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Solvent-dependent conformational switching of the aromatic *N*-methyl amides depending upon the acceptor properties of solvents

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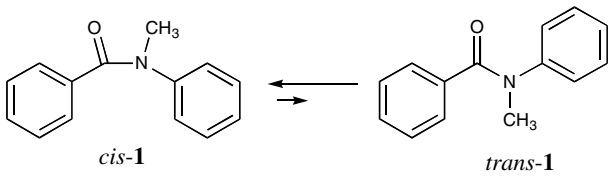
Abstract—An aromatic *N*-methyl amide containing *N*-(2-pyridyl) and 2,6-pyridinedicarboxamide moieties switches its conformation from *cis* to *trans* depending upon the acceptor number of solvents.

The conformation of a molecule or supramolecule can greatly influence function,[1] and the amide bond is a very attractive structural unit which can form two conformations, *cis* and *trans*.[2] Although most secondary aromatic amides, such as benzanilide or acetanilide, favor *trans* conformation, *N*-methyl derivatives such as **1** favor *cis* conformation (Scheme 1).[3] This characteristic building block can construct several unique compounds,[4] and the switching of amide conformation can lead to significant changes in the structure and function of large molecules.[5,6] If the conformational switching of these structural units can be controlled with the outer conditions, the molecules can work as external stimuli responsive molecular devices.

The pyridine ring serves as a ligand for metals or a hydrogen bond acceptor.[7] Therefore, we designed the pyridine-containing *N*-methyl aromatic amides **2**–**8** as congeners of *N*-methyl benzanilide that might be readily conformationally switchable. Here we report that the conformational preference is influenced by intramolecular dipole interaction, and we also describe the solvent-dependent conformational switching of **8**.

We first synthesized *N*-methyl-*N*-(2-pyridyl)-2-pyridinecarboxamide (**2**). ^{1}H NMR spectroscopy of **2** in CD_2Cl_2 showed the characteristic structural features of aromatic



cis-**1** *trans*-**1**

Scheme 1. The conformational preference of *N*-methylbenzanilide.

N-methyl amides such as **1**. While the spectrum of **2** at room temperature shows a single set of signals, lowering of the temperature resulted in peak broadening, leading to the appearance of two sets of signals, due to the *cis* and *trans* conformers. The aromatic proton signals of the *cis* conformer were shifted upfield from those of the *trans* conformer. The integration values at 183 K indicated a 95:5 ratio of *cis* and *trans* conformers (Table 1, entry 1).

Next we synthesized amides **3**–**8** and investigated their conformational ratios. ^{1}H NMR measurements were carried out in CD_2Cl_2 at 183 K, and the conformer ratios are summarized in Table 1. The ratios of *cis* and *trans* conformers for **3**–**6** were similar to that of **2** (entries 2–5). Table 1 also shows the data for amides **7** and **8**, which contain three pyridine rings and two amide bonds. The spectra of these amides at 183 K indicate that *cis–cis* is the major conformer and *cis–trans* is a minor conformer, while the *trans–trans* conformer was not detected. The ratio of *cis*-**7** and *trans*-**7**, representing *cis–cis* and *cis–trans*, respectively, was 88:12 (entry 6), which can be regarded as ratio similar to those of **2**–**6**

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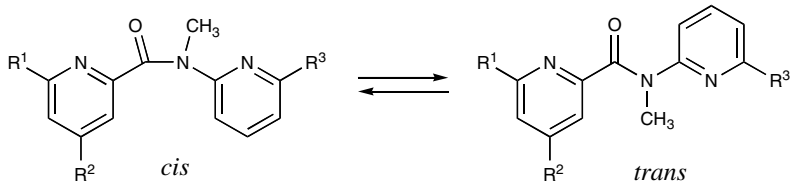
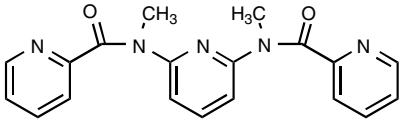
Table 1. The conformational ratio of amides **2**–**8** in CD_2Cl_2

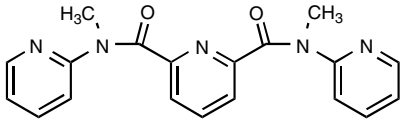


Entry	Amide	R^1	R^2	R^3	*Cis*:*trans*[a]
1	**2**	H	H	H	95:5
2	**3**	H	NO_2	H	98:2
3	**4**	Br	H	H	96:4
4	**5**	CO_2Me	H	H	96:4
5	**6**	H	H	Br	94:6
6	**7**[c]	H	H	*cis*-NMeCO-2-Py	88:12[b]
7	**8**[c]	*cis*-CONMe-2-Py	H	H	61:39[b]

[a] The ratios were calculated from integration values of ^{1}H NMR signals at 183 K.
[b] The ratios of *cis–cis* and *cis–trans* conformers are presented. *Trans-trans* conformer was not detected.
[c] The structures of **7** and **8** are as follows:



7



8

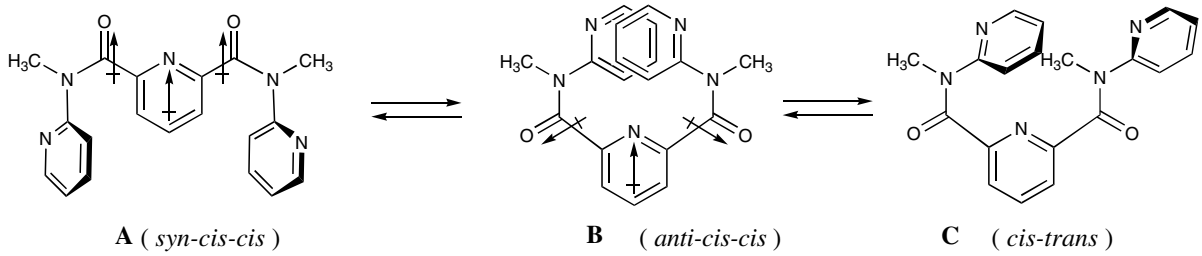
by considering symmetrical structure of **7** with two amide bonds. However, the ratio of **8** was clearly different from those of the other amides, that is, the ratio of the *trans* isomer was increased to 61:39 (entry 7).

This characteristic feature can be interpreted in terms of the dipole effect around the central pyridine ring and carbonyl groups (Scheme 2),[8] because the dipole interaction makes the two carbonyl groups of the amides lie in the *anti* direction (from **A** to **B**), and consequently the terminal pyridine rings exhibit steric repulsion. This steric repulsion in **B** can be released by conformational change to the *cis–trans* conformer (**C**), so that the population of *trans* conformer of **8** becomes larger than those of **2**–**7**.

In order to investigate the characteristics of **8** in more detail, several other solvents were used for NMR measurements; the results and physical properties of the solvents are summarized in Table 2. The *cis* conformer was preferred to the *trans* isomer both in methanol (entry 1) and in dichloromethane (entry 2), whereas acetone reduced the preference for the *cis* conformer (entry 4), and toluene and THF resulted in *trans* preference (entries 5 and 6). The results of entries 2, 3, and 5 demonstrate that the conformational switching between *cis* and *trans* conformers can be induced in dichloromethane/toluene by changing the solvent ratio.

Karelson and co-workers reported a correlation between the *cis–trans* preference and the dielectric constant of the solvent for some formamide derivatives.[2b] However in our case, it does not appear that the results can be interpreted in terms of dielectric constant or dipole moment of the solvent. On the other hand, acceptor number (AN), as proposed by Gutmann,[9] appeared to be a good predictor of *cis*-preference. Thus, amide **8** exhibited a higher *cis*-ratio in a solvent with higher AN, and *trans*-preference in a solvent with low AN. To our knowledge, this is the first example of the conformational switching of amides in accordance with the acceptor number of solvents.

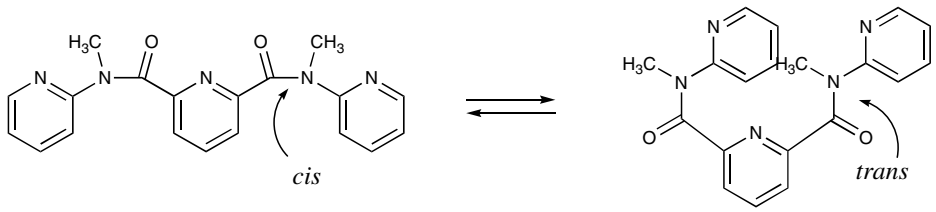
A solvent with higher AN can better coordinate or solvate to the amide carbonyl group, and hence reduce the dipole interaction with the central pyridine ring. This



A (*syn-cis-cis*) **B** (*anti-cis-cis*) **C** (*cis-trans*)

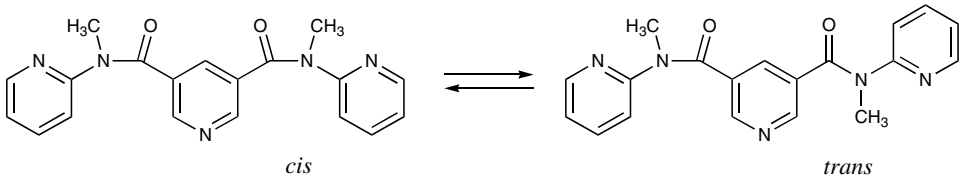
Scheme 2. The conformational equilibrium of **8**.

Table 2. The conformational ratio of amide **8** in various solvents at 183 K



Entry	Solvent	AN[a]	DN[a]	ε[a]	μ[a]	*Cis*:*trans*[b]
1	Methanol	41.3	19	32.6	1.7	88:12
2	Dichloromethane	20.4	—	9.0	1.6	61:39
3	(Dichloromethane + toluene)[c]	—	—	—	—	54:46
4	Acetone	12.5	17.0	20.7	2.9	52:48
5	Toluene	7.9[d]	0.1	2.3	0.3	25:75
6	THF	8.0	20.2	7.4	1.7	19:81

[a] AN: acceptor number, DN: donor number,[9] ε: relative dielectric constant, μ: dipole moment [D].[10]
[b] The ratios were calculated from integration values of ^{1}H NMR signals at 183 K. The ratios of *cis–cis* conformer and *cis–trans* conformer are presented. *Trans-trans* conformer was not detected.
[c] A mixture of dichloromethane and toluene (50:50) was used as a solvent.
[d] Calculated from AN of benzene according to the reported method.[11]



9

91 : 9 in CD_2Cl_2 (183 K)
80 : 20 in $C_6D_5CD_3$ (183 K)

Scheme 3. The solvent dependency of the conformational preference of **9**.

coordination makes the carbonyl group *syn* to pyridine nitrogen, and hence favors *cis*-conformation. Such a solvent with high AN can also coordinate to the nitrogen atom of terminal pyridine ring. Because *ortho* substitution of *N*-aryl group increases the ratio of *trans* conformer in some *N*-methyl amides,[12,3b] similar effect can be expected for amide **8**, resulting from coordination to terminal pyridine ring. However, considering the fact that the *cis–trans* conformational switching is the characteristic of amide **8**,[13] interaction around the central pyridine ring is also essential.

The importance of dipole interaction between the central pyridine ring and the carbonyl group was confirmed by examining amide **9**, having a positionally changed central pyridine ring. ^{1}H NMR of **9** revealed that *cis* conformation was preferred both in dichloromethane (AN: 20.4) and in toluene (AN: 7.9), as shown in Scheme 3, in contrast to entries 2 and 5 in Table 2.

In conclusion, we investigated the conformational preference of aromatic amides containing 2- and 2,6-substituted pyridine rings.[14] Among them, amide **8** showed a unique switching of the *cis–trans* conformation according to the solvent acceptor ability. This *N*-methyl pyridyl amide structure is very useful as a structural unit, because the conformational structure in a solvent can be predicted by considering its acceptor number.

Supplementary data

^{1}H NMR spectra of amides **2–9** in CD_2Cl_2, and **8** in various solvents are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.08.012.

References and notes

1. (a) Lehn, J.-M. *Supramolecular Chemistry*; VCH: Weinheim, 1995; (b) Balzani, V.; Credi, A.; Venturi, M. *Molecular Devices and Machines*; Wiley-VCH: Weinheim, 2004.
2. (a) Yamasaki, R.; Tanatani, A.; Azumaya, I.; Saito, S.; Yamaguchi, K.; Kagechika, H. *Org. Lett.* **2003**, *5*, 1265–1267; (b) Leis, J.; Klika, K. D.; Karelson, M. *Tetrahedron* **1998**, *54*, 7497–7504; (c) Troganis, A. N.; Sicilia, E.; Barbarossou, K.; Gerothanassis, I. P.; Russo, N. *J. Phys. Chem. A* **2005**, *109*, 11878–11884; (d) Plass, M.; Griehl, C.; Kolbe, A. *J. Mol. Struct.* **2001**, *570*, 203–214.
3. (a) Itai, A.; Toriumi, Y.; Tomioka, N.; Kagechika, H.; Azumaya, I.; Shudo, K. *Tetrahedron Lett.* **1989**, *30*, 6177–6180; (b) Azumaya, I.; Kagechika, H.; Fujiwara, Y.; Itoh, M.; Yamaguchi, K.; Shudo, K. *J. Am. Chem. Soc.* **1991**, *113*, 2833–2838.
4. (a) Azumaya, I.; Yamaguchi, K.; Okamoto, I.; Kagechika, H.; Shudo, K. *J. Am. Chem. Soc.* **1995**, *117*, 9083–9084; (b) Azumaya, I.; Kagechika, H.; Yamaguchi, K.; Shudo,

K. *Tetrahedron Lett.* **1996**, *37*, 5003–5006; (c) Azumaya, I.; Okamoto, I.; Nakayama, S.; Tanatani, A.; Yamaguchi, K.; Shudo, K.; Kagechika, H. *Tetrahedron* **1999**, *55*, 11237–11246; (d) Tanatani, A.; Yokoyama, A.; Azumaya, I.; Takakura, Y.; Mitsui, C.; Shiro, M.; Uchiyama, M.; Muranaka, A.; Kobayashi, N.; Yokozawa, T. *J. Am. Chem. Soc.* **2005**, *127*, 8553–8561.

5. Betson, M. S.; Clayden, J.; Lam, H. K.; Helliwell, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1241–1244.
6. (a) Clayden, J.; Lund, A.; Vallverdu, L.; Helliwell, M. *Nature* **2004**, *431*, 966–971; (b) Kern, D.; Zuiderweg, E. R. P. *Curr. Opin. Struct. Biol.* **2003**, *13*, 748–757; (c) Seebach, D.; Schreiber, J. V.; Abele, S.; Daura, X.; van Gunsteren, W. F. *Helv. Chim. Acta* **2000**, *83*, 34–57.
7. (a) Hofacker, A. L.; Parquette, J. R. *Angew. Chem., Int. Ed.* **2005**, *44*, 1053–1057; (b) Yue, N. L. S.; Jennings, M. C.; Puddephatt, R. J. *Inorg. Chem.* **2005**, *44*, 1125–1131; (c) Heemstra, J. M.; Moore, J. S. *Chem. Commun.* **2004**, 1480–1481; (d) Chatterjee, B.; Noveron, J. C.; Resendiz, M. J. E.; Liu, J.; Yamamoto, T.; Parker, D.; Cinke, M.; Nguyen, C. V.; Arif, A. M.; Stang, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 10645–10656; (e) Crabtree, R. H.; Siegbahn, P. E. M.; Eisenstein, O.; Rheingold, A. L.; Koetzle, T. F. *Acc. Chem. Res.* **1996**, *29*, 348–354; (f) Fujita, M.; Oguro, D.; Miyazawa, M.; Oka, H.; Yamaguchi, K.; Ogura, K. *Nature* **1995**, *378*, 469–471.
8. (a) Perlepes, S. P.; Kabanos, T.; Hondrellis, V.; Tsangaris, J. M. *Inorg. Chim. Acta* **1988**, *150*, 13–23; (b) Bould, J.; Brisdon, B. J. *Inorg. Chim. Acta* **1976**, *19*, 159–163; (c) Brown, R. F. C.; Radom, L.; Sternhell, S.; Rae, I. D. *Can. J. Chem.* **1968**, *46*, 2577–2587.
9. Acceptor number and donor number are empirical parameters describing electrophilic behavior and nucleophilic behavior of solvents, respectively: (a) Gutmann, V. *The Donor–Acceptor Approach to Molecular Interactions*; Plenum Press: New York, 1978; (b) Gutmann, V. *Electrochim. Acta* **1976**, *21*, 661–670.
10. *Chief CRC Handbook of Chemistry and Physics,* 71st ed.; Lide, D. R., Ed.; CRC Press: Boston, 1990; Vols. 1990–1991.
11. (a) Linert, W.; Jameson, R. F. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1415–1421; (b) Dimroth, K.; Reichardt, C.; Siepmann, T.; Bohlmann, F. *Liebigs Ann. Chem.* **1963**, *661*, 1–37.
12. (a) Azumaya, I. *Yakugaku Zasshi* **2001**, *121*, 117–129; (b) Azumaya, I.; Yamaguchi, K.; Kagechika, H.; Saito, S.; Itai, A.; Shudo, K. *Yakugaku Zasshi* **1994**, *114*, 414–430.
13. *Cis*:*trans* conformational ratios of **2** at 183 K in CD_2Cl_2, toluene-d_8, and THF-d_8 were 96:4, 91:9, and 93:7, respectively. In the case of this simple amide **2**, solvent-induced conformational switching cannot be observed.
14. *General procedure for the synthesis of amides is as follows*: A solution of pyridinecarboxylic acid (5.00 mmol) and triethylamine (10.0 mmol) in tetrahydrofuran was stirred at 0 °C, and ethyl chloroformate (5.00 mmol) was added, followed by stirring for 1 h. To this mixture, 2-(methylamino)pyridine (5.00 mmol) was added, and the resulting mixture was stirred at ambient temperature for 3 h, then filtrated. The solvent was removed by evaporation, and the resulting mixture was flash-chromatographed to afford the desired amide. Compound **2**: Mp 77.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (m, 2H), 7.71 (m, 2H), 7.54 (dt, $J = 1.9$, 7.8 Hz, 1H), 7.20 (m, 1H), 7.03 (m, 2H), 3.61 (s, 3H). Anal. Calcd for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.51; H, 5.22; N, 19.52. Compound **3**: Mp 141.0–142.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (m, 2H), 8.17 (dd, $J = 1.2$, 4.9 Hz, 1H), 7.91 (dd, $J = 2.2$, 5.1 Hz, 1H), 7.64 (dt, $J = 1.9$, 7.8 Hz, 1H), 7.13 (d, $J = 8.1$ Hz, 1H), 7.06 (ddd, $J = 0.9$, 4.9, 7.3 Hz, 1H), 3.63 (s, 3H). Anal. Calcd for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.90; N, 21.70. Found: C, 55.69; H, 3.62; N, 21.91. Compound **4**: Mp 104.0–105.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, $J = 5.0$ Hz, 1H), 7.73 (dd, $J = 0.9$, 7.7 Hz, 1H), 7.65 (dt, $J = 1.9$, 7.8 Hz, 1H), 7.57 (t, $J = 7.7$ Hz, 1H), 7.37 (d, $J = 7.9$ Hz, 1H), 7.14 (br d, $J = 9.0$ Hz, 1H), 7.11 (ddd, $J = 0.9$, 4.9, 7.4 Hz, 1H), 3.58 (s, 3H). Anal. Calcd for $C_{12}H_{10}N_3OBr$: C, 49.34; H, 3.45; N, 14.38. Found: C, 49.30; H, 3.43; N, 14.25. Compound **5**: Mp 71.5–72.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (dd, $J = 1.3$, 5.0 Hz, 1H), 8.02 (dd, $J = 1.5$, 7.6 Hz, 1H), 7.95 (dd, $J = 1.4$, 7.8 Hz, 1H), 7.87 (t, $J = 7.7$ Hz, 1H), 7.60 (dt, $J = 1.7$, 8.1 Hz, 1H), 7.16 (br d, $J = 8.3$ Hz, 1H), 7.05 (ddd, $J = 0.9$, 5.0, 7.5 Hz, 1H), 3.83 (s, 3H), 3.60 (s, 3H). Anal. Calcd for $C_{14}H_{13}N_3O_3$: C, 61.99; H, 4.83; N, 15.49. Found: C, 61.91; H, 4.92; N, 15.59. Compound **6**: Mp 145.0–146.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92 (ddd, $J = 0.9$, 1.6, 4.7 Hz, 1H), 7.55 (dt, $J = 1.7$, 7.8 Hz, 1H), 7.36 (d, $J = 6.8$ Hz, 1H), 7.27 (t, $J = 7.9$ Hz, 1H), 7.02 (m, 2H), 6.85 (1H, $J = 7.9$ Hz,1H), 3.09 (s, 3H). Anal. Calcd for $C_{12}H_{10}N_3OBr$: C, 49.34; H, 3.45; N, 14.38. Found: C, 49.30; H, 3.45; N, 14.43. Compound **7**: Mp 140.0–140.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (m, 2H), 7.73 (ddd, $J = 0.4$, 1.8, 7.6 Hz, 2H), 7.60 (m, 2H), 7.39 (t, $J = 7.9$ Hz, 1H), 7.24 (ddd, $J = 1.3$, 5.0, 7.7 Hz, 2H), 6.75 (d, $J = 7.9$ Hz, 2H), 3.23 (s, 6H). Anal. Calcd for $C_{19}H_{17}N_5O_2$: C, 65.69; H, 4.93; N, 20.16. Found: C, 66.07; H, 4.94; N, 20.19. Compound **8**: Mp 113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (ddd, $J = 0.9$, 2.0, 4.8 Hz, 2H), 7.75 (dd, $J = 7.3$, 8.2 Hz, 1H), 7.58 (m, 2H), 7.56 (m, 2H), 7.04 (ddd, $J = 1.0$, 4.9, 7.4 Hz, 2H), 7.00 (m, 2H), 3.33 (s, 6H). Anal. Calcd for $C_{19}H_{17}N_5O_2$: C, 65.69; H, 4.93; N, 20.16. Found: C, 65.83; H, 4.86; N, 20.23. Compound **9**: Mp 140.0–141.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (ddd, $J = 0.7$, 2.0, 4.9 Hz, 2H), 8.35 (d, $J = 2.2$ Hz, 2H), 7.76 (t, $J = 2.0$ Hz, 1H), 7.56 (dt, $J = 1.8$, 7.7 Hz, 2H), 7.12 (ddd, $J = 0.9$, 4.9, 7.5 Hz, 2H), 6.85 (br d, $J = 8.1$ Hz, 2H), 3.54 (s, 6H). Anal. Calcd for $C_{19}H_{17}N_5O_2$: C, 65.69; H, 4.93; N, 20.16. Found: C, 65.70; H, 4.74; N, 20.10.