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Acid-induced conformational alteration of cis-preferential aromatic amides bearing *N*-methyl-*N*-(2-pyridyl) moiety

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ABSTRACT

A series of cis-preferential aromatic *N*-methyl amides was designed and synthesized, and acid-induced conformational alteration of these compounds was investigated by means of NMR measurements in solution and X-ray crystal structure analysis. Compounds with a terminal *N*-methyl-*N*-(2-pyridyl) amide unit showed acid-induced conformational change from cis to trans, while those with a terminal *N*-methyl-2-pyridinecarboxamide unit showed a change of the carbonyl orientation from *anti* to *syn* with retention of cis conformation.

1. Introduction

The amide bond is one of the most important structural units for constructing molecules or supramolecules,[1] because it opens up the possibility of cis–trans conformational change.[2] Most aromatic amides, such as benzanilide or acetanilide, favor trans structure, whereas N-methylation of these compounds affords predominantly *cis*-amides both in the crystal and in solution (Fig. 1).[3] The use of amide to control the relationship of aromatic functionalities of a molecule permits spontaneous generation of chirality[4] and the formation of macrocyclic[5] and other characteristic structures.[6] Amide structure also has potential for use in molecular switches and devices,[7] and can work as an output control system, e.g., for bioactivity,[8] or as an external-stimulus-dependent functional controller.[9] We have developed several types of aromatic amides that are responsive to redox control[10] or solvent.[11]

In this study, we focused on pyridine-containing aromatic amides, which are found in many natural and synthetic bioactive compounds. Pyridine works as a base and a ligand for metals,[12] and also as a switch for functional molecules,[13] and we have already examined pyridine-related dynamic folding and unfolding.[14]

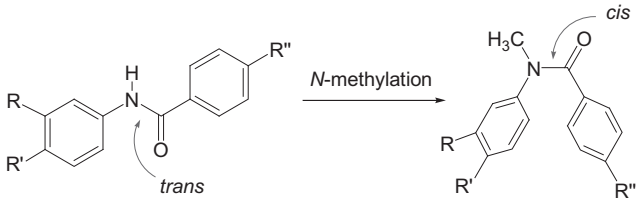

Fig. 1. cis-Favored conformation of *N*-methyl aromatic amide.

Further, we have shown that conformational alteration of *N*-methyl pyridyl amides can be induced by acid.[15] It is important to know whether this is a general phenomenon, and so in this work, we designed and synthesized a series of cis-preferential aromatic *N*-methyl amides, and systematically examined their acid-induced conformational change by means of NMR measurements in solution and X-ray crystal structure analysis.

2. Results and discussion

We synthesized aromatic amides **1**–**14** bearing 2-pyridyl and 2,6-pyridyl groups, as well as benzene and methyl derivatives for reference (Fig. 2). Each amide was prepared from the corresponding acid chloride or anhydride and amine under standard conditions. The conformations and acid-induced conformational changes of

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these aromatic *N*-methyl amides were investigated in the crystal and in solution.

Amides **2** and **3** show similar structures to that of **1**, with cis conformation and pyridine orientation toward the amide functionality. On the other hand, **4** takes a cis–trans structure about the two amide bonds, while **5** shows a cis–cis structure. The two amide carbonyl groups in **4** and **5** lie in the *anti* orientation to the pyridine nitrogen atom, because of dipole–dipole interaction, so that cis–-trans conformation of **4** is favored to avoid steric repulsion between the two terminal pyridine rings.

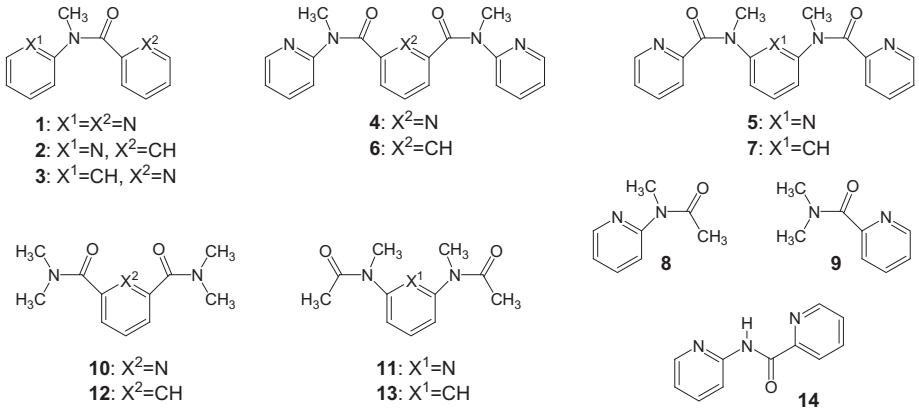


Fig. 2. Aromatic amides bearing 2-pyridyl moiety.

2.1. Conformational analyses using single-crystal X-ray crystallography

X-ray crystallographic analysis was conducted to establish the crystal structures of these amides. The crystal structures of amides **1**–**7** are illustrated in Fig. 3.

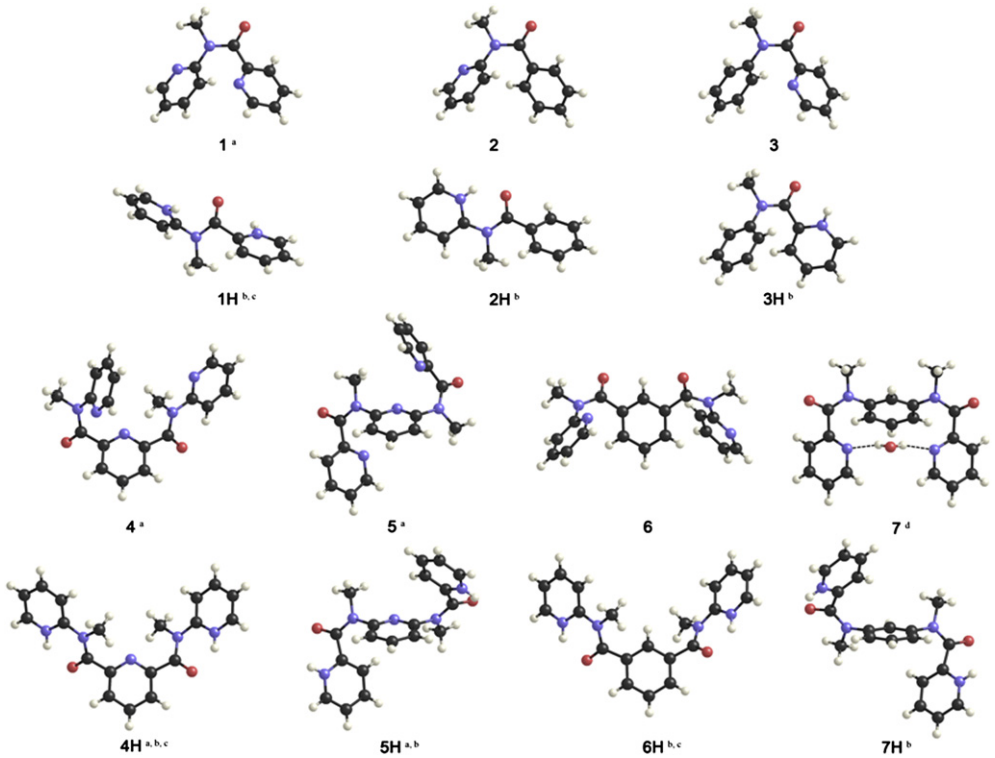


Fig. 3. Crystal structures of amides and their salts.[a] Counter anions of salts are omitted for clarity.[b]
[a]Crystallographic data of compound **1**, **4**, **5**, **4H**, and **5H** were reported in our previous paper.[15]
[b]Perchlorates **1H**, **4H**, **5H**, **6H**, and **7H** contain a 1:2 ratio of amide and $HClO_4$, whereas **2H** and **3H** contain a 1:1 ratio of amide and $HClO_4$.
[c]The crystals of **1H**, **4H**, and **6H** contain two types of conformers or disordered molecules. In the figure, representative structures are shown.
[d]The crystal of **7** includes water molecules. Hydrogen bonds between pyridyl nitrogen and water oxygen are indicated as black dotted lines.

Amide **1** shows the characteristic structural feature of aromatic *N*-methyl amides, that is, the two aromatic rings are located in a cis relationship. The nitrogen of the *C*-pyridine ring lies in the *anti* orientation to the carbonyl oxygen (Fig. 4).

Amides **6** and **7** take characteristic cis–cis structure linked by the central benzene ring. The crystal of **7** includes water molecules, and hydrogen bonding between the water molecules and pyridyl moieties results in a symmetrical conformation.

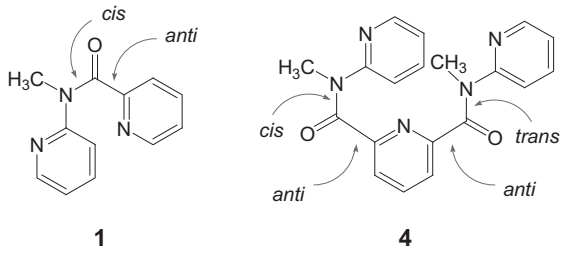


Fig. 4. Crystal structure of amides **1** and **4**.

In order to investigate the crystal structures of these amides in an acidic environment, the perchloric acid salts were prepared. Addition of perchloric acid to a solution of amide **1** in ethyl acetate gave a precipitate, which was recrystallized to afford the salt **1H**. Elemental analysis revealed that the salt **1H** contains **1** and perchloric acid in 1:2 ratio. Other amides **2**–**7** also gave the corresponding perchlorates, and recrystallization afforded **2H**–**7H**. Their crystal structures are also shown in Fig. 3.

Unfortunately, well-ordered crystals of **1H** and **2H** have not been obtained to date, but the data presented here suggest that conformational transformation does occur. That is, the addition of acid to **1** caused both pyridine rings to become protonated, leading to conformational change from cis to trans because of *N*-pyridine protonation, and from *anti* to *syn* because of *C*-pyridine protonation (Fig. 5).

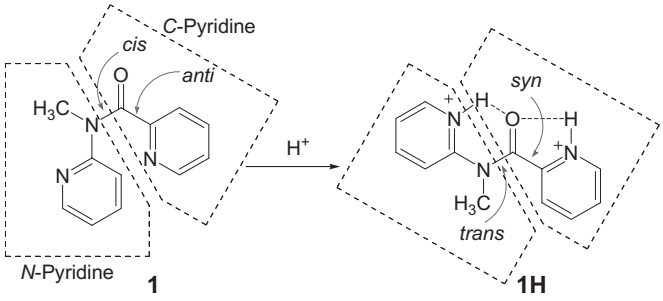


Fig. 5. Conformational transformation of amide **1**.

The results for **2H** support the idea that *N*-pyridine protonation causes cis–trans transformation, and those for **3H** confirm that *C*-pyridine protonation causes *anti*–*syn* transition.

The crystal structures of **4H** and **5H** indicate that protonation occurs at the two terminal pyridines prior to the central pyridine, even though the central pyridine of **5** is electron-rich. These protonations influence the conformation in the same way as in **1**–**3**, that is, **4H** takes trans–trans structure, while **5H** takes cis–cis and *syn* structure. Similar changes are seen in the structures of **6H** and **7H**.

2.2. Conformational analyses in solution using NMR study

The structures of the amides in solution were analyzed by means of ^{1}H NMR measurement. While the spectrum of **1** at room temperature shows a single set of signals because of fast equilibrium between cis and trans conformations, lowering the temperature caused peak broadening, followed by the appearance of two sets of signals (Fig. 6). Arrows show signals of the minor conformer observed at −90 °C.

The aromatic proton signals of the cis conformer were shifted upfield from those of the trans conformer because of the shielding effect of the aromatic rings. Comparison of the spectrum at −90 °C with the spectrum of *N*–H amide **14**, which exists in trans conformation,[16] indicates that the *N*-methyl pyridyl amide **1** exists mainly

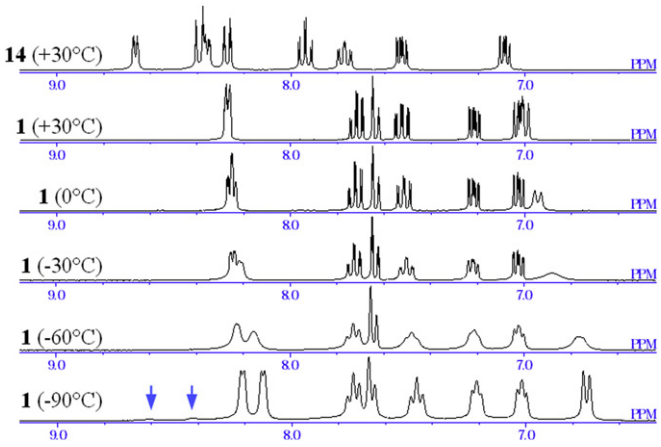


Fig. 6. ^{1}H NMR spectra of aromatic protons of amides **1** and **14** at various temperatures in CD_2Cl_2.

in cis conformation, like many other aromatic *N*-methyl amides (Fig. 7).[3]

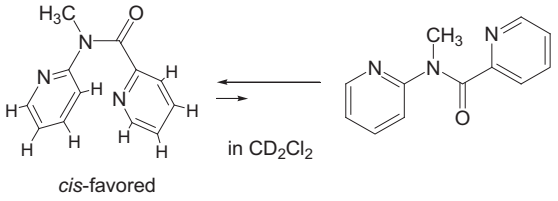


Fig. 7. Conformational preference of amide **1** in solution.

In order to examine the acid-induced structures in solution, the ^{1}H NMR spectra of **4** in the presence of acid were measured.[15]

Fig. 8 shows the spectra of **4**, **4H**, **4** with excess TFA-*d*, and **4** with excess $DClO_4$. Although these conformational studies are discussed about solution in dichloromethane, the salts of **4** with $DClO_4$ was not soluble enough in CD_2Cl_2. In order to compare the effects of acids, the spectra in Fig. 8 were measured in CD_3CN. Protonation of the amide **4** caused a lower-field shift of aromatic proton signals, and addition of perchloric acid-induced greater shifts than did TFA. Comparison of spectrum b with c indicates that excess TFA induces conversion from **4** to **4H**, that is, excess TFA protonates the terminal pyridines of **4**, while excess perchloric acid caused further protonation. These results suggested that it would be appropriate to carry out the ^{1}H NMR study using CD_2Cl_2 as the solvent, and TFA-*d* as the acid additive.

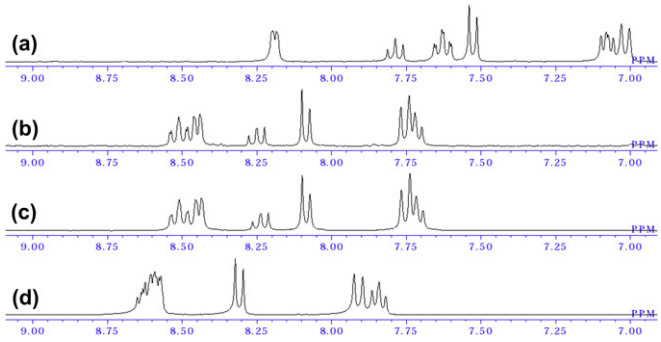


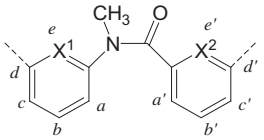
Fig. 8. ^{1}H NMR spectra of (a) amide **4**; (b) **4H**; (c) **4** with TFA-*d* (150 equiv); (d) **4** with $DClO_4$ (30 equiv) in CD_3CN.

The chemical shifts of aromatic protons of amides **1**–**13** and their change upon addition of TFA-*d* are summarized in Table 1. It is

Table 1
Chemical shifts of aromatic protons and lower-field shifts caused by the addition of TFA-*d*[a]

	H-*a*		H-*b*		H-*c*		H-*d*		H-*e*		H-*a*′		H-*b*′		H-*c*′		H-*d*′		H-*e*′	
1[b]	6.98	+0.9	7.52	+1.2	7.01	+0.9	8.27	+0.4			7.63	+0.7	7.72	+1.1	7.21	+1.1	8.27	+0.8		
2	6.86	+0.9	7.44	+1.2	7.02	+0.8	8.38	+0.1			7.29	+0.4	7.21	+0.4	7.32	+0.4				
3	7.08	+0.2	7.20	+0.3	7.13	+0.4					7.41	−0.1	7.62	+0.7	7.16	+0.9	8.33	+0.6		
4[b]	7.00	+0.7	7.56	+1.0	7.04	+0.8	8.25	+0.3			7.58	+0.5	7.75	+0.5						
5[b]	6.75	+0.6	7.39	+0.6							7.60	0	7.73	+0.7	7.24	+0.8	8.31	+0.6		
6	6.79	+1.0	7.47	+1.2	7.03	+0.8	8.37	+0.2			7.20	+0.7	7.05	+0.8					7.35	+0.7
7	6.84	+0.6	7.02	+0.7					6.81	+0.6	7.37	—[c]	7.62	—[c]	7.12	+1.0	8.31	+0.6		
8	7.29	+0.3	7.72	+0.8	7.15	+0.6	8.44	0												
9											7.54	+0.8	7.77	+1.0	7.31	+1.0	8.55	+0.5		
10											7.61	+0.1	7.89	+0.2						
11	7.24	0	7.76	+0.6																
12											7.40	+0.3	7.40	+0.3					7.37	+0.2
13	7.17	+0.3	7.44	+0.3					7.07	+0.2										

The aromatic proton is marked as follows:



[a] These values are recorded in ppm. In every case, 3–5 mg of amide in 0.5 mL of CD_2Cl_2 was used, and 150 equiv of TFA-*d* was added.
[b] Compounds **1**, **4** and **5** were reported in our previous paper.[15]
[c] The change could not be measured because of peak broadening.

natural that these *N*-methyl amides have broadly similar chemical shifts to each other, but some important differences were observed. To analyze the conformational change of the basic structure **1** in terms of changes of the *N*-pyridine unit and *C*-pyridine unit, these chemical shifts and changes were considered in detail.

Chemical shifts and shift changes of H-*a*, *b*, *c* and H-*d* of **2** are in good accordance with those of **1**, so **2** can be considered to be representative of the *N*-pyridine unit of **1**. Chemical shifts of **8**, an *N*-methyl amide without the *C*-aromatic ring, and **2** show clear differences at H-*a*, 7.29 and 6.86, indicating that the benzoyl group of **2** causes a high-field shift in **2**. The protonation of **8** changes the chemical shift of H-*a* by +0.3, while the change in **2** was +0.9. This large lower-field shift indicates disappearance of high-field shift, that is, it reflects conformational change from cis to trans (Fig. 9). The resulting coordination mode is similar to chelation of *N*–H type *trans* amide.[17] However, this type of hydrogen bonding in these *N*-methyl amides is different from the well-known interaction in *N*–H pyridyl oligo amides,[13a,18] because our amides lack amide hydrogen, and originally favor cis conformation.

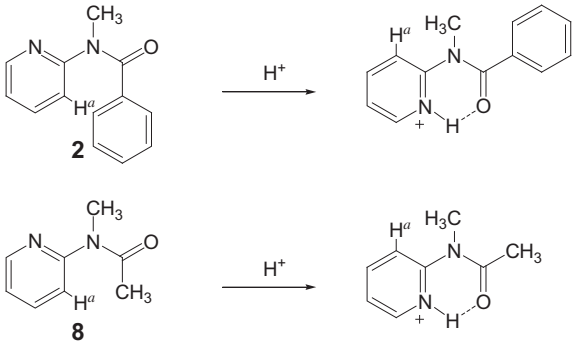


Fig. 9. Conformational change of amides **2** and **8**.

Similar effects were observed in the *N*-pyridine unit of **4** and **6**, suggesting that these amides **4** and **6**, with two *N*-methyl amide functionalities, change their conformation from cis–cis to trans–trans upon addition of acid (Fig. 10).

On the other hand, the central parts of **4** and **10** have similar chemical shift values. This shows that the central pyridine ring of **4** does not experience high-field shift from the terminal aromatic group, that is, **4** takes cis conformation along with *anti*-preferential carbonyl orientation (Fig. 11). Isophthaloyl amide **6** has smaller chemical shifts of H-*a*′ and H-*b*′ than **12**. In this amide **6**, the carbonyl orientation is less strained around the central benzene ring compared to pyridine.

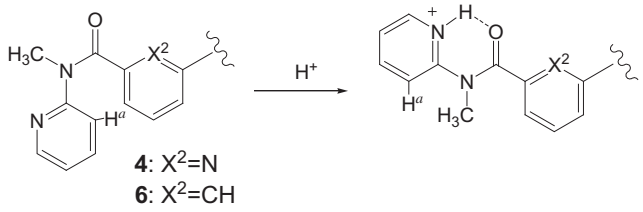


Fig. 10. Conformational change of amides **4** and **6**.

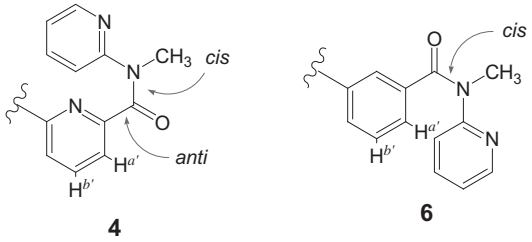


Fig. 11. Conformations of **4** and **6**.

These similarities in chemical shifts and conformational changes show a general tendency that a terminal *N*-pyridine unit of *N*-methylamide works as a cis–trans conformational switching unit upon addition of acid (Fig. 12).

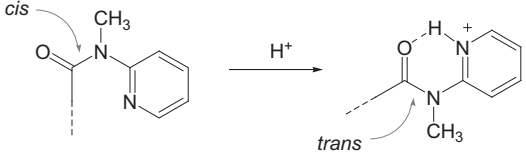


Fig. 12. Conformational change of *N*-pyridine unit.

The effect of carbonyl orientation can be seen more clearly in the *C*-pyridine terminal unit. Chemical shifts of the *C*-pyridine unit in **3** are in good accordance with those of **1**, whereas the chemical shift changes are not. The important structural difference between **3** and **1** is the *N*-aromatic part, that is, **3** cannot be conformationally switched because it lacks nitrogen on the *N*-aromatic unit. Comparison with **9** shows a characteristic change in H-*a*′, that is, although the pyridine ring is considered to be protonated, the H-*a*′ proton on the pyridine ring of **3** shows a higher-field shift. This clearly indicates conformational change from *anti* to *syn* orientation around the carbonyl–pyridine bond of **3** (Fig. 13).

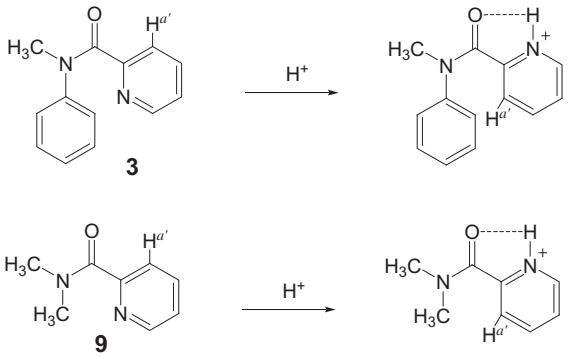


Fig. 13. Conformational change of amides **3** and **9**.

The behavior of *N*-methyl amides with three aromatic rings is consistent with the general trend of these conformational changes. Chemical shift comparison of H-*a* in **5** and H-*a* in **11** indicates cis–cis-favored conformation of **5**, based on the high-field shift caused by the terminal pyridine rings. Similar findings for H-*a* in **7** and **13** can also be considered as evidence for cis–cis conformation. Comparison of the *C*-pyridine unit of **5** and **7** with that of **3** shows a similar structural trend. In the case of H-*a*′ of **5**, the lower-field shift upon addition of acid is absent. This terminal 2-pyridine carboxylic unit should behave similarly, that is, its orientation should be changed from *anti* to *syn*, with unchanged cis conformation (Fig. 14).

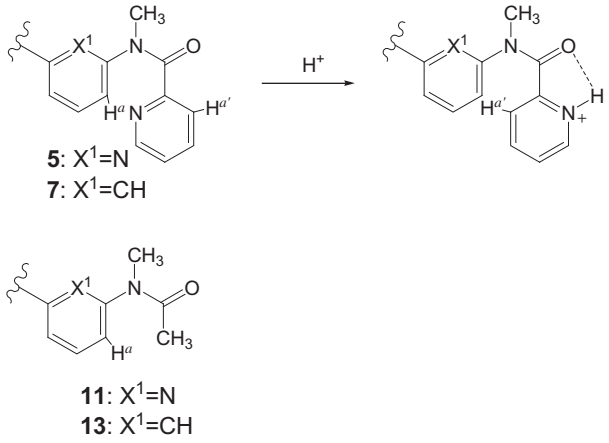


Fig. 14. Conformations of amides **5**, **7**, **11**, and **13**.

Unfortunately, amide **7** with similar terminal structure showed marked peak broadening upon addition of acid, but the chemical shifts and changes of H-*c*′ and H-*d*′ signals suggest similar conformational behavior.

Overall, these results indicate that the terminal *C*-pyridine of *N*-methyl amide works as an acid-induced *anti–syn* rotation unit, but cis conformation of the *N*-methyl amide moiety is retained if TFA is used as the inducing acid (Fig. 15).

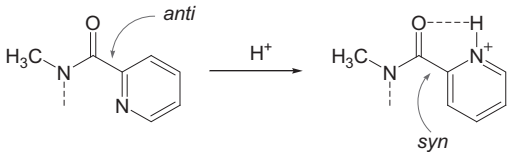


Fig. 15. Conformational change of *C*-pyridine unit.

3. Conclusion

N-Methyl aromatic amides bearing a 2-pyridyl group show conformational switching upon acid addition. The terminal *C*-(2-pyridyl) unit undergoes a change in carbonyl orientation, and the terminal *N*-(2-pyridyl) unit shows a change from cis to trans conformation. These structural features and alterations appear to be general for *N*-methyl pyridyl amides. Thus, the conformation of the terminal amide-(2-pyridyl) moiety can be switched by the use of an appropriate acid.

4. Experimental section

4.1. General

Melting points were determined by using a Yanaco melting point apparatus MP-S3 and are uncorrected. Elemental analyses were carried out on Thermo Finnigan Flash EA1112, and antipyrine was used as a standard. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL AL-300, and chemical shifts are expressed in parts per million relative to tetramethylsilane. IR spectra were recorded on a Shimadzu FTIR-8200A. Mass spectra were measured on a JEOL MS700 or HX110. Silica gel [silica gel 40–50 μm neutral (Kanto Chemical Co., Inc.)] was used for all chromatographic procedures.

*4.1.1. N-Methyl-N-(2-pyridyl)-2-pyridinecarboxamide (**1**).* To a mixture of picolinic acid (617 mg, 5.00 mmol), triethylamine (1.37 mL, 10.0 mmol), and THF (15 mL), ethyl chloroformate (0.48 mL, 5.00 mmol) was added. The mixture was stirred at ambient temperature for 1.5 h, then 2-(methylamino)pyridine (0.52 mL, 5.00 mmol) was added and stirring was continued for 1 h. The solvent was evaporated in vacuo to give the crude product, which was purified by flash chromatography (ether) to give **1** (594 mg, 56%) as pale brown prisms. Mp 77.5 °C (AcOEt/hexane); [Anal. Found: C, 67.51; H, 5.22; N, 19.52. $C_{12}H_{11}N_3O$ requires C, 67.59; H, 5.20; N, 19.71%]; ν_{max} (KBr) 1655, 1587, 1568 cm^{-1}; ^{1}H NMR (300 MHz, CD_2C1_2) δ 8.27 (2H, m), 7.72 (1H, dt, *J* 1.7, 7.9 Hz), 7.63 (1H, dt, *J* 7.9, 1.3 Hz), 7.52 (1H, dt, *J* 2.0, 8.1 Hz), 7.21 (1H, ddd, *J* 7.5, 4.8, 1.5 Hz), 7.01 (1H, ddd, *J* 7.5, 4.9, 1.1 Hz), 6.98 (1H, br d, *J* 8.2 Hz), 3.54 (3H, s); ^{13}C NMR (75 MHz, $CDC1_3$) δ 169.1, 156.6, 154.0, 148.2, 148.0, 137.4, 136.6, 124.3, 124.0, 120.8, 120.0, 35.9; *m*/*z* (EI) 213.

*4.1.2. N-Methyl-N-(2-pyridyl)benzamide (**2**).* A mixture of 2-(methylamino)pyridine (1.0 mL, 9.73 mmol), pyridine (20 mL), and benzoyl chloride (2.2 mL, 19.5 mmol) was stirred at ambient temperature for 17 h. After the addition of water, the mixture was poured into satd $NaHCO_3$ solution, and extracted with CH_2Cl_2. The organic solution was washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give the crude product, which was purified by flash chromatography (AcOEt/hexane 1:2) to afford **2** (1.92 g, 93%) as a colorless solid. Mp 41.5–43.0 °C (hexane); [Anal. Found: C, 73.38; H, 5.72; N, 13.17. $C_{13}H_{12}N_2O$ requires C, 73.57; H, 5.70; N, 13.20%]; ν_{max} (KBr) 1649, 1585, 1359 cm^{-1}; ^{1}H NMR (300 MHz, CD_2C1_2) δ 8.38 (1H, ddd, *J* 0.9, 2.0, 4.9 Hz), 7.44 (1H, dt, *J* 2.0, 7.5 Hz), 7.32 (1H, m), 7.29 (2H, m), 7.21 (2H, m), 7.02 (1H, ddd, *J* 1.0, 5.0, 7.5), 6.86 (1H, dt, *J* 8.0, 0.9 Hz), 3.51 (3H, s); ^{13}C NMR (75 MHz, $CDC1_3$)

δ 170.9, 156.7, 148.7, 137.3, 136.0, 130.1, 128.5, 128.0, 121.5, 120.8, 35.9; *m*/*z* (EI) 212.

*4.1.3. N-Methyl-N-phenyl-2-pyridinecarboxamide (**3**).* To a mixture of picolinic acid (2.27 g, 18.4 mmol), triethylamine (5.12 mL, 36.8 mmol), and THF (60 mL), ethyl chloroformate (1.76 mL, 18.4 mmol) was added. The mixture was stirred at ambient temperature for 2 h, then *N*-methylaniline (2.0 mL, 18.4 mmol) was added and stirring was continued for 22 h. The solvent was evaporated in vacuo to give the crude product, which was purified by flash chromatography (AcOEt/hexane 2:1) to afford **3** (1.75 g, 45%) as colorless needles. Mp 47.0–50.5 °C (hexane); [Anal. Found: C, 73.60; H, 5.64; N, 12.97. $C_{13}H_{12}N_2O$ requires C, 73.57; H, 5.70; N, 13.20%]; ν_{max} (KBr) 1654, 1583, 1380 cm^{-1}; ^1H NMR (300 MHz, CD_2C1_2) δ 8.33 (1H, br s), 7.62 (1H, br t, *J* 7.2 Hz), 7.41 (1H, br d, *J* 7.5 Hz), 7.20 (1H, m), 7.16 (1H, m), 7.13 (1H, m), 7.08 (1H, m), 3.45 (3H, s); ^{13}C NMR (75 MHz, $CDC1_3$) δ 168.7, 154.3, 148.4, 144.3, 136.1, 128.9, 126.6, 126.4, 123.8, 123.6, 38.0; *m*/*z* (EI) 212.

*4.1.4. N,N′-Dimethyl-N,N′-di(2-pyridyl)-2,6-pyridinedicarboxamide (**4**).* Using the same method as above, **4** was obtained from pyridine-2,6-carbonyldichloride (1.0 g, 4.9 mmol), triethylamine (2.7 mL, 19.6 mmol), and 2-(methylamino)pyridine (1.10 mL, 10.8 mmol). Chromatography (AcOEt) afforded a colorless solid (813 mg, 48%). Mp 113 °C (AcOEt/hexane); [Anal. Found: C, 65.83; H, 4.86; N, 20.23. $C_{19}H_{17}N_5O_2$ requires C, 65.69; H, 4.93; N, 20.16%]; ν_{max} (KBr) 1666, 1645, 1585, 1483, 1435, 1420, 1377, 1296 cm^{-1}; ^1H NMR (300 MHz, CD_2C1_2) δ 8.25 (2H, ddd, *J* 5.0, 2.0, 0.9 Hz), 7.75 (1H, dd, *J* 8.3, 7.2 Hz), 7.58 (2H, d, *J* 7.3 Hz), 7.56 (2H, dt, *J* 2.0, 7.3 Hz), 7.04 (2H, ddd, *J* 7.5, 5.0, 1.1 Hz), 7.00 (2H, br d, *J* 7.9 Hz), 3.34 (6H, s); ^{13}C NMR (75 MHz, $CDC1_3$) δ 168.0, 156.0, 152.2, 148.0, 137.5, 137.4, 124.8, 120.9, 120.1, 35.8; *m*/*z* (EI) 347.

*4.1.5. 2,6-Bis(N-methyl-2-pyridinecarboxamido)pyridine (**5**).* Using the same method as above, **5** was obtained from picolinic acid (1.0 g, 8.13 mmol), thionyl chloride (4.0 mL, 56 mmol), triethylamine (1.70 mL, 12.2 mmol), and **15** (557 mg, 4.07 mmol). Chromatography (AcOEt) afforded a colorless solid (232 mg, 17%). Mp 140.0–140.5 °C (AcOEt/hexane); [Anal. Found: C, 66.07; H, 4.94; N, 20.19. $C_{19}H_{17}N_5O_2$ requires C, 65.69; H, 4.93; N, 20.16%]; ν_{max} (KBr) 1672, 1649, 1585, 1570 cm^{-1}; ^1H NMR (300 MHz, CD_2C1_2) δ 8.31 (2H, dd, *J* 5.9, 1.1 Hz), 7.73 (2H, dt, *J* 1.7, 7.9 Hz), 7.60 (2H, dt, *J* 7.9, 1.3 Hz), 7.39 (1H, t, *J* 7.9 Hz), 7.24 (2H, m), 6.75 (2H, d, *J* 7.9 Hz), 3.23 (6H, s); ^{13}C NMR (75 MHz, $CDC1_3$) δ 169.2, 154.7, 154.1, 148.1, 138.8, 136.7, 124.5, 124.0, 115.7, 35.3; *m*/*z* (EI) 347.

*4.1.6. N,N′-Dimethyl-N,N′-di(2-pyridyl)-1,3-benzenedicarboxamide (**6**).* Using the same method as above, **6** was obtained from isophthalic acid (600 mg, 3.61 mmol), thionyl chloride (5.0 mL, 70 mmol), triethylamine (1.97 mL, 14.4 mmol), and 2-(methylamino)pyridine (0.74 mL, 7.22 mmol). Chromatography (CH_2Cl_2/AcOEt 1:1) afforded a colorless solid (673 mg, 54%). Mp 149.5–151.0 °C (AcOEt/hexane); [Anal. Found: C, 69.25; H, 5.18; N, 16.02. $C_{20}H_{18}N_4O_2$ requires C, 69.35; H, 5.24; N, 16.17%]; ν_{max} (KBr) 1645, 1585 cm^{-1}; ^1H NMR (300 MHz, CD_2C1_2) δ 8.37 (2H, ddd, *J* 0.8, 2.0, 4.9, Hz), 7.47 (2H, m), 7.35 (1H, m), 7.20 (2H, dd, *J* 1.5, 7.3 Hz), 7.05 (1H, m), 7.03 (2H, m), 6.79 (2H, d, *J* 8.1 Hz), 3.43 (6H, s); ^{13}C NMR (75 MHz, $CDC1_3$) δ 169.9, 156.3, 148.8, 137.4, 136.2, 129.9, 128.6, 127.7, 121.3, 121.0, 35.9; *m*/*z* (EI) 346.

*4.1.7. 1,3-Bis(N-methyl-2-pyridinecarboxamido)benzene (**7**).* To a solution of picolinic acid (543 mg, 4.41 mmol) in tetrahydrofuran, triethylamine (0.90 mL, 6.60 mmol) and ethyl chloroformate (0.42 mL, 4.41 mmol) were added, and the mixture was stirred at ambient temperature for 1 h. A solution of **16** (300 mg, 2.20 mmol) in tetrahydrofuran was added and stirring was continued for 13 h. The mixture was filtered and the filtrate was evaporated in vacuo to give the crude product, which was purified by flash chromatography (AcOEt) to afford **7** (351 mg, 46%) as a colorless solid. Recrystallization from CH_2Cl_2/AcOEt gave colorless prisms; mp 165.0–166.0 °C; [Anal. Found: C, 69.41; H, 5.24; N, 15.98. $C_{20}H_{18}N_4O_2$ requires C, 69.35; H, 5.24; N, 16.17%]; ν_{max} (KBr) 1649, 1598, 1589, 1568 cm^{-1}; ^1H NMR (300 MHz, CD_2C1_2) δ 8.31 (2H, m), 7.62 (2H, dt, *J* 1.7, 7.7 Hz), 7.37 (2H, m), 7.12 (2H, ddd, *J* 1.1, 4.9, 7.7 Hz), 7.02 (1H, m), 6.84–6.81 (3H, m), 3.29 (6H, s); ^{13}C NMR (75 MHz, $CDC1_3$) δ 168.4, 153.9, 148.3, 144.8, 136.4, 129.2, 124.7, 124.5, 124.0, 123.6, 37.9; *m*/*z* (EI) 346.

*4.1.8. N-Methyl-N-(2-pyridyl)acetamide (**8**).* A mixture of 2-(methylamino)pyridine (857 mg, 7.92 mmol) and acetic anhydride (4.23 g, 41.4 mmol) was heated at 70 °C for 4 h. After removal of the solvent under reduced pressure, chromatography (AcOEt) of the residue gave **8** as a pale brown oil in quantitative yield. ν_{max} (KBr) 1663, 1587, 1379 cm^{-1}; ^1H NMR (300 MHz, CD_2C1_2) δ 8.44 (1H, ddd, *J* 0.8, 2.0, 4.8 Hz), 7.72 (1H, dd, *J* 2.0, 7.5 Hz), 7.29 (1H, d, *J* 8.1 Hz), 7.15 (1H, ddd, *J* 1.0, 4.8, 7.3 Hz), 3.31 (3H, s), 2.03 (3H, s); ^{13}C NMR (75 MHz, $CDC1_3$, 55 °C) δ 170.7, 156.5, 148.9, 138.0, 121.5, 120.3, 35.4, 23.0; *m*/*z* (EI) 150; HRMS (EI): M^+, found 150.0807. $C_8H_{10}N_2O$ requires 150.0794.

*4.1.9. N,N-Dimethyl-2-pyridinecarboxamide (**9**).* A mixture of picolinic acid (322 mg, 2.62 mmol), thionyl chloride (5.0 g, 42 mmol) and a small amount of DMF was heated at reflux for 3 h, then volatile materials were removed under reduced pressure. The resulting crude acid chloride was dissolved in 5 mL of THF, and added slowly to dimethylamine (2.0 g, 44 mmol) at −78 °C, followed by stirring in a sealed tube at ambient temperature for 18 h. The resulting mixture was poured into satd $NaHCO_3$ solution, and extracted with CH_2Cl_2 The organic solution was washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give the crude product, which was purified by flash chromatography (AcOEt) to afford **9** (328 mg, 84%) as a pale yellow oil. ν_{max} (KBr) 1637, 1538, 1398 cm^{-1}; ^1H NMR (300 MHz, CD_2C1_2) δ 8.55 (1H, br s), 7.77 (1H, dt, *J* 1.7, 7.7 Hz), 7.54 (1H, d, *J* 7.7 Hz), 7.31 (1H, ddd, *J* 0.8, 5.0, 7.7 Hz), 3.03 (6H, s); ^{13}C NMR (75 MHz, $CDC1_3$) δ 168.8, 154.4, 148.1, 136.8, 124.2, 123.3, 38.8, 35.5; *m*/*z* (EI) 150; HRMS (EI): M^+, found 150.0784. $C_8H_{10}N_2O$ requires 150.0794.

*4.1.10. N,N,N′,N′-Tetramethyl-2,6-pyridinedicarboxamide (**10**).* Using the same method as above, **10** was obtained from 2,6-pyridinedicarbonyl dichloride (529 mg, 2.59 mmol) and dimethylamine (2.75 g, 61 mmol). Colorless plates (406 mg, 71%). Mp 144.5–148.0 °C (AcOEt); [Anal. Found: C, 59.62; H, 6.84; N, 18.87. $C_{11}H_{15}N_3O_2$ requires C, 59.71; H, 6.83; N, 18.99%]; ν_{max} (KBr) 1635, 1508, 1421 cm^{-1}; ^1H NMR (300 MHz, CD_2C1_2) δ 7.89 (1H, t, *J* 7.7 Hz), 7.61 (2H, d, *J* 7.7 Hz), 3.09 (6H, s), 3.02 (6H, s); ^{13}C NMR (75 MHz, $CDC1_3$,) δ 168.2, 153.1, 138.0, 123.9, 39.0, 35.6; *m*/*z* (EI) 221.

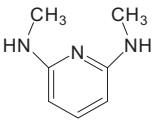
*4.1.11. 2,6-Bis(N-methylacetamido)pyridine (**11**).* Using the same method as above, **11** was obtained from **15** (100 mg, 0.73 mmol) and acetic anhydride (2 mL, 21 mmol). Pale brown oil (90 mg, 55%). ν_{max} (KBr) 1670, 1522, 1375 cm^{-1}; ^1H NMR (300 MHz, CD_2C1_2) δ 7.76 (1H, t, *J* 7.9 Hz), 7.24 (2H, d, *J* 7.7 Hz), 3.34 (6H, s), 2.12 (6H, s); ^{13}C NMR (75 MHz, $CDC1_3$) δ 170.7, 154.6, 139.7, 117.0, 35.3, 23.4; *m*/*z* (EI) 221; HRMS (EI): M^+, found 221.1167. $C_{11}H_{15}N_3O_2$ requires 221.1164.

*4.1.12. N,N,N′,N′-Tetramethyl-1,3-benzenedicarboxamide (**12**).* Using the same method as above, **12** was obtained from isophthaloyl chloride (520 mg, 2.56 mmol) and dimethylamine (10 mL, 153 mmol). Pale yellow solid (442 mg, 78%). Mp 125.0–129.0 °C (AcOEt/hexane); [Anal. Found: C, 65.54; H, 7.38; N, 12.47. $C_{12}H_{16}N_2O_2$ requires C, 65.43; H, 7.32; N, 12.72%]; ν_{max} (KBr) 1631,

1502, 1398 cm^{-1}; ^1H NMR (300 MHz, CD_2C1_2) δ 7.40 (3H, m), 7.37 (1H, m), 2.96 (12H, s); ^{13}C NMR (75 MHz, $CDC1_3$) δ 170.7, 136.5, 128.5, 128.1, 125.6, 39.5, 35.3; *m*/*z* (EI) 220.

*4.1.13. 1,3-Bis(N-methylacetamido)benzene (**13**).* Using the same method as above, **13** was obtained from **16** (100 mg, 0.73 mmol) and acetic anhydride (2 mL, 21 mmol). Colorless solid (151 mg, 94%). Mp 153.0–157.5.0 °C (toluene); [Anal. Found: C, 65.33; H, 7.46; N, 12.53. $C_{12}H_{16}N_2O_2$ requires C, 65.43; H, 7.32; N, 12.72%]; ν_{max} (KBr) 1650, 1494, 1350 cm^{-1}; ^1H NMR (300 MHz, CD_2C1_2) δ 7.44 (1H, t, *J* 7.9 Hz), 7.17 (2H, d, *J* 8.3 Hz), 7.07 (1H, t, *J* 1.8 Hz), 3.23 (6H, s), 1.86 (6H, s); ^{13}C NMR (75 MHz, $CDC1_3$, 55 °C) δ 169.9, 145.9, 130.7, 125.9, 125.8, 37.3, 22.3; *m*/*z* (EI) 220.

*4.1.14. N-(2-Pyridyl)-2-pyridinecarboxamide (**14**).* Using the same method as above, **14** was obtained from picolinic acid (394 mg, 3.20 mmol), thionyl chloride (6.36 g, 54 mmol), 2-aminopyridine (251 mg, 2.67 mmol). Chromatography (AcOEt/hexane 1:4 then 1:2) afforded **14** as colorless needles (232 mg, 42%). Mp 118.5–120.5 °C (AcOEt/hexane); [Anal. Found: C, 66.23; H, 4.51; N, 20.98. $C_{11}H_9N_3O$ requires C, 66.32; H, 4.55; N, 21.09%]; ν_{max} (KBr) 3348, 1692, 1304 cm^{-1}; ^1H NMR (300 MHz, CD_2C1_2) δ 10.45 (1H, br s), 8.66 (1H, ddd, *J* 4.8, 1.8, 1.1 Hz), 8.39 (1H, dt, *J* 8.4, 1.1 Hz), 8.36 (1H, ddd, *J* 5.9, 1.8, 1.1 Hz), 8.27 (1H, dt, *J* 7.7, 1.1 Hz), 7.94 (1H, dt, *J* 1.8, 7.7 Hz), 7.77 (1H, dt, *J* 1.5, 7.9 Hz), 7.53 (1H, ddd, *J* 7.3, 4.8, 1.1 Hz), 7.09 (1H, ddd, *J* 7.3, 4.8, 1.1 Hz); ^{13}C NMR (75 MHz, $CDC1_3$) δ 162.6, 151.2, 149.3, 148.2 (overlapped), 138.2, 137.5, 126.7, 122.4, 119.8, 113.9; *m*/*z* (EI) 199.



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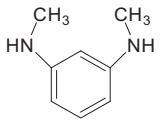

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*4.1.15. N,N′-Dimethyl-2,6-diaminopyridine (**15**).* A mixture of 2,6-dibromopyridine (25.0 g, 105.5 mmol) and 40% methylamine solution in water (100 mL) was heated in a sealed tube at 190 °C for 17 h. After cooling, the solution was filtered and the filtrate was diluted with water (400 mL), then extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give the crude product, which was purified by flash chromatography (CH_2Cl_2 then AcOEt/hexane 1:1) to afford **15** (11.76 g, 81%) as a pale brown solid. This was used without further purification for syntheses. Mp 70.5 °C (AcOEt/hexane); ^1H NMR (300 MHz $CDC1_3$) δ 7.28 (1H, t, *J* 7.9 Hz), 5.73 (2H, d, *J* 7.9 Hz), 4.26 (2H, s), 2.84 (6H, d, *J* 5.1 Hz); ^{13}C NMR (75 MHz, $CDC1_3$) δ 159.1, 139.0, 93.9, 29.1; *m*/*z* (EI) 137; HRMS (EI): M^+, found 137.0945. $C_7H_{11}N_3$ requires 137.0953.

4.1.16. 1,3-Bis(formamido)benzene. A mixture of formic acid (80 mL, 2.1 mol) and acetic anhydride (170 mL, 1.8 mol) was heated at 70 °C for 2 h, then cooled to −10 °C. A solution of *m*-phenylenediamine (25 g, 0.23 mol) in THF (150 mL) was added dropwise to the above solution over a period of 4 h at −10 °C with stirring. After a further 15 min, the product was collected by filtration (17.9 g, 47%). Colorless powder. Mp 156.5–159.0 °C; [Anal. Found: C, 58.36; H, 4.77; N, 17.11. $C_8H_8N_2O_2$ requires C, 58.53; H, 4.91; N, 17.06%]; ^1H NMR (300 MHz, DMSO-d_6, 150 °C) δ 9.59 (2H, s), 8.38 (2H, s), 7.59 (1H, s), 7.21 (3H, m); *m*/*z* (EI) 164.

*4.1.17. N,N′-Dimethyl-1,3-diaminobenzene (**16**).* To a solution of **16** (1.5 g, 9.15 mmol) in THF, borane dimethyl sulfide complex (4.34 mL, 45.8 mmol) was added at 0 °C, followed by stirring at the same temperature for 0.5 h, then for 1.5 h at ambient temperature. After addition of methanol with cooling, 10% HCl was added, and the mixture was basified with 10% NaOH aq, then extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give the crude product, which was purified by flash chromatography (CH_2Cl_2/AcOEt 20:1) to afford **16** (924 mg, 74%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 6.99 (1H, t, *J* 8.1 Hz), 6.02 (2H, dd, *J* 2.2, 8.1 Hz) 5.88 (1H, t, *J* 2.2 Hz), 2.80 (6H, s); *m*/*z* (EI) 136; HRMS (EI): M^+, found 136.1006. $C_8H_{12}N_2$ requires 136.1000.

4.2. General procedure for perchlorate preparation

To a solution of amide **1**–**7** in ethyl acetate, 60% perchloric acid was added at ambient temperature to give the corresponding perchlorate. The salt was collected by filtration and recrystallized.

Perchlorate **1H** (**1**+2$HClO_4$): Mp 217.0–221.0 °C (recryst from CH_3CN/CH_2Cl_2, colorless rods). Anal. Found: C, 34.97; H, 2.92; N, 9.97. $C_{12}H_{13}N_3Cl_2O_9$ requires C, 34.80; H, 3.16; N, 10.15%.

Perchlorate **2H** (**2**+$HClO_4$): Mp 128.0–129.0 °C (recryst from AcOEt/hexane, powder). Anal. Found: C, 49.84; H, 3.86; N, 8.63. $C_{13}H_{13}N_2ClO_5$ requires C, 49.93; H, 4.19; N, 8.96%.

Perchlorate **3H** (**3**+$HClO_4$): Mp 219.0–221.0 °C (recryst from AcOEt, colorless powder). Anal. Found: C, 49.68; H, 3.96; N, 8.75. $C_{13}H_{13}N_2ClO_5$ requires C, 49.93; H, 4.19; N, 8.96%.

Perchlorate **4H** (**4**+2$HClO_4$): Mp 196.5–198.0 °C (recryst from CH_3CN/AcOEt, colorless prisms). Anal. Found: C, 41.87; H, 3.31; N, 12.77. $C_{19}H_{19}N_5Cl_2O_{10}$ requires C, 41.62; H, 3.49; N, 12.77%.

Perchlorate **5H** (**5**+2$HClO_4$): Mp 170.5–173.0 °C (recryst from CH_3CN/AcOEt, colorless prisms). Anal. Found: C, 41.59; H, 3.27; N, 12.47. $C_{19}H_{19}N_5Cl_2O_{10}$ requires C, 41.62; H, 3.49; N, 12.77%.

Perchlorate **6H** (**6**+2$HClO_4$): Mp 214.0–216.5 °C (recryst from CH_3CN/EtOH, colorless prisms). Anal. Found: C, 43.81; H, 3.54; N, 10.04. $C_{20}H_{20}N_4Cl_2O_{10}$ requires C, 43.89; H, 3.68; N, 10.24%.

Perchlorate **7H** (**7**+2$HClO_4$): Mp 251.0–253.0 °C(dec) (recryst from CH_3CN/EtOH, colorless prisms). Anal. Found: C, 43.70; H, 3.55; N, 10.05. $C_{20}H_{20}N_4Cl_2O_{10}$ requires C, 43.89; H, 3.68; N, 10.24%.

4.3. Single-crystal X-ray crystallography

Crystallographic data were collected on a four-circle diffractometer with Cu Kα (λ=1.54178 Å) radiation (for **7H**) or on a CCD diffractometer with Mo Kα (λ=0.71073 Å) radiation (for other compounds). Data collections were carried out at low temperature (120–150 K) using liquid nitrogen. All of the crystal structures were solved by direct methods with SHELXS-97 and refined with full-matrix least-squares SHELXL-97.[19] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms of the amides were included at their calculated positions. Hydrogen atoms of water molecules (for **7**) were determined based on the electron density distribution. Crystallographic data are summarized below (for published data, only CCDC deposit numbers are given).[15] Thermal ellipsoid models and details of refinements for the crystals are described in supplementary data.

Compound **1**: CCDC-625148.

Compound **2**: $C_{13}H_{12}N_2O$, M_r=212.25, Monoclinic, $P2_1/c$, a=11.5293(12), b=7.5151(8), c=13.2121(14) Å, β=107.8690(10)°, V=1089.5(2) $Å^3$, Z=4, D_c=1.294 Mg m^{-3}, $2\theta_{max}$=54.36°, T=120 K, 5171 reflections measured, 2149 unique (R_{int}=0.0202), μ (Mo Kα)= 0.084 mm^{-1}. The final R_1 and wR_2 were 0.0497 and 0.1148 (all data). CCDC-836681.

Compound **3**: $C_{13}H_{12}N_2O$, M_r=212.25, Tetragonal, $I4_1/a$, a=b=23.9263(8), c=7.8199(5) Å, V=4476.6(4) $Å^3$, Z=16, D_c=1.260 Mg m^{-3}, $2\theta_{max}$=54.30°, T=150 K, 10,543 reflections measured, 2328 unique (R_{int}=0.0240), μ (Mo Kα)=0.082 mm^{-1}. The final R_1 and wR_2 were 0.0483 and 0.0933 (all data). CCDC-836683.

Compound **4**: CCDC-625151.

Compound **5**: CCDC-625149.

Compound **6**: $C_{20}H_{18}N_4O_2$, M_r=346.38, Monoclinic, $P2_1/n$, a=11.2733(7), b=11.8136(7), c=13.1965(8) Å, β=106.8140(10)°, V=1682.35(18) Å^3, Z=4, D_c=1.368 Mg m^{-3}, $2\theta_{max}$=56.42°, T=150 K, 9207 reflections measured, 3791 unique (R_{int}=0.0152), μ (Mo Kα)= 0.091 mm^{-1}. The final R_1 and wR_2 were 0.0447 and 0.1009 (all data). CCDC-836685.

Compound **7**: $C_{20}H_{18}N_4O_2 \cdot H_2O$, M_r=364.40, Orthorhombic *Pnma*, a=7.0821(4), b=21.7993(14), c=11.6085(7) Å, V=1792.18(19) Å^3, Z=4, D_c=1.351 Mg m^{-3}, $2\theta_{max}$=56.52°, T=150 K, 9312 reflections measured, 2136 unique (R_{int}=0.0180), μ (Mo Kα)=0.093 mm^{-1}. The final R_1 and wR_2 were 0.0409 and 0.1036 (all data). CCDC-836687.

Perchlorate **1H**: $C_{12}H_{13}N_3O \cdot 2ClO_4$, M_r=414.15, Monoclinic, *Cc*, a=14.664(6), b=8.180(3), c=13.523(5) Å, β=95.160(5)°, V=1615.6(11) Å^3, Z=4, D_c=1.703 Mg m^{-3}, $2\theta_{max}$=56.16°, T=150 K, 4286 reflections measured, 2434 unique (R_{int}=0.0306), μ (Mo Kα)= 0.459 mm^{-1}. The final R_1 and wR_2 were 0.0719 and 0.1675 (all data). CCDC-836680.

Perchlorate **2H**: $C_{13}H_{13}N_2O \cdot ClO_4$, M_r=312.70, Monoclinic, $P2_1/c$, a=6.3357(5), b=7.4244(6), c=28.397(2) Å, β=95.4480(10)°, V=1329.71(18) Å^3, Z=4, D_c=1.562 Mg m^{-3}, $2\theta_{max}$=54.40°, T=120 K, 6404 reflections measured, 2638 unique (R_{int}=0.0222), μ (Mo Kα)= 0.312 mm^{-1}. The final R_1 and wR_2 were 0.0429 and 0.0883 (all data). CCDC-836682.

Perchlorate **3H**: $C_{13}H_{13}N_2O \cdot ClO_4$, M_r=312.70, Triclinic, $P-1$, a=6.4095(10), b=9.0554(14), c=12.1921(19) Å, α=88.436(2), β=79.761(2), γ=76.214(2)°, V=676.22(18) Å^3, Z=2, D_c=1.536 Mg m^{-3}, $2\theta_{max}$=53.72°, T=150 K, 3223 reflections measured, 2490 unique (R_{int}=0.0121), μ (Mo Kα)=0.307 mm^{-1}. The final R_1 and wR_2 were 0.0550 and 0.1316 (all data). CCDC-836684.

Perchlorate **4H**: CCDC-625152.

Perchlorate **5H**: CCDC-625150.

Perchlorate **6H**: $C_{20}H_{20}N_4O_2 \cdot 2ClO_4$, M_r=547.30, Monoclinic, $P2_1/n$, a=16.470(4), b=16.248(4), c=16.467(4) Å, β=93.553(3)°, V=4398.3(18) Å^3, Z=8, D_c=1.653 Mg m^{-3}, $2\theta_{max}$=55.24°, T=120 K, 24086 reflections measured, 9747 unique (R_{int}=0.0526), μ (Mo Kα)=0.364 mm^{-1}. The final R_1 and wR_2 were 0.0988 and 0.1450 (all data). CCDC-836686.

Perchlorate **7H**: $C_{20}H_{20}N_4O_2 \cdot 2ClO_4$, M_r=547.30, Orthorhombic *Fdd2*, a=12.7608(11), b=28.645(4), c=12.4297(12) Å, V=4543.5(9)Å^3, Z=8, D_c=1.600 Mg m^{-3}, $2\theta_{max}$=135.94°, T=150 K, 2058 reflections measured, 1412 unique (R_{int}=0.0222), μ (Cu Kα)=3.173 mm^{-1}. The final R_1 and wR_2 were 0.0418 and 0.0934 (all data). CCDC-836688.

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Supplementary data

Supplementary data are available in PDF format: X-ray crystallographic data for **2,3,6,7,1H,2H,3H,6H** and **7H**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.08.085.

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