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Acid-induced molecular-structural transformation of *N*-methyl aromatic oligoamides bearing pyridine-2-carboxamide

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ABSTRACT

Amide oligomers composed of pyridine-2-carboxamide as the repeating unit were synthesized in a stepwise manner and their structures were examined by means of ^{1}H NMR, NOE measurements, and DFT calculations. All the synthesized oligomers adopted a folded conformation, but became partially unfolded at the C-terminal upon addition of acid. A characteristic long-range hydrogen bond, which stabilizes local folding, was present in oligomers with a long main chain.

Introduction

Foldamers and folding mechanisms have attracted intense attention in connection with studies to comprehend and imitate the structures and functions of biological relevant molecules, such as peptides, proteins, and nucleic acids.[1] The past several decades have witnessed an enormous expansion of this field, and one of the hottest topics is the development of stimulus-responsive folding/unfolding transformation systems.[2] Indeed, many proteins, such as receptors and channels, change their structure in response to various external stimuli, such as ligands, ions, and acid.[3] Although there are many reports concerning foldamers whose conformational behavior is controlled by ligands or anions, there are only a few examples of acid-induced conformational switching systems.[4,5]

Among reported stimulus-responsive folding/unfolding systems, oligo aromatic amides are particularly attractive, mainly because of their potential for structure-based molecular design.[6–10] We have developed pyridine-containing aromatic amides as acid-responsive molecular switching units.[4,11] In general, aromatic amide compounds, such as benzanilide and acetanilide, exist predominantly in *trans* conformation. However, their conformational preference is dramatically switched by *N*-methylation, and most *N*-methylated aromatic amides favor *cis* conformation.[12] We found that addition of acid to compounds bearing an *N*-methyl-*N*-(2-pyridyl) moiety, such as **1**, altered the predominant conformation from *anti-cis* to *syn-trans* (Fig. 1).[11] These conformational features are different from those of other related foldamers containing hydrogen-bonding networks of N–H protons in amide functionalities,[8] and the dynamical behavior has unique characteristics. In the previous study, we discovered the unique folding and unfolding behavior of an *N*-methyl amide compound containing five pyridine rings (**2**) (Fig. 2); specifically, the structure changed from *layered* to *spiral* to *flat* form in response to addition of acid.[4] It is noteworthy that this folding nature emerges as a result of oligomerization of multiple amide bond units, and does not simply represent the sum of the behaviors of the individual amide units. Because of the *C*s symmetry of compound **2**, *N*-methyl amide was grouped into only two types, which limits dynamic behavior. In order to investigate the nature of longer and less symmetric pyridyl oligoamides, we designed head-to-tail type 2-pyridyl oligo amides containing continuous non-equivalent *N*-methyl amide bonds. In this Letter, we describe the synthesis of 2-pyridyl amides **3**–**5** (Fig. 2) and their conformational changes induced by the addition of acid.

Results and discussion

Aromatic oligoamides **3**–**5** were synthesized as shown in Schemes 1 and 2, featuring 2-nitrobenzenesulfonyl (Ns) as a protecting group.[13] The main chain was elongated by means of repeated deprotection and coupling cycles of compound **6**, similarly to peptide synthesis, as shown in Scheme 1. Compound **6** was coupled with *N*-methyl-2-pyridine using thionyl chloride as

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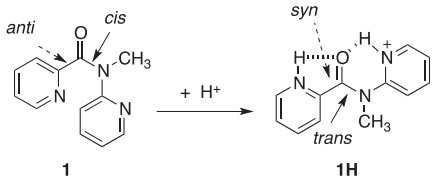


Figure 1. Conformational transformation of pyridyl aromatic amide **1** elicited by acid.

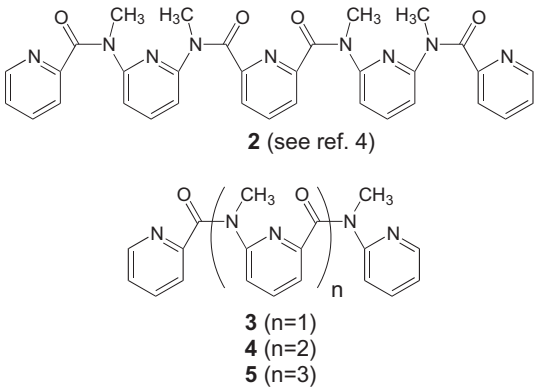
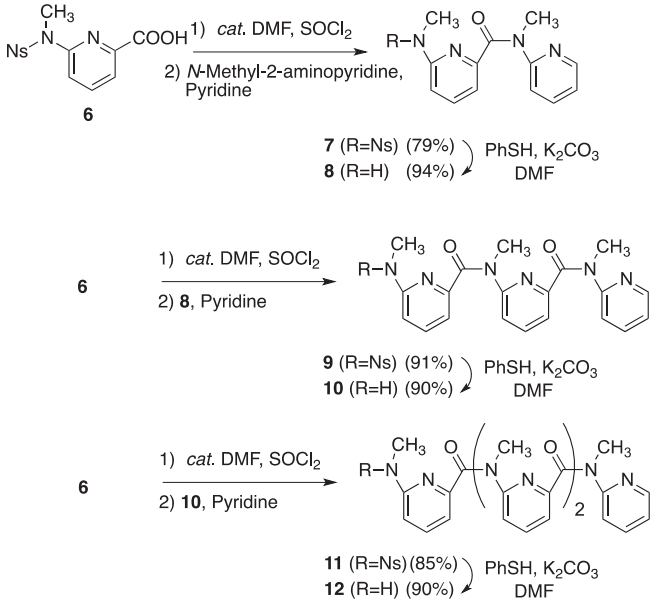


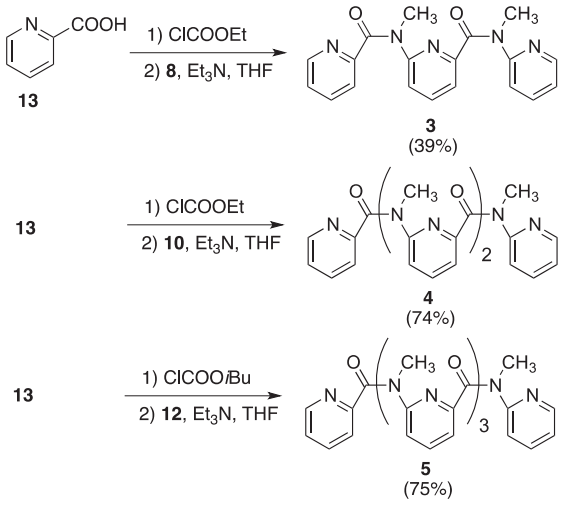
Figure 2. *Cs* symmetric aromatic oligoamides **2**, and **3**–**5** bearing pyridine-2-carboxamide.



Scheme 1. Elongation cycles of pyridine-2-carboxamide.

an activating reagent to afford **7** in good yield. The Ns group was removed in the presence of anionic thiol and the resultant secondary amine, **8**, was reacted with activated **6** to afford amide dimer **9**. This deprotection and elongation cycle was repeated to afford amide trimer **11** and the corresponding amine **12** in a good overall yield.

The designed oligoamides **3**–**5** were synthesized by capping free secondary amines with picolinic acid (**13**) activated with ethylchloroformate or isobutylchloroformate, in moderate to good yields (Scheme 2).



Scheme 2. Synthesis of oligoamides **3**–**5**.

The structures of the oligoamides **3**–**5** in solution were analyzed by means of ^{1}H NMR measurements in CD_2Cl_2 (Fig. 3). As already mentioned, *N*-methyl-*N*-2-pyridyl amide has *cis* conformational preference, which is a general preference of secondary aromatic amide compounds.[11] These pyridyl amides also showed *cis* conformational preference, compared with simple pyridyl amide compounds; the signal of aromatic protons at the ortho position was shifted to a higher field, which is a typical feature of *cis* aromatic amides.[11b]

To obtain further insights into the folding structures of these oligomers, NOE experiments were performed. Most signals were assigned by means of spin population transfer (SPT) experiments (see Supplementary data), and the results are shown in Figure 4. Irradiation of each *N*-methyl proton of **3** revealed correlations with aromatic protons of *N*-terminal pyridine, indicating that the whole molecular skeleton adopts a *zigzag* shape, not the *cage*-like *syn* conformation observed in sterically hindered oligo-*m*-benzanilide.[14] This result can be rationalized in terms of both *cis*-amide preference and the dipole relationship between carbonyl and nitrogen at pyridine. Since similar trends can be found in pyridine tetramer **4** and pyridine pentamer **5**, adaptation of a zigzag shape appears to be a general trend of these head-to-tail types of *N*-methyl oligopicolinamides.

To examine acid-induced conformational alterations in solution, oligoamides **3**–**5** were exposed to acidic conditions and observed by ^{1}H NMR. Figure 3 shows the ^{1}H NMR spectra of the aromatic region of oligoamides **3**–**5** in the absence (upper) and presence of excess trifluoroacetic acid-*d* (TFA-*d*, 150 equiv) (lower, expressed as **3H**–**5H**). In our previous studies,[4,11b] the use of TFA-*d* allowed us to partially protonate the pyridine nitrogen atom; only the C-terminal and N-terminal pyridines are protonated, whereas the central pyridine nitrogen atom is not protonated even when an excess amount of TFA-*d* is used. In the cases of **3** and **5**, the lower field shift of aromatic protons upon addition of TFA-*d* indicates protonation at the terminal pyridine nitrogen. In contrast, addition of acid to a solution of **4** broadened the whole ^{1}H NMR spectrum, which precluded detailed analysis. In the cases of oligomers **3H** and **5H**, all proton signals were assigned by means of SPT experiments (see Supplementary data), and the observed NOE enhancement of oligoamides by excess TFA-*d* is illustrated in Figure 5. In addition, the changes in the chemical shifts of oligoamides **3** and **5** elicited by acid are summarized in Figure 6. The conformational behavior of oligomers **3** and **5** was quite similar to that of the model compound **1** (vide infra).[11]

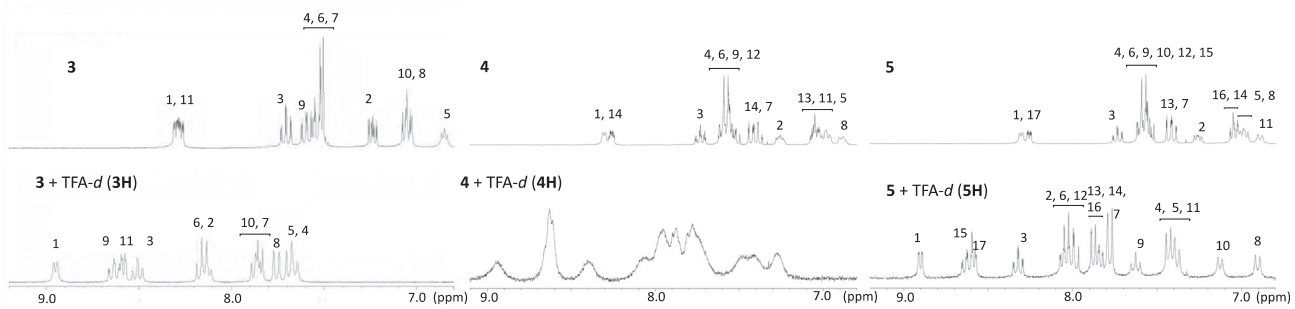


Figure 3. ^{1}H NMR spectra of **3**–**5** (upper) and **3H**–**5H** (lower) in CD_2Cl_2 Assignment was given based on the structures in Fig. 4.

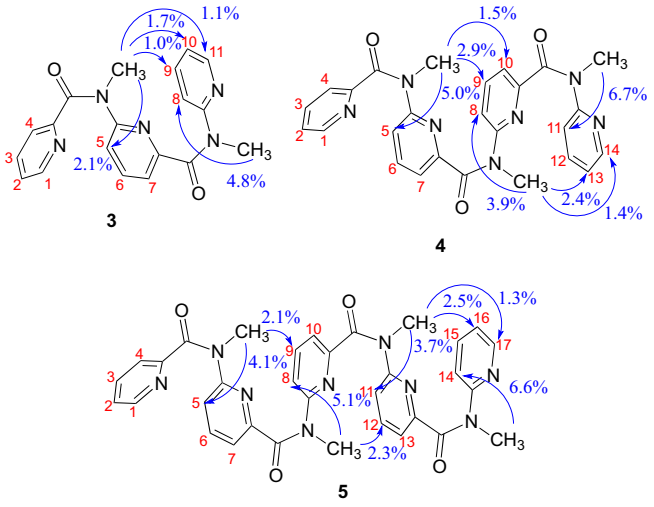


Figure 4. Observed NOE correlations of oligoamides **3**–**5**.

In the C-terminal pyridine unit of **3H** and **5H**, the peak of the proton at the 3-position was relatively unchanged, compared to the other protons of the corresponding pyridine ring. This can be attributed to the conformational alteration from *anti* to *syn*, which is the same as in the case of **1**.[11] On the other hand, the values of the chemical shifts of all of N-terminal pyridine protons increased by 0.3–1.0 ppm upon acidification; these large shifts are interpreted as being due to conformational inversion from *cis*-amide to *trans*-amide, as well as protonation at pyridine nitrogen. This conformational alteration is also supported by the results of NOE enhancement experiments (Figs. 4 and 5). The enhancement observed for *N*-methyl protons of the central pyridine and aromatic protons of *N*-terminal pyridine (**3**), or the second *N*-methyl protons from the *N*-terminal and the aromatic protons of N-terminal pyridine (**5**) disappeared in **3H** and **5H**. This conformational alteration is reasonable, taking 6-membered-ring hydrogen bonding of the pyridinium proton and amide carbonyl into account.

Many of the ^{1}H NMR changes induced by TFA-*d* were common to **3** and **5**, but a notable difference emerged with elongation of the amide chain. Oligoamide **5** showed unique behavior of the central pyridine ring, which exhibited higher field shifts (−0.4 ppm for 3-position and −0.1 ppm for 5-position) upon addition of TFA-*d* (Fig. 6). This is unusual, since protonation on pyridine nitrogen generally causes a lower field shift of pyridine aromatic proton peaks. Presumably the shift resulted from an aromatic ring current effect due to local folding. Considering the observed NOE correlation between the *N*-methyl group attached to the central pyridine and the C6-proton of *C*-terminal pyridine (0.6%), involvement of a hydrogen bond between the carbonyl attached to central pyridine and the *C*-terminal pyridinium proton seems likely (Fig. 7). The NOE correlation between the third *N*-methyl group from the C-terminal and the C-5 proton of the central pyridine unit (3.0%) implies *syn* conformation of the central pyridine unit, supporting the long-range hydrogen bonding. This long-range intramolecular hydrogen bond would contribute to stabilization of the local folding. In contrast, the stabilization by intramolecular hydrogen bonding would be weak for **4H** because of competition with the more stable six-membered hydrogen bonding between the *N*-terminal pyridinium proton and the corresponding carbonyl (Fig. 7).[4] This

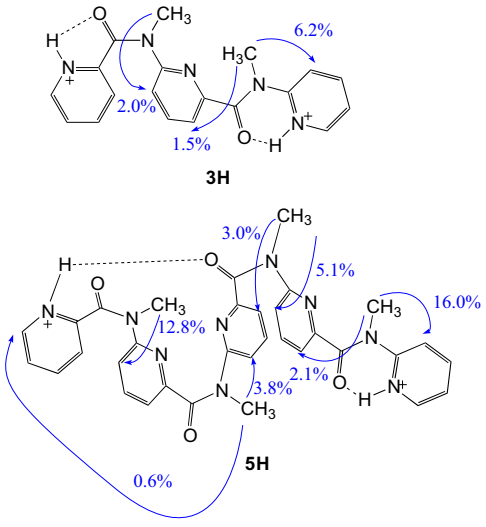


Figure 5. Observed NOE correlations of protonated oligoamides **3H** and **5H**.

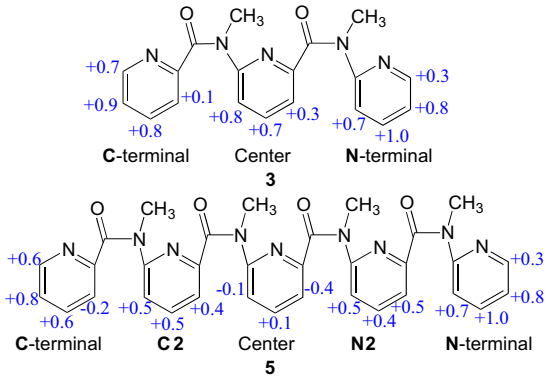


Figure 6. Change of ^{1}H NMR chemical shift induced by the addition of acid.

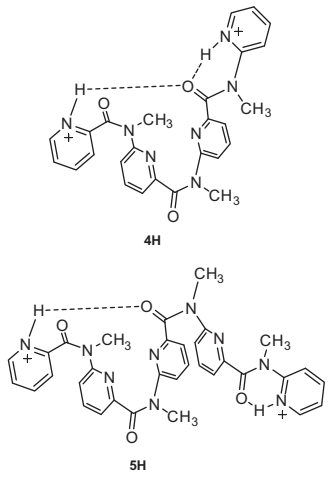


Figure 7. Plausible intramolecular hydrogen bonding scheme to promote tight folding of aromatic amides **4H** and **5H**.

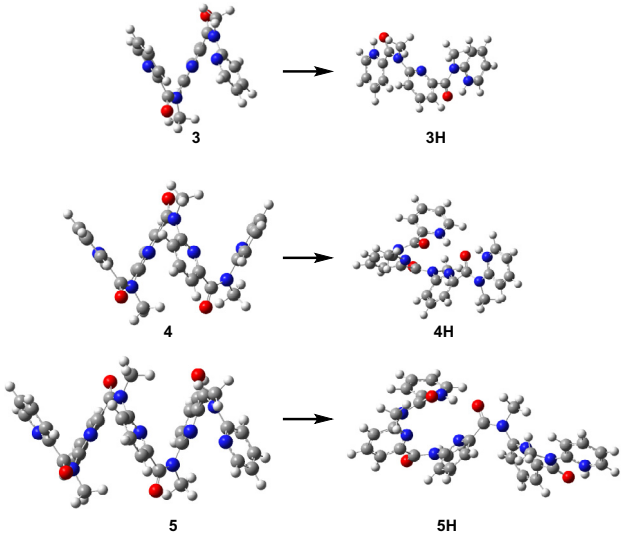


Figure 8. Optimized structures of **3**–**5** and **3H**–**5H** obtained by DFT calculation.

would lead to instability of local folding and might account for the peak broadening in the ^{1}H NMR spectrum of **4H** (Fig. 3).

Unfortunately, attempts to obtain suitable crystals for X-ray crystallography of those oligomers have not been successful to date. Therefore, to obtain insights into the structures of the oligomers (**3**, **3H**, **4**, **4H**, **5**, and **5H**), DFT calculations at the B3LYP/6-31G* level were performed.[15] Optimized structures of those oligomers before and after addition of acid are illustrated in Figure 8. The *layered* (folded) structures of protonation-free oligomers were supported by DFT calculations. The partially unfolded structures of the protonated oligomers, supported by the ^{1}H NMR spectra, are also presented. Conformations of amide bonds in those oligomers are *cis*–*trans* (**3H**), *cis*–*cis*–*trans* (**4H**), and *cis*–*cis*–*cis*–*trans* (**5H**) from the C-terminal to the N-terminal. The observed long-range intramolecular interaction, indicated by ^{1}H NMR, was also supported by the DFT calculation, and the distance between the C-terminal pyridinium proton and the corresponding carbonyl was 1.95 Å for **4H** and 1.76 Å for **5H**.

In conclusion, we synthesized oligoamides composed of pyridine 2-carboxamide by stepwise elongation of up to five pyridine units. The oligomer having five pyridine units exhibited a drastic conformational transformation from the folded form to the partially unfolded form, which is considered to be exhibit long-range hydrogen bonding that stabilizes the local folding. Four successive amide linkages were required for the emergence of this hydrogen bonding. The observed long-range hydrogen bonding is similar to that in the *Cs* symmetric oligoamide **2**,[4] but the conformational behavior is different, presumably due to the loss of symmetry. Our findings may be applicable for the design of pH-responsive conformation-switching foldamers.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.11.058.

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