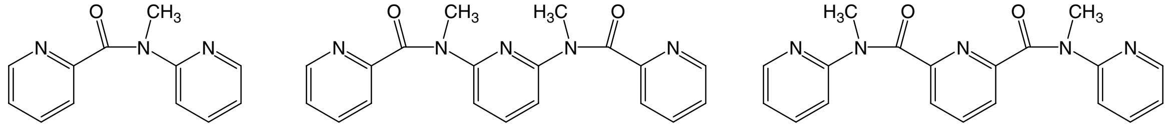
Conformational switching, especially switching induced by environmental change, plays a key role in controlling the functions of materials that respond to external stimuli.[1] Among various compounds that are available as components of such functionalized materials, amide is one of the most promising chemical structures because it can be conformationally altered by either structural modification or alteration of their chemical environment. For example, N-methylation of benzanilide causes almost complete conformational change from trans to cis (Scheme 1), which are generally observed in N-alkylation of secondary aromatic amides.[2,3]



Scheme 1. Trans- and cis-formed aromatic amides.

N,*N*-Diaryl type amides also show characteristic features of conformational preference.[4a,5] On the other hand, only a few examples have been reported of environmental change causing complete conformational conversion of an amide skeleton; these examples include conformational switching of *N*,*N*-diphenylamides induced by protons and of *N*-phenylhydroxamic acid induced by solvent effects.[4]

We have reported that an *N*-methyl amide containing *N*-(2-pyridyl) and 2,6-pyridinedicarboxamide moieties switches its conformation depending upon the acceptor ability of the solvent.[6] Here, we describe the steric features of pyridine-containing aromatic *N*-methyl amides **1**–**3** (Scheme 2), and their conformational characteristics



1 **2** **3**

Scheme 2. Pyridine-containing aromatic *N*-methyl amides.

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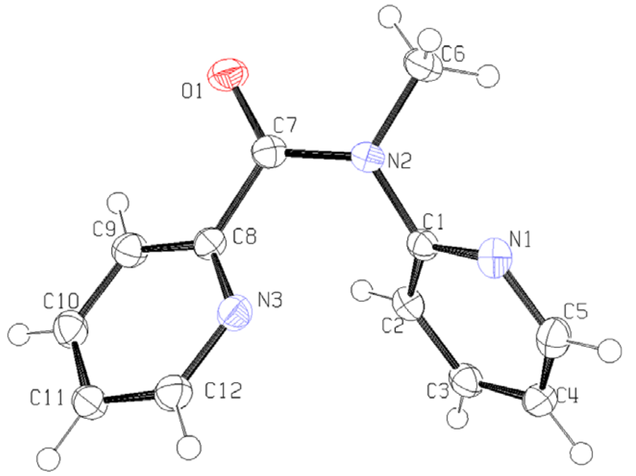


Figure 1. Crystal structure of amide **1**.

in solution and in the crystal state. Each amide undergoes an acid-induced conformational change, and **1** and **3** switch their conformation from cis to trans in the presence of acid.

The amide bonds of **1** and **2** exist mainly in cis conformation in solution. Amide **3** exists predominantly in cis–cis conformation in dichloromethane or methanol, but tends to form cis–trans conformation in other solvents.[6]

X-ray crystallographic analysis was conducted to establish the crystal structures of these *N*-methyl pyridyl amides.[7] Compound **1** shows the characteristic structural features of aromatic *N*-methyl amides, that is, the two aromatic rings are in a cis relationship (Fig. 1). The dihedral angle of the amide bond plane and pyridine ring connected with the amide carbonyl group (*C*-pyridine) is smaller than that of the amide plane and *N*-pyridine,[8] and the nitrogen atom of the *C*-pyridine ring lies in the *anti* direction to the carbonyl oxygen.

The crystal structures of amides **2** and **3**, bearing three pyridine rings, were also examined (Fig. 2).[9] Although the two amide bonds in **2** take cis conformation, those in **3** take cis–trans conformation. The two carbonyl groups in **3** lie in the *anti* direction to the central pyridine nitrogen atom, and the steric repulsion between the two terminal pyridine rings is apparently released in this trans conformation.

Next we investigated the conformational change of these amides upon addition of acid. The addition of perchloric acid to a solution of amide **1** in ethyl acetate gave perchlorate **1H** as a precipitate. Elemental analysis revealed that **1H** contains **1** and $HClO_4$ in 1:2 ratio. Similar treatments of solutions of **2** and **3** gave the corresponding salts **2H** and **3H**, respectively, which also contain the amide and $HClO_4$ in 1:2 ratio.[10] On the other hand, addition of trifluoroacetic acid to solutions of **1**–**3** in various solvents did not result in precipitation of the salts.

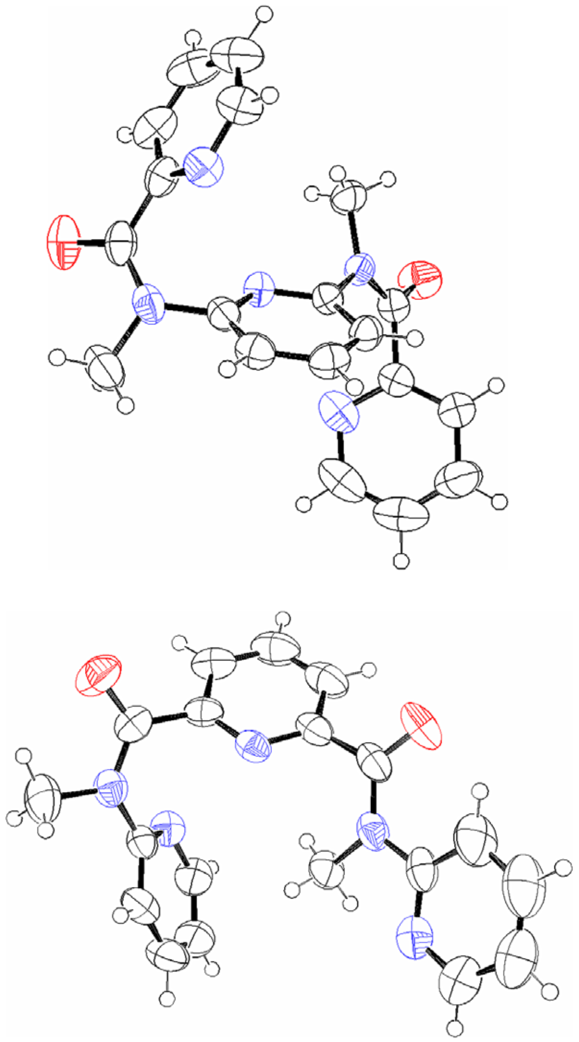


Figure 2. Crystal structures of amides **2** (upper) and **3** (lower).

Comparison of the ^{1}H NMR spectra of the amides in the presence of acids revealed the proton-accepting character of **1**–**3**. Addition of TFA-*d* to the amides produced a lower field shift of the aromatic proton signals. Excess TFA-*d* saturated this field shift. Figure 3 shows the spectra of **3**, **3** in the presence of excess TFA-*d*, and **3H**, and **3** in the presence of excess $DClO_4$. Since the spectrum of **3** in the presence of excess TFA (b) is similar to that of **3H** (c) and shows equivalent signals of terminal pyridines, it is considered that only the two terminal pyridine rings are protonated by TFA.

In order to examine the nature of the conformational change, the chemical shifts and the lower field shifts caused by addition of TFA were compared (Table 1). Since entries 1 and 3 show that H-3′, H-4′, H-5′, and H-6′ of **1** and those of **3** each show good accordance of chemical shift and lower field shift, the *N*-pyridine rings of **1** and **3** apparently undergo similar structural conversions. However, a comparison of entries 1 and 2 reveals significant differences. Although the chemical shifts of H-3, H-4, H-5, and H-6 in the *C*-pyridine rings of amide **2** take similar values to those of amide **1**, the

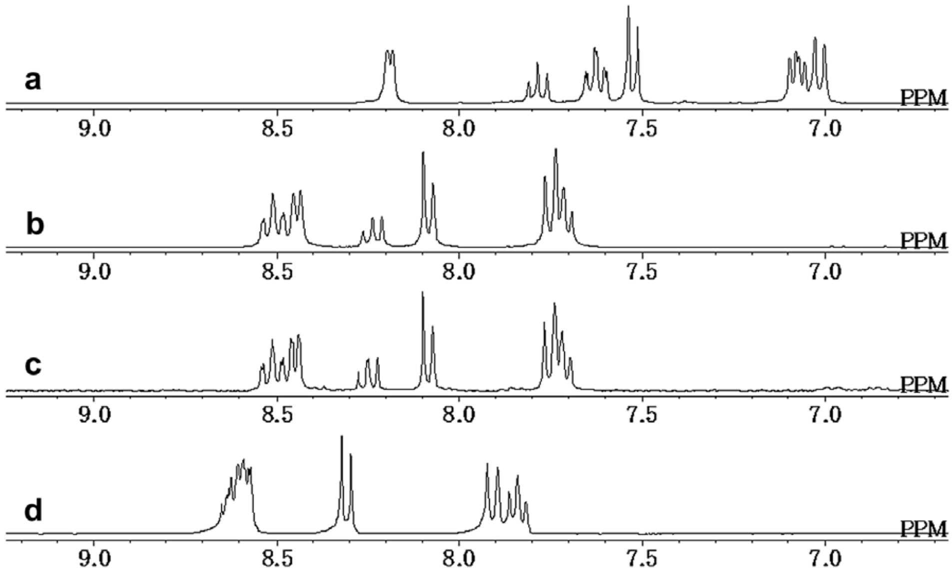
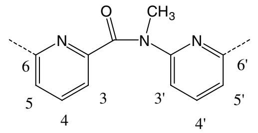


Figure 3. ^{1}H NMR spectra in CD_3CN of (a) **3**; (b) **3** with TFA-*d* (150 equiv); (c) **3H**, and (d) **3** with $DClO_4$ (30 equiv).

Table 1. Chemical shifts of amides **1**–**3** and their lower field shifts upon addition of TFA-*d* (150 equiv)

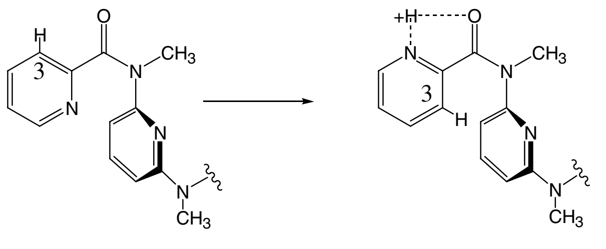
Entry	Amide	H-3[a]		H-4		H-5		H-6		H-3′		H-4′		H-5′		H-6′	
1	**1**	7.63[b]	+0.7[b]	7.72	+1.1	7.21	+1.1	8.27	+0.8	7.01	+0.9	7.52	+1.2	7.01	+0.9	8.27	+0.4
2	**2**	7.60	±0.0	7.73	+0.7	7.24	+0.8	8.31	+0.6	6.75	+0.6	7.39	+0.6	—	—	—	—
3	**3**	7.58	+0.5	7.75	+0.5	—	—	—	—	7.00	+0.7	7.56	+1.0	7.04	+0.8	8.25	+0.3

[a] The numbering of aromatic protons is as follows:



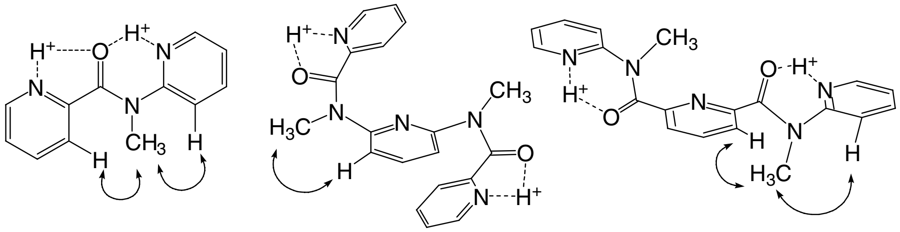
[b] Chemical shifts are recorded in ppm in the left column, and lower field shifts are recorded in the right column in ppm.

lower field shifts of H-3, H-4, and H-5 are apparently smaller in the case of **2**.[11] These differences suggest that while amide **1** changes its major conformation from cis to trans on addition of TFA, amide **2** does not switch to trans form. In the case of **2**, the protonated *C*-pyridine nitrogen atom may lie in the *syn* position with respect to the carbonyl group owing to hydrogen bond formation. This rotation results in an anisotropic effect of the neighboring aromatic group in the cis position on the H-3 proton of **2**, resulting in the absence of any lower field shift (Scheme 3).[12]



Scheme 3. Conformational change of **2** induced by addition of acid.

Conformational switching to the trans conformer was also confirmed by NOE measurements on **1**, **2**, and **3** with TFA-*d* (Scheme 4).



1 2 3

Scheme 4. NOE measurements of amides **1**–**3** with TFA-*d* in CD_3CN.

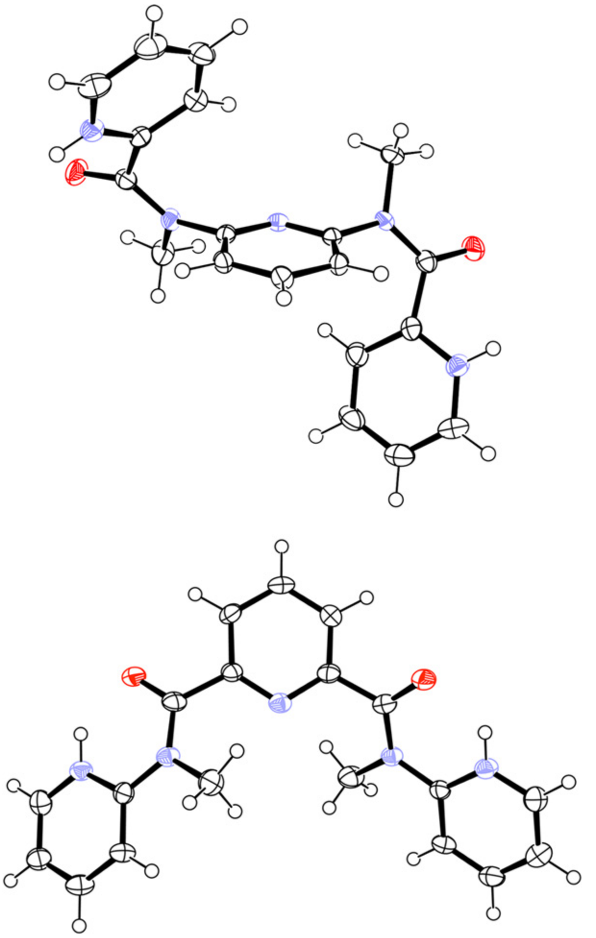


Figure 4. Crystal structures of salts **2H** (upper) and **3H** (lower). Counter anions are omitted for clarity.

Recrystallization of the protonated salts **2H** and **3H** afforded suitable crystals for X-ray crystallography. The crystal structures of perchlorates **2H** and **3H** are shown in Figure 4.[13]

Both salts consist of amide and perchloric acid in 1:2 ratio. In **2H**, the two terminal pyridine nitrogen atoms are protonated, whereas the more electron-rich central pyridine is not protonated. Both amide bonds remain in cis conformation, while the protonated pyridine nitrogen atoms lie in the *syn* direction with respect to carbonyl oxygen, in contrast to the structure of **2**. On the other hand, salt **3H**, in which the two terminal pyridine nitrogen atoms are protonated, shows trans–trans conformation. Conformational switching from cis to trans was observed in this case.

In conclusion, we investigated the acid-induced conformational switching of aromatic amides containing 2- and 2,6-disubstituted pyridine rings. Amide **1** showed protonation-dependent switching of cis–trans conformation. The pyridyl amides with three pyridine rings were protonated preferentially at terminal pyridine nitrogens, and this protonation leads to cis–trans conformational switching of **3**. These results indicate that the aromatic amides containing a sterically unhindered pyridine ring can be used as functional structural units that can work as acid-induced molecular switches.

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7. Crystallographic data were collected on a Bruker ApexII CCD detector (for compounds **1** and **3H**) or a Bruker Smart 1000 CCD detector (for compounds **2**, **3**, and **2H**). All of the crystal structures were solved by direct methods with SHELXS-97 (Sheldrick, 1997) and refined with full-matrix least-squares SHELXL-97 (Sheldrick, 1997). All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included at their calculated positions. Crystallographic data for amide **1** (recrystallized from ethyl acetate–hexane): $C_{12}H_{11}N_3O$, $M = 213.24$, monoclinic, $a = 11.1477(7)$, $b = 7.5193(5)$, $c = 13.3589(8)$ Å, $\beta = 110.2600(10)^\circ$, $V = 1050.50(11)$ Å^3, $T = 150$ K, space group $P2_1/c$ (no. 14), $Z = 4$, $D_c = 1.348$ Mg m^{-3}, $\mu(\text{Mo-K}_\alpha) = 0.090$ mm^{-1}, 5675 reflections measured, 2376 unique ($R_{\text{int}} = 0.0121$) which were used in all calculations. The final R_1 and $wR(F^2)$ were 0.0444 and 0.1111 (all data). CCDC-625148.
8. The dihedral angle of the amide plane and *C*-pyridine was defined as that of N2–C7–C8–N3 (37.0°). Similarly, the dihedral angle of the amide plane and *N*-pyridine was defined as that of C7–N2–C1–C2 (45.5°).
9. Crystallographic data for amide **2** (recrystallized from ethyl acetate–hexane): $C_{19}H_{17}N_5O_2$, $M = 347.38$, orthorhombic, $a = 8.8592(10)$ $b = 15.8880(18)$ $c = 25.207(3)$ Å, $V = 3548.1(7)$ Å^3, $T = 298$ K, space group $Pbca$ (no. 61), $Z = 8$, $D_c = 1.301$ Mg m^{-3}, $\mu(\text{Mo-K}_\alpha) = 0.088$ mm^{-1}, 19,829 reflections measured, 4068 unique ($R_{\text{int}} = 0.0446$) which were used in all calculations. The final R_1 and $wR(F^2)$ were 0.0746 and 0.1464 (all data). CCDC-625149. Crystallographic data for amide **3** (recrystallized from ethyl acetate–hexane): $C_{19}H_{17}N_5O_2$, $M = 347.38$, triclinic, $a = 9.5646(17)$, $b = 9.6316(17)$, $c = 10.7245(19)$ Å, $\alpha =$

67.646(2), $\beta = 71.556(2)$, $\gamma = 83.517(2)°$, $V = 866.8(3)$ Å^3, $T = 298$ K, space group $P - 1$ (no. 2), $Z = 2$, $D_c = 1.331$ Mg m^{-3}, μ(Mo-Kα) $= 0.090$ mm^{-1}, 5270 reflections measured, 3856 unique ($R_{\mathrm{int}} = 0.0271$) which were used in all calculations. The final R_1 and $wR(F^2)$ were 0.0687 and 0.1367 (all data). CCDC-625151.

10. A typical procedure for the preparation of salts is as follows. To a solution of amides **1**–**3** in ethyl acetate, 60% perchloric acid was added at ambient temperature to give the corresponding perchlorate of the amide. This salt was collected by filtration and recrystallized. Compound **1H**: Mp 217.0–221.0 °C (recrystallized from acetonitrile–dichloromethane, colorless rods). Anal. Calcd for $C_{12}H_{13}N_3Cl_2O_9$: C, 34.80; H, 3.16; N, 10.15. Found: C, 34.97; H, 2.92; N, 9.97. Compound **2H**: Mp 170.5–173.0 °C (recrystallized from acetonitrile–ethyl acetate, colorless prisms). Anal. Calcd for $C_{19}H_{19}N_5Cl_2O_{10}$: C, 41.62; H, 3.49; N, 12.77. Found: C, 41.59; H, 3.27; N, 12.47. Compound **3H**: Mp 196.5–198.0 °C (recrystallized from acetonitrile–ethyl acetate, colorless prisms). Anal. Calcd for $C_{19}H_{19}N_5Cl_2O_{10}$: C, 41.62; H, 3.49; N, 12.77. Found: C, 41.87; H, 3.31; N, 12.77.
11. Comparison of ^{1}H NMR spectra of **1**, **1H**, **2**, and **2H** revealed similar tendency of lower field shifts as that of **3** in Figure 3. The slight differences are as follows: **1** was less protonated by TFA in comparison to **1H**, and **2** was more protonated by TFA in comparison to **2H**. These are reasonable because one carbonyl oxygen should form two intramolecular hydrogen bonds in diprotonated **1**, and the central pyridine ring of **2** can be considered as more basic than that of **3**. In this point of view, it is also clear that the absence of lower field shift of H-3 (Table 1, entry 2) indicates the difference of conformational change of **1** and **2**.
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13. Crystallographic data for amide **2H** (recrystallized from acetonitrile–ethyl acetate): $C_{19}H_{19}Cl_2N_5O_{10}$, $M = 548.29$, orthorhombic, $a = 12.7706(17)$, $b = 28.439(4)$, $c = 12.4114(16)$ Å, $V = 4507.7(10)$ Å^3, $T = 150$ K, space group $Fdd2$ (no. 43), $Z = 8$, $D_c = 1.616$ Mg m^{-3}, μ(Mo-Kα) $= 0.357$ mm^{-1}, 6641 reflections measured, 2476 unique ($R_{\mathrm{int}} = 0.0373$) which were used in all calculations. The final R_1 and $wR(F^2)$ were 0.0627 and 0.1518, respectively (all data). CCDC-625150.Crystallographic data for amide **3H** (recrystallized from acetonitrile–ether): $C_{19}H_{19}Cl_2N_5O_{10}$, $M = 548.29$, monoclinic, $a = 16.547(6)$, $b = 16.058(5)$, $c = 23.401(4)$ Å, $\beta = 135.001(10)°$, $V = 4397(2)$ Å^3, $T = 150$ K, space group $P2_1/c$ (no. 14), $Z = 8$, $D_c = 1.657$ Mg m^{-3}, μ(Mo-Kα) $= 0.366$ mm^{-1}, 23,195 reflections measured, 9716 unique ($R_{\mathrm{int}} = 0.0478$) which were used in all calculations. The final R_1 and $wR(F^2)$ were 0.0973 and 0.1890, respectively (all data). CCDC-625152.