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Hydrogen Bonding-Induced Aromatic Oligoamide Foldamers as Spherand Analogues to Accelerate the Hydrolysis of Nitro-Substituted Anisole in Aqueous Media

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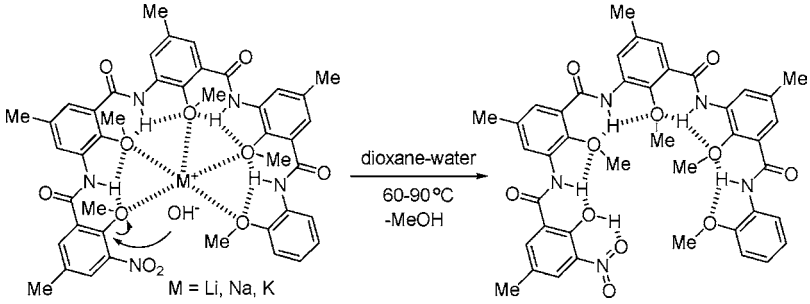

Four intramolecular hydrogen bonding-driven aromatic amide foldamers **2**−**5** have been designed and synthesized in which a 2-methoxy-3-nitrobenzamide unit was incorporated at the end of the backbone. Kinetic studies in dioxane−water (4:1, v/v) at 60−90 °C have revealed that the folded backbone of the oligomers was, like the rigidified spherand, able to complex Li^+, Na^+, and K^+ and, consequently, accelerated the hydrolysis of the nitro-appended anisole unit of the foldamers. Generally, longer foldamers displayed an increased accelerating effect, and LiOH displayed the highest reactivity probably due to the most efficient complexation by the folded oligomers. Addition of excessive potassium chloride substantially reduced the complexing interaction, and the hydrolysis of the longer oligomers became slower than that of the shorter ones due to an increased steric effect. The results indicate that, even in a hot aqueous medium of high polarity, intramolecular hydrogen bonding is still able to induce structurally matched oligomers to generate a preorganized rigidified conformation.

Introduction

Folding is a prerequisite for enzymes to catalyze various reactions in physiological media.[1] Generally, an active cavity is formed in which two or more reactants are constrained in close proximity, resulting in the dramatic rate enhancement of a prescribed chemical reaction. In the past decade, synthetic cavitand molecules have been intensively investigated as supramolecular enzyme mimics to facilitate discrete reactions.[2] Nevertheless, structurally flexible linear molecules usually could not be utilized as enzyme mimics because of the unfavorable entropic effect.

In recent years, there has been intense interest in designing foldamers, the artificial oligomers that utilize noncovalent forces to modulate folding or helical structures.[3,4] With an increasing number of structurally unique folding patterns being developed, the applications of such abiotic secondary structures in discrete areas have begun to receive attention. For example, several folded β-peptides have been revealed to exhibit strong antibacterial and antimicrobial activity.[5] An aromatic oligoamide foldamer has been used to mimic the binding surface of protein helices.[6] More recently, Moore et al. found that hydrophobically driven oligo(phenyleneethynylene)-derived foldamers are able to promote the methylation of (dimethylamino)pyridine.[7] Huc et al. also reported that the hydrogen bonding-induced folded conformation of an oligopyridine−dicarboxamide strand facili-

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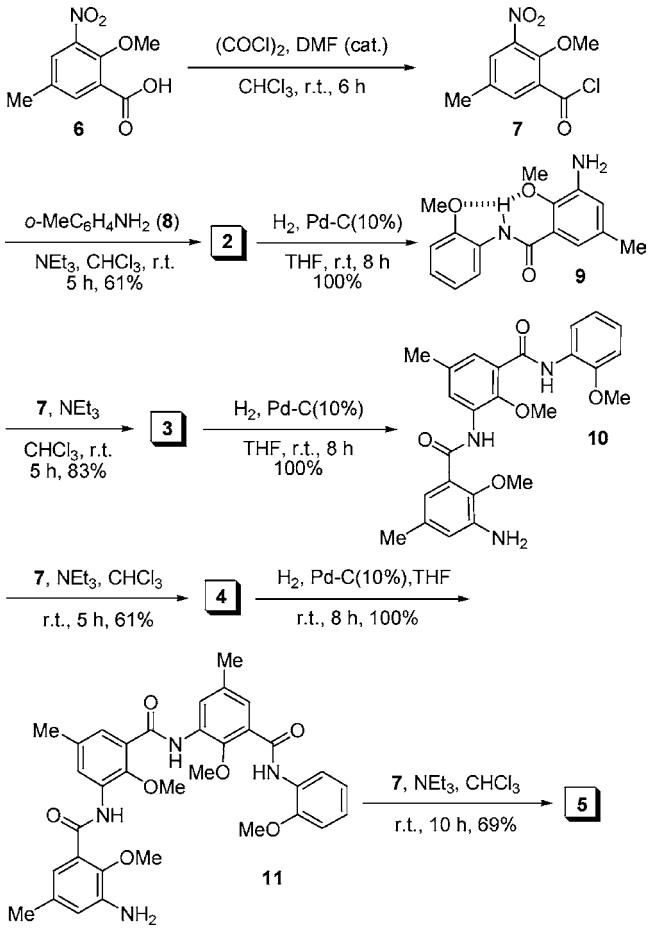
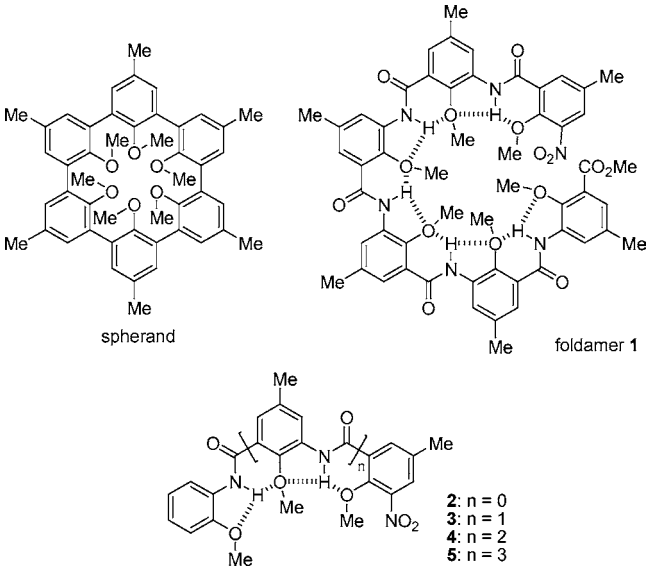
tates the N-oxidation of its peripheral pyridine unit.[8] Although the reactions investigated are quite simple, these studies have shown that artificial folded backbones are new interesting building blocks in the design of enzyme mimics. Previously, we have demonstrated that hydrogen bonding-driven aromatic amide foldamers could function as synthetic receptors for efficient recognition of saccharides,[9] alkyl ammoniums,[10] and fullerenes and derivatives.[11,12] We herein show how the hydrogen bonding-induced folded conformation of oligobenzamides remarkably accelerates the hydrolysis of nitro-substituted anisoles in aqueous media of high polarity.

Results and Discussion

It has been well established by Cram et al. that the spherand and many of its derivatives are able to efficiently complex alkali metal ions.[13−15] Our previous study has shown that hydrogen bonding-induced foldamer **1** could complex aliphatic ammoniums in chloroform.[10a] The rigidified folded conformation of **1** resembles that of a spherand in that all of the methoxyl groups are regularly orientated at the center of the backbone in both molecules. It was therefore envisioned that such a preorganized framework might also complex metal ions. Therefore, oligomers **2**−**5** have been designed and synthesized. We hypothesized that, if these folded oligomers could complex the metal ion of an alkali hydroxide, the ionic bond within the alkali hydroxide should be weakened and the effective concentration of the hydroxide anion increased.[16] As a result, the nucleophilic ability of the corresponding hydroxide anion would be enhanced, which should promote the hydrolysis of the nitro-appended anisole unit in the oligomers.

SCHEME 1





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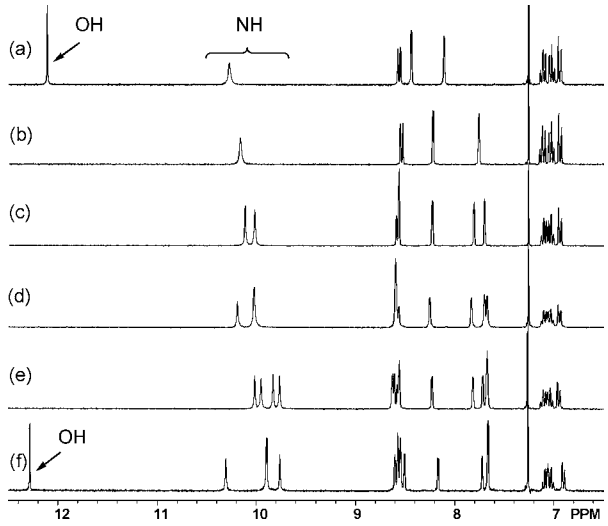


FIGURE 1. Partial ^{1}H NMR spectra (400 MHz) of (a) **12**, (b) **2**, (c) **3**, (d) **4**, (e) **5**, and (f) **15** in $CDCl_3$ (4 mM).

The synthetic route for oligomers **2**−**5** is shown in Scheme 1. Thus, compound **6** was first treated with oxalyl chloride in chloroform to produce **7**. The latter was reacted with **8** in chloroform in the presence of NEt_3 to afford dimer **2** in a 61% yield. The palladium-catalyzed hydrogenation of **2** in THF yielded **9** quantitatively. The aniline was again coupled with **7** to give trimer **3** in an 83% yield. By repeating the hydrogenation and coupling procedures under similar conditions, longer molecules **4** and **5** could be produced in good yields.

The ^{1}H NMR spectra of oligomers **2**−**5** in $CDCl_3$ are provided in Figure 1b−e. It was found that all of the signals of the amide protons of the oligomers appeared in the downfield area (9.77−10.28 ppm). These observations are consistent with those of foldamer **1**,[10a,17] supporting the existence of intramolecular hydrogen bonding and the folded conformation of the backbones. A single crystal of **3** was also grown from chloroform, and its X-ray diffraction structure is shown in Figure 2a. As expected, four intramolecular hydrogen bonds were produced, which induces the trimer to adopt a rigid planar conformation. Because the hydrolytic experiments (vide infra) were all conducted in polar aqueous environments, the ^{1}H NMR spectrum of oligomers **2**−**5** in a DMSO-d_6−acetone-d_6 mixture (4:1, v/v) of high polarity was also recorded to detect if intramolecular hydrogen bonding existed in polar solvents.[18] It was found that, compared to the counterparts in the ^{1}H NMR spectrum in $CDCl_3$, the signals of the amide protons of all of the oligomers moved downfield only slightly to modestly ($\Delta\delta \leq 0.29$ ppm). The shifting was substantially smaller than that observed for 4-methoxy-*N*-(4-methoxyphenyl)benzamide ($\Delta\delta$ 1.85 ppm),[19] in which no intramolecular hydrogen bonds could be formed. These results clearly supported the finding that important intramolecular hydrogen bonding existed for **2**−**5** in the polar solvent,[19] which remarkably weakened the effect of the polar solvent on the chemical shifts of the amide protons as a result of the formation of the competitive intermolecular hydrogen bonding.

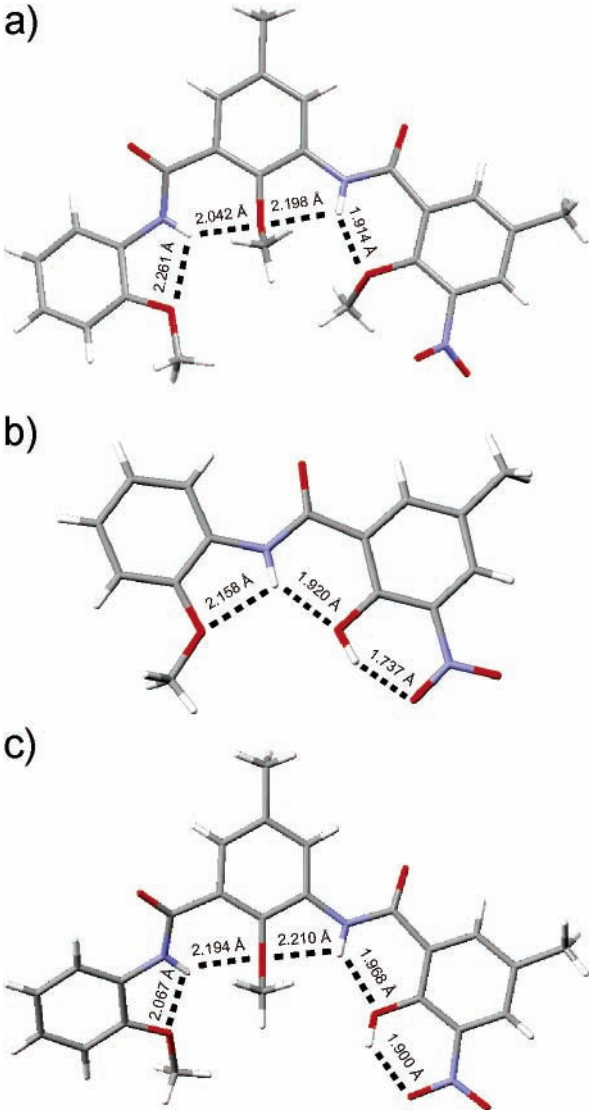
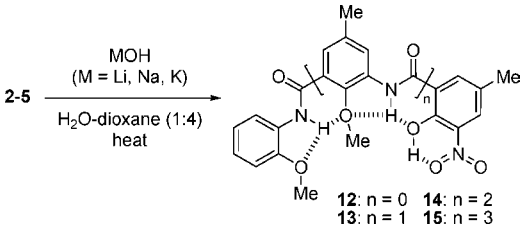


FIGURE 2. The X-ray diffraction structures of (a) **3**, (b) **12**, and (c) **13**. All of the crystals were grown from evaporation of a solution in chloroform.

SCHEME 2



The hydrolysis of **2**−**5** with potassium hydroxide in refluxing water−dioxane (1:4) was then carried out (Scheme 2). The reactions selectively gave rise to the corresponding phenol derivatives **12**−**15**.[20] Under similar conditions, no reaction occurred for compounds **16**, the nitro-free analogue of **3**, and

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(18) Compounds **2**−**5** were insoluble in the binary solvent of water−dioxane (1:4, v/v) used for the hydrolytic experiments.

(19) A value of $\Delta\delta$ of 2.34 ppm was reported when the solvent was changed from $CDCl_3$ to DMSO-d_6; see: Parra, R. D.; Zeng, H.; Zhu, J.; Zheng, C.; Zeng, X.-C.; Gong, B. *Chem.—Eur. J.* **2001**, *7*, 4352.

(20) The cleavage of the oligoamide backbones did not occur during the reactions because only traces of the byproducts (≤1.2%, determined by HPLC) were produced.

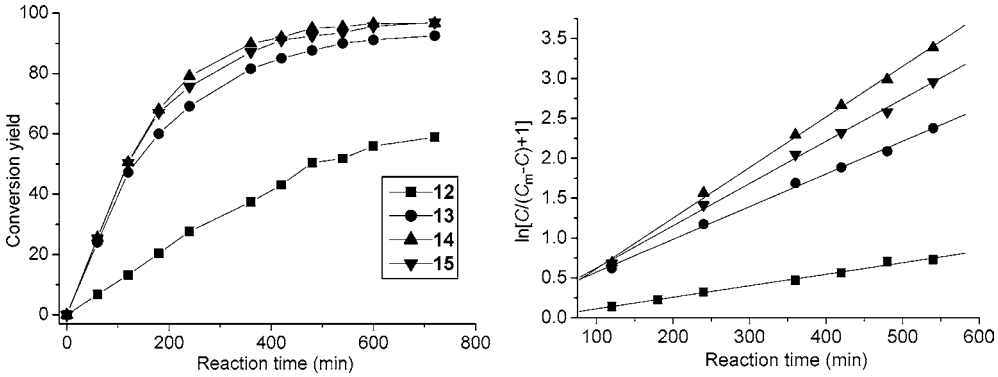
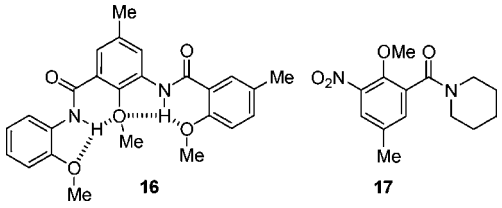


FIGURE 3. Left: The hydrolytic yield of **12** (■), **13** (●), **14** (▲), and **15** (▼) determined by HPLC in the presence of KOH (6.0 mM) at 90 °C. (The concentration of the reactants is 0.1 mM.) The lines are for guiding the eye only. Right: The corresponding plot of interpolation. The rates were estimated by the slopes of the straight lines (C_m, the original concentration of the reactant; C, the concentration of the product).[22]

17. The structures of oligomers **12**−**15** have been established by the (2D) ^{1}H and ^{13}C NMR and HRMS spectroscopy. Because of being involved in a strong six-membered hydrogen bond to the neighboring electron-withdrawing nitro oxygen, the signal of the hydroxyl proton of all of the oligomers appeared in the much downfield area (>12.11 ppm) in the ^{1}H NMR spectrum in $CDCl_3$. As examples, the ^{1}H NMR spectra of **12** and **15** are presented in Figure 1. The single crystals of **12** and **13** suitable for the X-ray analysis have been grown from chloroform. Their solid-state structures are provided in Figure 2b and 2c. It was found that only the methoxyl group adjacent to the nitro group was hydrolyzed, and the resulting OH proton hydrogen-bonded to the nitro oxygen.[21] This is not surprising considering the strong electron-withdrawing ability of the nitro group.



After the structures of compounds **12**−**15** had been established, the kinetic studies of the hydrolytic reaction of oligomers **2**−**5** (0.1 mM) by KOH were first performed.[22] The reactions were first carried out in refluxing (90 °C) water−dioxane (1:4) under the pseudo-first-order reaction conditions of using a large excess of KOH (60 times). The binary solvent system was chosen because all of the oligomers were soluble in the solvent at the investigated temperature. In addition, all of the hydrolysis reactions occurred on the time scale of hours, and the formation of the product could be accurately analyzed by HPLC. The plots of the yields of the phenol derivatives against the reaction time are provided in Figure 3. The reaction was found to be first order in **2**−**5**, and the corresponding hydrolysis rates, k_{obs}, were derived according to the reported method[22] and are listed in Table 1 (entries 1−4).

It can be found that the k_{obs} values for the production of longer oligomers **13**, **14**, and **15** are quite comparable, although the value of **14** is slightly higher. However, all of these values are pronouncedly larger than that of **12**. It is reasonable to assume that, without any additional promoting effect, the hydrolytic rate of the oligomers should be decreased with the chain elongation due to the increased hindrance of the longer oligomers. The pronouncedly increased hydrolytic rates of longer oligomers **3**−**5** relative to that of **2** strongly suggest that an important complexation occurred between the methoxyl oxygen atoms of longer oligomers **3**−**5** and the potassium cation. Such an interaction increased the effective molar concentration of the base and also promoted the elimination of the methoxide anion in the nucleophilic substitution, as shown in Figure 4.[16] Further evidence for the mechanism shown in Figure 4 came from competition experiments performed in the presence of an excessive amount of KCl (0.6 M). It was found that, compared to the corresponding value obtained in the absence of KCl, the hydrolytic rate of the oligomers was decreased remarkably (entries 5−8 in Table 1). In addition, the rate was increasingly decreased with the elongation of the oligomers. These observations can be rationalized by considering that the interaction

TABLE 1. The Kinetic Data of the Hydrolysis of Oligomers 2−5 in Water−Dioxane (1:4, v/v)

entry	temperature (°C)	reactant	product	base	k_{obs}[a] (10^{-3} min^{-1})
1	90	**2**	**12**	KOH	1.47
2	90	**3**	**13**	KOH	5.27
3	90	**4**	**14**	KOH	6.36
4	90	**5**	**15**	KOH	5.63
5[b]	90	**2**	**12**	KOH	0.38
6[b]	90	**3**	**13**	KOH	0.26
7[b]	90	**4**	**14**	KOH	0.19
8[b,c]	90	**5**	**15**	KOH	–
9[c]	60	**2**	**12**	KOH	–
10	60	**3**	**13**	KOH	0.10
11	60	**4**	**14**	KOH	0.61
12	60	**5**	**15**	KOH	0.53
13	70	**3**	**13**	LiOH	1.20
14	70	**3**	**13**	NaOH	0.80
15	70	**3**	**13**	KOH	0.89
16	90	**3**	**13**	LiOH	6.36
17	90	**3**	**13**	NaOH	3.95
18	90	**2**	**12**	LiOH	2.76
19	90	**4**	**14**	LiOH	8.04
20	90	**5**	**15**	LiOH	7.42
21	90	**18**	**19**	KOH	4.60

[a] With error ≤10%. [b] Obtained in the presence of KCl (0.6 M). [c] No reaction was observed after 10 h.

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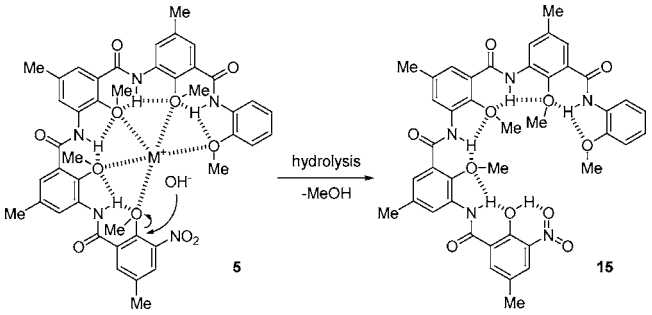


FIGURE 4. The proposed model for the complexation-promoted hydrolytic acceleration of the folding oligomers (with **5** as an example).

between the oligomers and KCl substantially weakened their complexation toward KOH, and consequently, the steric effect played an important role, increasingly retarding the hydrolytic process. The fact that the hydrolytic rates of **4** and **5** are only slightly larger than that of **3** in the absence of KCl should reflect the combined result of the complexation-induced accelerating effect and the hindrance-resulted decelerating effect.

Kinetic studies of the reactions of **2**−**5** with KOH under identical conditions at 60 °C were also performed (Figure 5). The corresponding hydrolysis rates, k_{obs}, are shown in Table 1 (entries 9−12). At this reduced temperature, dimer **2** did not undergo hydrolysis. As expected, the k_{obs} values of oligomers **3**−**5** were also remarkably decreased compared to the corresponding values obtained at 90 °C. In addition, the values of **4** and **5** are substantially higher than that of **3**. All of these results support that the hydrolysis of the longer oligomers displayed an enhanced complexation-induced accelerating effect at the lowered reaction temperature.

The influence of varying the alkaline hydroxide on the hydrolysis of the oligomers was also investigated at 70 and 90 °C, with trimer **3** as the reactant. The corresponding hydrolysis rates, k_{obs}, are presented in Table 1 (entries 2, 13−17). At both reaction temperatures, the k_{obs} values of the reactions of LiOH of the lowest basicity are higher than those of NaOH and KOH. These observations appear to suggest that the reactant oligomers were able to complex Li^+ more efficiently than Na^+ or K^+, resulting in a larger enhancement of the reactivity of LiOH. The kinetic results of the reactions of LiOH with oligomers **2**−**5** at 90 °C were also determined and are provided in Table 1 (entries 16 and 18−20). It can be found that the accelerating behavior is very similar to that of the reactions of KOH (entries 1−4), and once again, LiOH displayed a larger reactivity than KOH for all of the reactions.

In order to obtain more insight into the effect of the steric hindrance on the hydrolytic reaction, the kinetic behavior of the hydrolysis of **18** to **19** by KOH was also studied at 90 °C, which gave rise to a k_{obs} value of 4.60×10^{-3} min^{-1}. Comparison of this value with that of **2** (entry 1, Table 1) revealed that the *ortho*-MeO group in the aniline moiety of **2** functioned more as a hindrance unit to retard the hydrolysis reaction than as a binding unit to promote the hydrolytic reaction. Nevertheless, the values of longer oligomers **3**−**5** (entries 2−4, Table 1) are all higher than that of **18**, showing the increased efficiency of the longer oligomers to enhance the reactivity of KOH by complexing the K^+ cation.

Finally, the hydrolytic reactions of **20a** and **20b** by LiOH at 90 °C were investigated. Both reactions gave rise to two products, **21** and **22**, respectively. No product generated from the hydrolysis of the methoxyl group adjacent to the ester unit was detected in the form of an ester or its acid (Scheme 4). This result implied that the electron-withdrawing ability of the ester group is not strong enough to enable the hydrolysis of the neighboring ether unit. The yields of the products at three reaction times were determined by HPLC and are shown in Figure 6. It can be found that the yields of **22b** were all substantially higher than that of **22a**, which once again illustrates the increased reactivity of the longer oligomer compared to that of the shorter one.

Conclusions

Kinetic investigations of the hydrolysis of a series of foldamer-based 2-methoxy-3-nitrobenzamide derivatives by alkaline hydroxide in dioxane−water have revealed that intramolecular hydrogen bonding-driven aromatic amide foldamers can function as spherand or crown ether mimics to complex an alkaline cation and, consequently, enhance the reactivity of the alkaline bases. Because all of the reactions were carried out at a relatively high temperature and in the dioxane−water binary solvent of high polarity, the observed folding-induced acceleration effect for the longer oligomers is quite impressive. The work also indicates that, even in an aqueous medium of high polarity, intramolecular hydrogen bonding is still able to induce structurally matched oligomers to generate a preorganized rigidified conformation. The result may open the door for the design of new foldamer-based enzyme mimics to promote intermolecular nucleophilic reactions.

Experimental Section

Compound 2. To a solution of **6** (3.39 g, 16.1 mmol) in chloroform (25 mL) were added oxalyl chloride (2.95 g, 23.2 mmol) and DMF (50 μL). The solution was stirred at room temperature for 6 h and then concentrated under reduced pressure. The resulting pale yellow residue (**7**) was dissolved in chloroform (20 mL), and the solution was added to a stirred solution of **8** (2.37 g, 19.3 mmol) and triethylamine (3 mL, 20.5 mmol) in chloroform (30 mL). Stirring was continued for another 5 h, and the solvent was removed under reduced pressure. The resulting residue was triturated in chloroform (100 mL). The organic phase was washed with dilute hydrochloric acid (1 N, 15 mL × 2), water (30 mL × 2), and brine (30 mL) and dried over sodium sulfate. Upon removal of the solvent in vacuo, the resulting crude product was purified by flash chromatography (petroleum ether/chloroform, 3:1) to afford **2** as a pale-greenish solid (3.12 g, 61%): ^{1}H NMR ($CDCl_3$) δ 10.17 (s, 1H), 8.55 (d, d, J_1 = 1.2 Hz, J_2 = 7.8 Hz, 1H), 8.23 (d, J = 2.4 Hz, 1H), 7.77 (d, J = 1.8 Hz, 1H), 7.15−7.10 (m, 1H), 7.06−7.01 (m, 1H), 6.95 (d, d, J_1 = 1.8 Hz, J_2 = 7.8 Hz, 1H), 4.02 (s, 3H), 3.95 (s, 3H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.2, 149.1, 148.6, 144.2, 136.9, 135.3, 129.3, 128.5, 127.6, 124.4, 121.2, 120.6, 110.1, 64.2, 55.8, 20.7; MS (EI) *m*/*z* 317 $[M + H]^+$; HRMS (ESI) calcd for $C_{16}H_{16}N_2O_5Na$, 339.2984; found, 339.3110. Anal. Calcd for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.86. Found: C, 61.02; H, 5.09; N, 8.60.

Compound 3. A suspension of **2** (2.18 g, 6.90 mmol) and Pd−C (10%, 0.20 g) in THF (40 mL) was stirred at room temperature under 1 atm of hydrogen gas for 8 h. The solid was filtered off, and the solvent was removed under reduced pressure to give **9** (1.96 g, 100%) as a yellowish solid. This product was then treated with **7**, as described for the preparation of **2**. After workup, the resulting residue was purified by column chromatography (dichloromethane/EtOAc, 35:1) to afford **3** as a brown solid (2.74 g, 83%): ^{1}H NMR ($CDCl_3$) δ 10.13 (s, 1H), 10.04 (s, 1H), 8.60 (d, J = 1.2 Hz, 1H), 8.57 (d, J = 1.5 Hz, 1H), 8.24 (d, J = 2.1 Hz, 1H), 7.81 (d, J = 1.8 Hz, 1H), 7.71 (d, J = 1.8 Hz, 1H), 7.14−7.01 (m, 2H), 6.94

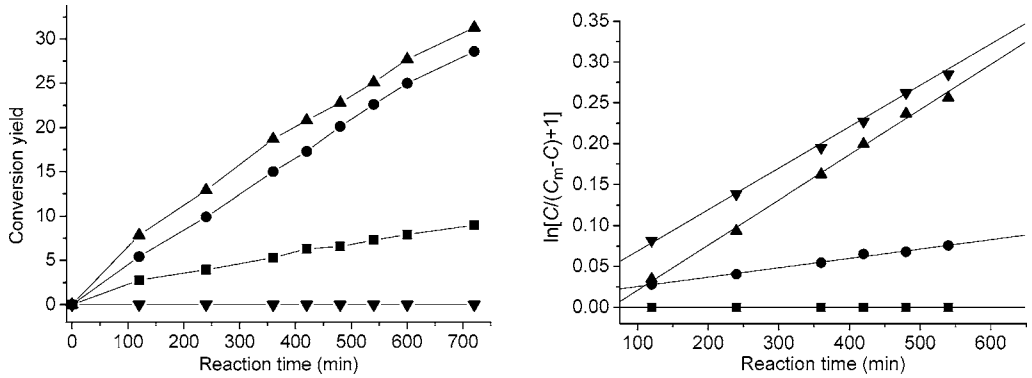
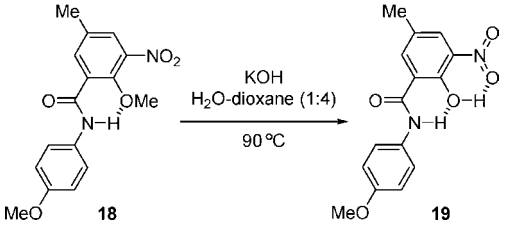
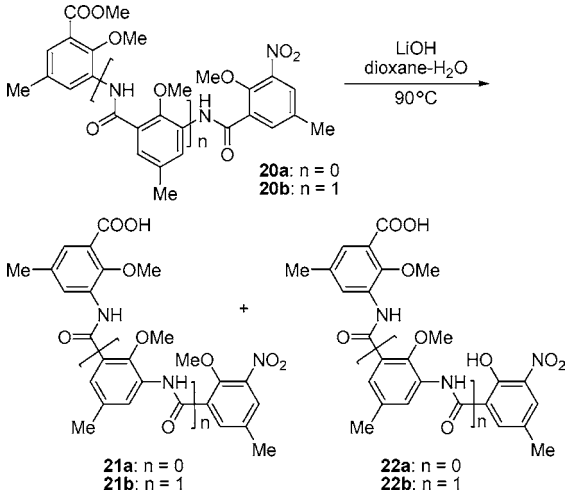


FIGURE 5. Left: The hydrolytic yield of **12** (▼), **13** (■), **14** (▲), and **15** (●) determined by HPLC in the presence of KOH (6.0 mM) at 60 °C. (The concentration of the reactants is 0.1 mM.) Right: The corresponding plot of interpolation. The rates were estimated by the slopes of the straight lines (C_m, the original concentration of the reactant; C, the concentration of the product).[22]

SCHEME 3



SCHEME 4



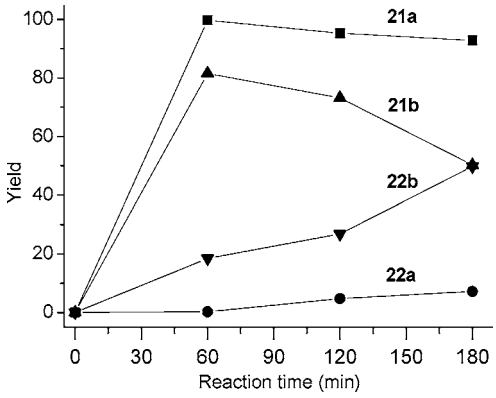


FIGURE 6. The change of the yield of **20** and **21** for the reaction in Scheme 4 with the reaction time.

(d, d, J_1 = 1.2 Hz, J_2 = 8.1 Hz, 1H), 4.15 (s, 3H), 3.95 (s, 3H), 3.91 (s, 3H), 2.48 (s, 3H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 162.7, 161.6, 149.0, 148.5, 145.2, 144.1, 136.9, 135.6, 135.5, 131.5, 128.9, 128.9, 128.0, 127.0, 126.5, 124.8, 124.0, 121.3, 120.5, 110.1, 64.4, 62.9, 29.7, 21.4, 20.7; MS (MALDI−TOF) *m*/*z* 480 $[M + H]^+$; HRMS (MALDI−TOF) calcd for $C_{25}H_{26}N_3O_7$ $[M + H]^+$, 480.4898; found, 480.4881. Anal. Calcd for $C_{25}H_{25}N_3O_7$: C, 62.62; H, 5.26; N, 8.76. Found: C, 62.74; H, 5.58; N, 8.31.

Compound 4. A suspension of **3** (1.06 g, 2.10 mmol) and Pd−C (10%, 0.10 g) in THF (25 mL) was stirred at room temperature under 1 atm of hydrogen gas for 8 h. The solid was filtered off, and the solvent was removed under reduced pressure to give **10** as a yellowish solid (0.94 g, 100%). This product was then treated with **7**, as described for the preparation of **2**. After workup, the crude product was chromatographed (dichloromethane/EtOAc, 30:1) to afford **4** as a brown solid (0.82 g, 61%): ^{1}H NMR ($CDCl_3$) δ 10.20 (s, 1H), 10.03 (s, 2H), 8.60−8.57 (m, 3H), 8.26 (s, 1H), 7.84 (s, 1H), 7.71 (d, J = 1.5 Hz, 1H), 7.68 (d, J = 1.5 Hz, 1H), 7.14−7.04 (m, 2H), 6.95 (d, J = 7.8 Hz, 1H), 4.11 (s, 3H), 3.98 (s, 3H), 3.95 (s, 3H), 3.91 (s, 3H), 2.49 (s, 3H), 2.46 (s, 3H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.0, 162.8, 161.5, 149.0, 148.4, 145.1, 145.0, 144.0, 136.9, 135.9, 135.7, 135.5, 131.8, 131.6, 129.1, 128.7, 128.0, 126.9, 126.5, 126.4, 126.3, 125.2, 124.7, 124.0, 121.3, 120.5, 110.1, 64.3, 63.2, 62.8, 55.8, 21.4, 21.3, 20.7; MS (MALDI−TOF) *m*/*z* 665 $[M + Na]^+$. Anal. Calcd for $C_{34}H_{34}N_4O_9$: C, 63.54; H, 5.33; N, 8.72. Found: C, 63.46; H, 5.43; N, 8.53.

Compound 5 was prepared in a 69% yield (two steps) from **4** by using the procedures described for **4** (eluting solvent for column chromatography: dichloromethane/EtOAc, 20:1): ^{1}H NMR ($CDCl_3$) δ 10.01 (s, 1H), 9.94 (s, 1H), 9.82 (s, 1H), 9.76 (s, 1H), 8.62 (d, J = 6.6 Hz, 2H), 8.58−8.56 (m, 2H), 8.23 (s, 1H), 7.81 (d, J = 1.5 Hz, 1H), 7.72 (s, 1H), 7.66−7.67 (m, 2H), 7.11−7.01 (m, 2H), 6.94 (d, J = 7.8 Hz, 1H), 4.06 (s, 3H), 3.98 (s, 3H), 3.97 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H), 2.51 (s, 3H), 2.48 (s, 3H), 2.47 (s, 3H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.4, 163.2, 162.9, 161.7, 148.9, 148.4, 145.2, 145.1, 145.0, 144.1, 136.8, 135.9, 135.8, 135.7, 135.4, 131.8, 131.7, 131.6, 131.5, 129.0, 128.7, 128.0, 127.0, 126.6, 126.5, 126.4, 126.3, 126.2, 125.5, 125.4, 125.1, 124.0, 121.3, 120.6, 64.1, 63.1, 63.0, 62.7, 55.8, 31.9, 29.3, 21.4, 14.1; MS (MALDI−TOF) *m*/*z* 828 $[M + Na]^+$; HRMS (MALDI−TOF) calcd for $C_{43}H_{43}N_5O_{11}Na$ $[M + Na]^+$, 828.8182; found, 828.8310. Anal. Calcd for $C_{43}H_{43}N_5O_{11}$: C, 64.09; H, 5.38; N, 8.69. Found: C, 64.38; H, 5.41; N, 8.56.

Compound 12. A solution of **2** (0.20 g, 0.63 mmol) and potassium hydroxide (2.12 g, 38.0 mmol) in water (60 mL) and dioxane (60 mL) was heated under reflux for 7 h and then cooled to room temperature. The solution was neutralized with hydrochloric acid (1 N) to pH = 3. Upon removal of the solvent under reduced pressure, the resulting residue was suspended in cold water (10 mL). The solid was filtered and washed with cold water thoroughly. After dried under reduced pressure, the crude product was subjected

to flash chromatography (petroleum ether/AcOEt/CH_2Cl_2, 10:1:1) to give **12** as a yellow powder (0.12 g, 63%): ^{1}H NMR ($CDCl_3$) δ 12.12 (s, 1H), 10.29 (s, 1H), 8.57 (d, d, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 8.44 (d, J = 2.4 Hz, 1H), 8.11 (d, J = 2.4 Hz, 1H), 7.12 (d, t, J_1 = 7.8 Hz, J_2 = 2.1 Hz, 1H), 7.03 (d, t, J_1 = 7.8 Hz, J_2 = 2.1 Hz, 1H), 6.95 (d, d, J_1 = 8.1 Hz, J_2 = 1.2 Hz, 1H), 4.02 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 161.0, 156.9, 150.9, 141.4, 134.1, 130.9, 130.5, 128.4, 123.3, 122.4, 114.3, 33.8, 31.9, 29.7, 29.5, 29.4, 20.4, 14.1; MS (EI) *m*/*z* 302 $[M]^+$; HRMS (EI) calcd for $C_{15}H_{14}N_2O_5$, 302.3002; found, 302.2988. Anal. Calcd for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27. Found: C, 60.08; H, 4.97; N, 9.10.

Compound 13. The reaction of **3** (0.13 g, 0.27 mmol) and potassium hydroxide (0.90 g, 16.2 mmol) in refluxing water (40 mL) and dioxane (40 mL) for 10 h, after workup and column chromatography (petroleum ether/AcOEt/CH_2Cl_2, 10:1:2), afforded **13** as a yellow solid (88 mg, 70%); ^{1}H NMR ($CDCl_3$) δ 12.26 (s, 1H), 10.34 (s, 1H), 10.12 (s, 1H), 8.59 (d, d, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 1H), 8.55 (s, 1H), 8.51 (s, 1H), 8.18 (s, 1H), 7.74 (s, 1H), 7.14−6.95 (m, 2H), 6.96 (d, J = 8.1 Hz, 1H), 3.99 (s, 3H), 3.95 (s, 3H), 2.46 (s, 3H), 2.43 (s, 3H), 2.420 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 162.7, 161.1, 150.8, 148.6, 145.5, 141.8, 135.3, 134.0, 131.6, 130.7, 128.8, 128.0, 127.1, 126.3, 125.4, 124.0, 123.4, 121.2, 120.7, 110.1, 29.7, 29.6, 21.4, 20.4; MS (ESI) *m*/*z* 465 $[M]^+$.

Compound 14. The reaction of **4** (0.10 g, 0.16 mmol) and KOH (0.54 g, 9.62 mmol) in dioxane (35 mL) and water (35 mL) was refluxed for 10 h. After workup, the resulting residue was subjected to column chromatography (petroleum ether/CH_2Cl_2/EtOAc, 6:1:1) to afford **14** (37 mg, 37%) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 12.34 (s, 1H), 10.40 (s, 1H), 10.04 (s, 2H), 8.59−8.55 (m, 3H), 8.52 (d, J = 1.5 Hz, 1H), 8.19 (s, 1H), 7.72 (s, 1H), 7.69 (s, 1H), 7.14−7.01 (m, 2H), 6.95 (d, J = 7.8 Hz, 1H), 4.07 (s, 3H), 4.00 (s, 3H), 3.96 (s, 3H), 2.54 (s, 3H), 2.46 (s, 3H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.2, 162.9, 161.2, 148.5, 145.5, 145.3, 141.9, 135.7, 135.4, 134.1, 131.9, 131.8, 130.9, 128.9, 128.0, 127.2, 127.0, 126.6, 126.5, 126.2, 125.8, 125.1, 124.0, 123.3, 121.3, 120.7, 110.2, 31.9, 29.7, 29.4, 29.2, 22.7, 14.1; MS (MALDI−TOF) *m*/*z* 628 $[M]^+$; HRMS (EI) calcd for $C_{33}H_{33}N_4O_9$ $[M + H]^+$, 629.2239; found, 629.2242. Anal. Calcd for $C_{33}H_{32}N_4O_9$: C, 63.05; H, 5.13; N, 8.91. Found: C, 62.96; H, 5.26; N, 8.70.

Compound 15. The solution of **5** (78 mg, 0.097 mmol) and potassium hydroxide (0.32 g, 5.80 mmol) in dioxane (10 mL) and water (10 mL) was heated under reflux for 24 h. After workup, the crude product was purified by column chromatography (petroleum ether/CH_2Cl_2/EtOAc, 5:1:1) to afford **15** (43 mg, 35%) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 12.28 (s, 1H), 10.30 (s, 1H), 9.89 (s, 2H), 9.76 (s, 1H), 8.60 (d, J = 1.5 Hz, 1H), 8.57 (d, J = 1.5 Hz, 2H), 8.55 (s, 1H), 8.51 (d, J = 2.1 Hz, 1H), 8.17 (d, J = 1.8 Hz, 1H), 7.72 (d, J = 2.1 Hz, 1H), 7.66 (s, 2H), 7.11−7.00 (m, 2H), 6.91 (d, J = 8.1 Hz, 1H), 4.13 (s, 3H), 4.11 (s, 3H), 3.91 (s, 3H), 3.90 (s, 3H), 2.46 (s, 6H), 2.43 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 163.5, 163.4, 163.0, 161.2, 150.8, 148.4, 145.6, 145.3, 141.9, 135.8, 135.7, 135.4, 131.9, 131.7, 131.7, 130.9, 128.9, 127.0, 126.6, 126.5, 126.2, 126.1, 125.7, 125.3, 124.0, 123.2, 121.4, 120.7, 110.2, 63.2, 62.9, 62.8, 55.9, 53.4, 31.9, 29.7, 29.3, 22.7, 21.4, 31.3, 20.4, 14.1; MS (MALDI−TOF) *m*/*z* 791 $[M]^+$; HRMS (MALDI−TOF) calcd for $C_{42}H_{42}N_5O_{11}$ $[M + H]^+$, 792.8097; found, 792.8080. Anal. Calcd for $C_{42}H_{41}N_5O_{11}$: C, 63.71; H, 5.22; N, 8.84. Found: C, 63.38; H, 5.74; N, 8.59.

Compound 16 was prepared as a white solid (71%) from the reaction of **9** with 5-methyl-2-methoxybenzoyl chloride according to the procedure described for the preparation of **2**: ^{1}H NMR ($CDCl_3$) δ 10.61 (s, 1H), 10.18 (s, 1H), 8.62−8.59 (m, 2H), 8.14 (d, J = 2.4 Hz, 1H), 7.67 (d, J = 2.1 Hz, 1H), 7.33 (d, d, J_1 = 4.5 Hz, J_2 = 8.4 Hz, 1H), 7.10−7.04 (m, 2H), 7.00−6.93 (m, 2H), 4.11 (s, 3H), 3.96 (s, 3H), 3.92 (s, 3H), 2.42 (s, 3H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.4, 163.0, 155.3, 148.4, 145.3, 135.3, 133.9, 132.8, 132.4, 131.2, 128.2, 126.1, 125.3, 123.8, 121.3, 121.3, 120.6, 111.6, 110.1, 62.3, 56.1, 55.8, 29.7, 21.4, 20.4; MS (MALDI−TOF) *m*/*z* 435 $[M + H]^+$; HRMS (MALDI−TOF) calcd for $C_{25}H_{27}N_2O_5$ $[M + H]^+$, 435.4844; found, 435.4880. Anal. Calcd for $C_{25}H_{26}N_2O_5$: C, 69.11; H, 6.03; N, 6.45. Found: C, 69.16; H, 6.25; N, 6.43.

Compound 17 was prepared as a white solid (47%) from the reaction of **7** and piperidine under similar conditions: ^{1}H NMR ($CDCl_3$) δ 7.63 (d, J = 1.8 Hz, 1H), 7.29 (d, J = 1.8 Hz, 1H), 3.93 (s, 3H), 3.74 (d, J = 22.5 Hz, 2H), 3.18 (d, J = 23.4 Hz, 2H), 2.38 (s, 3H), 1.67−1.58 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 165.5, 147.3, 143.6, 134.9, 133.7, 133.1, 125.8, 63.4, 48.2, 42.9, 29.7, 26.3, 25.6, 24.4, 20.5; MS (ESI) *m*/*z* 278 $[M + H]^+$. Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.11; H, 6.92; N, 9.81.

Compound 18 was prepared as a white solid (0.61 g, 60%) from the reaction of **7** (0.68 g, 3.24 mmol) and 4-methoxyaniline (0.52 g, 4.22 mmol) according to the procedure described for the preparation of **2**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.17 (d, J = 1.8 Hz, 1H), 7.77 (d, J = 1.8 Hz, 1H), 7.58 (d, d, J_1 = 1.8 Hz, J_2 = 9.0 Hz, 2H), 6.95 (d, d, J_1 = 1.8 Hz, J_2 = 9.3 Hz, 2H), 4.01 (s, 3H), 3.82 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 161.3, 156.9, 148.7, 144.1, 136.7, 135.6, 130.8, 129.3, 128.4, 121.9, 114.4, 64.2, 55.5, 20.7; MS (EI) *m*/*z* 316 $[M]^+$. Anal. Calcd for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.86. Found: C, 60.83; H, 4.97; N, 8.66.

Compound 19 was prepared as an orange powder (26 mg, 57%) from the reaction of **18** (60 mg, 0.19 mmol) and potassium hydroxide (0.32 g, 5.69 mmol) in dioxane (40 mL) and water (10 mL) under similar conditions: ^{1}H NMR ($CDCl_3$) δ 12.18 (s, 1H), 9.59 (s, 1H), 8.46 (d, J = 1.8 Hz, 1H), 8.11 (d, d, J_1 = 1.8 Hz, J_2 = 1.2 Hz, 1H), 7.61 (s, 1H), 7.58 (s, 1H), 6.94 (s, 1H), 6.91 (s, 1H), 3.83 (s, 3H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.0, 156.85, 150.9, 141.4, 134.1, 130.9, 130.5, 128.4, 123.3, 122.4, 114.3, 55.5, 29.5; MS (EI) *m*/*z* 302 $[M]^+$; HRMS (EI) calcd for $C_{15}H_{15}N_2O_5$, 303.2900 $[M + H]^+$; found, 303.2880. Anal. Calcd for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.59; H, 4.54; N, 9.23.

Compounds 21a and 22a. A solution of **20a**[10a] (0.23 g, 0.60 mmol) and lithium hydroxide hydrate (76 mg, 1.80 mmol) in methanol (40 mL) and water (20 mL) was heated under reflux for 3 h and then cooled to room temperature. Dilute hydrochloric acid was added to pH = 4. The formed precipitate was filtered, washed with cold water, dried in vacuo, and subjected to flash chromatography (dichloromethane/methanol, 25:1) to give **21a** (white solid, 0.19 g, 85%) and **22a** (yellow solid, 26 mg, 12%). **21a**: ^{1}H NMR ($CDCl_3$) δ 10.27 (s, 1H), 8.67 (d, J = 2.1 Hz, 1H), 8.25 (d, J = 2.4 Hz, 1H), 7.81 (d, J = 2.4 Hz, 1H), 7.64 (d, J = 2.1 Hz, 1H), 4.07 (s, 3H), 3.96 (s, 3H), 2.47 (s, 3H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.6, 149.2, 147.7, 144.0, 136.8, 135.4, 135.0, 132.3, 129.1, 128.5, 127.8, 126.7, 121.7, 64.4, 63.0, 29.7, 21.3, 20.7; MS (EI) *m*/*z* 374 $[M]^+$. Anal. Calcd for $C_{18}H_{18}N_2O_7$: C, 57.75; H, 4.85; N, 7.48. Found: C, 57.90; H, 4.86; N, 7.93. **22a**: ^{1}H NMR ($CDCl_3$) δ 12.19 (s, 1H), 10.40 (s, 1H), 8.59 (s, 1H), 8.46 (s, 1H), 8.14 (s, 1H), 7.57 (s, 1H), 3.97 (s, 1H), 2.48 (s, 1H), 2.39 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 173.8, 166.7, 163.6, 137.7, 136.6, 136.4, 133.0, 131.7, 131.6, 129.0, 128.6, 126.7, 126.4, 121.8, 61.9, 20.6, 19.6; MS (ESI) *m*/*z* 360 $[M]^+$. Anal. Calcd for $C_{17}H_{16}N_2O_7$: C, 56.67; H, 4.48; N, 7.77. Found: C, 56.34; H, 4.43; N, 7.56.

Compounds 21b and 22b were prepared from the reaction of **20b**[10a] and lithium hydroxide according to the procedure for the preparation of **21a** and **22a**. **21b** (white solid): ^{1}H NMR ($CDCl_3$) δ 10.25 (s, 1H), 10.20 (s, 1H), 8.75 (s, 1H), 8.62 (s, 1H), 8.26 (s, 1H), 7.84 (s, 1H), 7.73 (s, 1H), 7.62 (s, 1H), 4.09 (s, 3H), 3.98 (s, 3H), 3.96 (s, 3H), 2.49 (s, 3H), 2.46 (s, 3H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.1, 161.9, 149.1, 148.0, 147.4, 147.4, 145.3, 144.4, 136.9, 135.9, 135.5, 135.2, 132.6, 131.6, 129.1, 127.5, 127.1, 126.7, 126.7, 125.7, 125.4, 121.5, 74.1, 64.4, 63.3, 63.0, 62.9, 21.4, 21.3, 20.7, 15.3; MS (ESI) *m*/*z* 537 $[M]^+$. Anal. Calcd for $C_{27}H_{27}N_3O_9$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.88; H, 5.53; N, 7.58. **22b** (yellow solid): ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.33 (d, J = 3 Hz, 1H), 10.40 (s, 1H), 10.29 (s, 1H), 8.73 (d, J = 2.1

Hz, 1H), 8.60 (d, $J = 2.1$ Hz, 1H), 8.52 (d, $J = 2.1$ Hz, 1H), 8.20 (d, $J = 2.4$ Hz, 1H), 7.76 (d, $J = 2.4$ Hz, 1H), 7.65 (d, $J = 2.1$ Hz, 1H), 4.00 (s, 3H), 3.98 (s, 3H), 2.48 (s, 3H), 2.45 (s, 3H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 166.4, 161.9, 161.5, 149.7, 146.3, 145.4, 138.9, 134.0, 132.6, 131.6, 130.7, 129.0, 128.1, 126.0, 125.6, 124.9, 123.8, 123.0, 121.7, 61.93, 61.47, 28.54, 20.36, 20.26, 19.35; MS (ESI) *m*/*z* 523 $[M]^+$. Anal. Calcd for $C_{26}H_{25}N_3O_9$: C, 59.65; H, 4.81; N, 8.03. Found: C, 59.91; H, 5.17; N, 8.42.

Determination of the Rate Constant. The first-order rate constant, k_{obs}, in oligomers **12**−**15** was determined by $\ln([S]_{max} - [S])$ versus time plots. The rates have been estimated by the slopesof the straight lines obtained by linear correlation using the equation $\ln[S]_{max} - \ln([S]_0 - [S]) = k_{obs} \times t$, where $[S]_0$ and [S] represent the concentration of the reactant at the beginning of the measured time.[22]

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Supporting Information Available: The general experimental method and the crystallographic information (CIF files) of compounds **3**, **12**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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