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Halide-Guided Oligo(aryl-triazole-amide)s Foldamers: Receptors for Multiple Halide Ions

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Abstract: We synthesized and characterized a series of oligo(phenyl-amide-triazole)s that can fold into a helical conformation guided by halide ions. Their binding models and affinities are highly dependent on the length of the foldamer, media and the inducing capability of halide ions. The short foldamer with one helical turn shows a 1:1 binding stoichiometry to all halides, while the longer foldamer with two or three helical turns in principle can form 1:2 complexes with chloride anions even bromide anions with an enhancement on binding affinities. A result of quantitative NOE calculations imply that the longer foldamer should increase its helical pitch so as to release the electrostatic repulsion between halide ions.

Keywords: amides · binding stoichiometry · foldamers · halide ions · triazoles

Introduction

Ions display an essential physiological role to the living cell.[1] In nature, peptides have been discovered to orient parallel to the surface of the membrane to recognize ions and subsequently function as ion channels.[2] Effort on developing artificial ions receptors can help us to gain deeper insight into the ion-binding mechanism in nature and to find a new strategy for treating ion-related diseases, such as cystic fibrosis which caused by chloride channel malfunctions.[3] Accordingly, a number of artificial ions receptors have been developed.[4] Among them, synthetic oligomers that can adopt specific folding patterns to mimic the structure of proteins and DNA, so-called foldamers,[5–6] provide a simple and efficient approach for investigating the ions-binding properties of their natural counterparts. In the past decade, a few foldamers capable of hosting guest molecules with stable yet dynamic conformation have been reported,[7–16] but only a few, which can bind anions, exist at present.[12–15] The scarcity is mainly due to the lack of suitable anion receptors that could be easily engineered as foldamers. In this aspect, the prominent examples are the oligoindole[13] and oligotriazole-based[14] foldamers, which induced by indole N-H···Cl^- and C-H···Cl^- hydrogen bonds, respectively. Both of which were found to form 1:1 complex with chloride ions. A plausible explanation for this behavior is due to the strong static repulsion between two chloride anions binding to the cavities of foldamers.[15] However, little is known about the influence of the static repulsion on the foldamers and the binding stoichiometry between the foldamer and anions, which lead to that the rational design of foldamers able to host multiple anions remains a very difficult problem to resolve. Herein, we report on a new type of oligomers **1**–**3** (Scheme 1) based on aryl-triazole-amides which can form a stable helical conformation as binding one halide ion. The longer foldamers **2** and **3** are able to host more than one chloride anion even bromide anion. Importantly, to host two halide ions, the foldamer was found to increase its helical pitch so as to release the electrostatic repulsion between the two halide ions.

Recently, several groups reported that shape-persistent macrocycles[17] or quasifoldamers[14] containing triazole moieties provide strong affinity for chloride ions with C-H···Cl^- hydrogen bonds. In our previous work,[15] we also found that oligo(phenylene-1,2,3-triazole)s composed of alternating *meta*-phenyl groups bearing water-soluble side-chains fold and aggregate in aqueous solution. Furthermore, these oligomers are able to recognize fluoride and chloride ions, consequently preventing the aggregation of oligo(phenylene-1,2,3-triazole)s in aqueous solution. On the other hand, the

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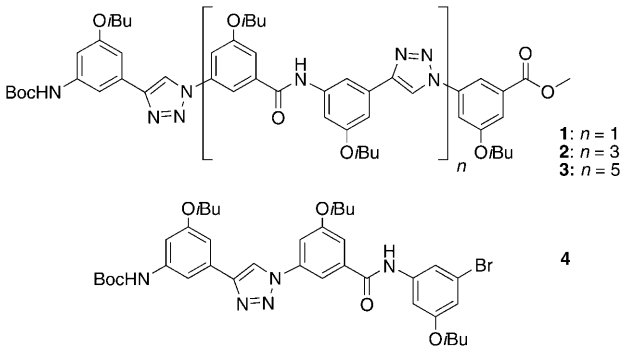


Scheme 1. Oligomers studied herein.

amide N-H group is widely used as hydrogen-bond donor to construct anion receptors.[4f–i] These facts inspired us to design oligo(phenyl-amide-triazole)s **1**–**4**, which possess two phenyl rings, a triazole and an amide group in the repeat unit that is supposed to provide moderate affinities for halide ions. According to molecular modelling (Figure S1 in the Supporting Information), oligomer **1** exists as a helical conformation in one turn in the presence of halide ions. The longer oligomers such as **2** and **3**, in principle, were designed to yield two and three helical turns, respectively. We hypothesized that longer oligomers could bind more than one anion like chloride ions. Short oligomer **4** was designed to assess the affinity between phenyl-amide-triazole motif and halide ions and also to study the conformation of their complex in the solid state.

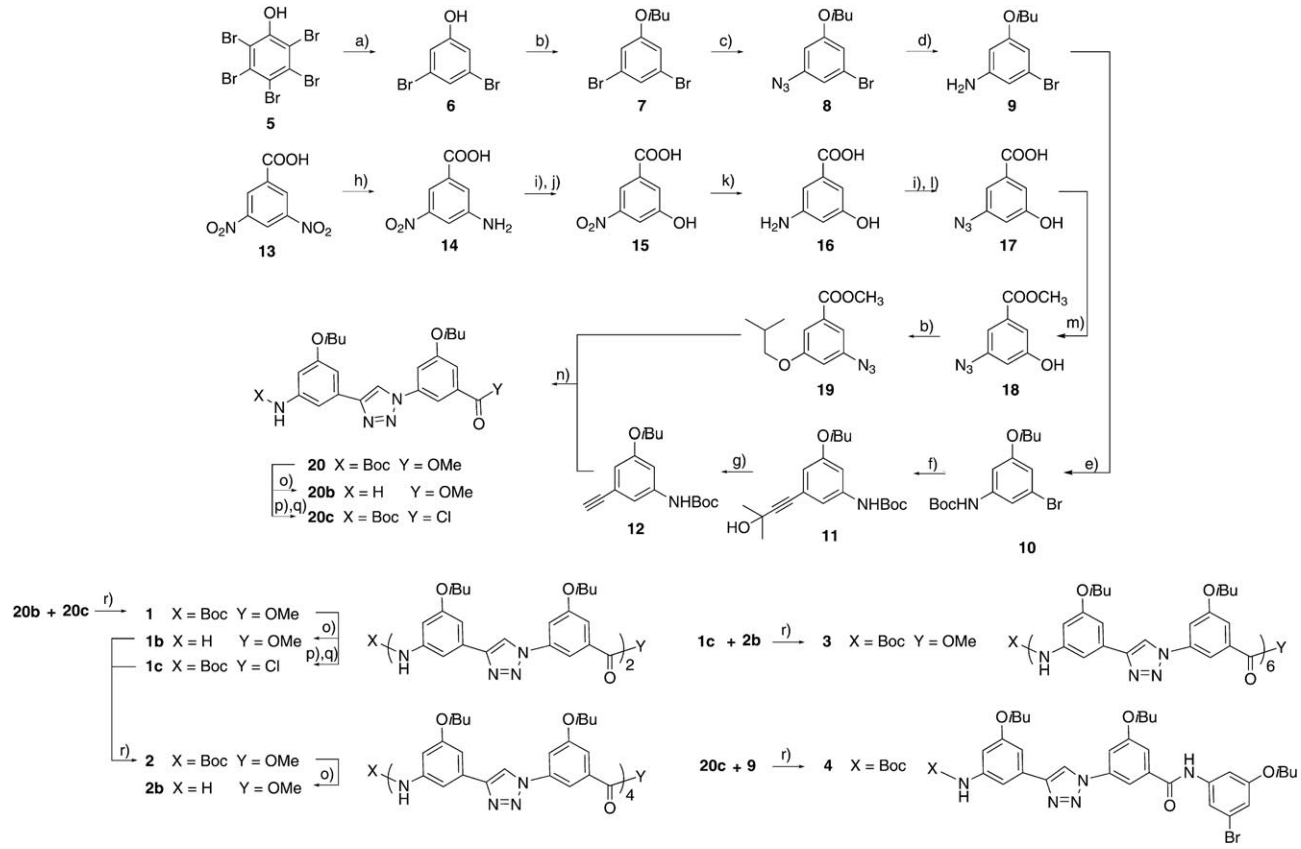
Results and Discussion

Synthesis: The preparations of the proposed oligomers **1**–**4** consisting of two functional group in the repeated units, that is, amide and 1,2,3-triazole, are depicted in Scheme 2. The key issue in this approach is to obtain two essential precursors, that is, *N*-Boc-3-ethynyl-5-isobutoxyaniline and methyl 3-azido-5-isobutoxybenzoate. Initially, 3,5-dibromophenol (**6**), which was prepared from the comercially available pentabromophenol (**5**) according to the method reported by Tour,[18] was alkylated under an alkaline condition to produce 3,5-dibromo isobutoxybenzene (**7**). By treating with *n*BuLi and TsN_3, one of the bromo groups in **7** was converted to azide to yield **8** at −78 °C in an acetone bath. Compound **8** was reduced by $NaBH_4$ to generate amine compound **9**, which was protected by *tert*-butoxycarbonyl (Boc) group via $(Boc)_2O$ to provide **10**. Then, Sonogashira reaction[19] of **10** with excess 2-methylbut-3-yn-2-ol at 78 °C yielded **11**. In this reaction, we selected 2-methylbut-3-yn-2-ol instead of trimethylsilylacetylene to avoid the tube-sealing operation due to the fact that the boiling point of trimethylsilylacetylene (53 °C) is lower than the reaction temperature. Treatment of **11** with NaH in anhydrous toluene produced **12**. On the other hand, **14** can be prepared from 3,5-dinitrobenzoic acid as previously reported.[15] The amine group in **14** went through diazotation and then hydrolyzed to yield 3-hydroxy-5-nitrobenzoic acid (**15**), which could be converted to azide **17** by reduction using ammonium ferrous sulfate in concentrated ammonia and subsequently diazotized in the presence of NaN_3. Protecting the acid group in **17** to give ester **18**, which was alkylated to yield **19**. Thus, through the "click" coupling[20] of the two essential precursors mentioned above, monomer bearing 1,2,3-triazole group in the middle of two phenyl groups and two function groups of BocNH and ester at both ends can be obtained. A segment doubling strategy involving selective deprotections and couplings via acid chlorides was then adopted to generate oligomers **1**, **2** and **3**. Note that to protect the Boc group, the acid was activated to the corresponding acid chloride under mild conditions using the Ghosez reagent (1-chloro-*N*,*N*,2-trimethylpropenylamine).[21] Compound **4** was obtained after coupling the monomer acid chloride **20c** with **9**.

Binding properties: The folding behaviors of oligomers **1**–**4** were investigated by ^{1}H NMR spectroscopy. ^{1}H NMR spectra of **1** and **4** initially recorded in $CDCl_3$ show one set of sharp signals indicative of nonaggregation taking place. Unexpectedly, the longer oligomers **2** and **3** were found to aggregate under the identical conditions. This aggregation of **2** can clearly be detected by concentration-dependent ^{1}H NMR spectra and 2D DOSY experiments (Figures S2, S3 and S4). To avoid this aggregation, several other commercially available deuterated solvents were tested, and $[D_5]$Pyridine ($[D_5]$Pyr) and the mixture of $[D_6]$DMSO/$[D_5]$Pyr were chosen for investigations as indicated (see below and Figures S5 and S6).

The ^{1}H NMR spectrum of **4** in $[D_5]$Pyr shows considerable changes in the chemical shift upon addition of halide ions, indicative of strong interactions between the phenyl-amide-triazole motif and halide ions. In details, upon addition of $Bu_4N^+Cl^-$, the chemical shifts of the triazole and amide protons shifted downfield up to $\Delta\delta = 1.8$ and 1.1 ppm, respectively, as a result of the formation of hydrogen bonding (Figure S7). The titrations of bromide also produced a large change in the chemical shift of the protons at triazole and amide moieties but less than that of chloride ions, and the titrations of iodide ions gave the smallest change in chemical shift (Figures S10 and S13). The fitting analyses of binding data[22] yield the association constants (K) of 540, 83 and 11 M^{-1} in a 1:1 binding model for chloride, bromide and iodide ions, respectively (Table 1), suggesting the binding is highly dependent on the inducing capability of halide ions. Although an attempt to co-crystallize **4** and chloride ion failed, the results mentioned above still unambiguously suggest the interaction between the phenyl-amide-triazole motif and halide ions is directional and sufficiently strong so as to induce the longer oligomer to fold into a helical conformation.

The folding of oligomer **1** in the presence of chloride ions were first demonstrated by ^{1}H NMR titration experiments. The marked signals of **1** were assigned on the basis of COSY, HSQC, TOCSY and 2D NOESY experiments (see Supporting Information). It can be found that the ^{1}H NMR



Scheme 2. Preparation of **1**–**4**. a)$AlCl_3$, toluene; b) 1-iodo-2-methylpropane, K_2CO_3, DMF; c) *n*BuLi, TsN_3, THF; d) $NaBH_4$, MeOH; e) $(Boc)_2O$, dioxane; f) 2-methyl-3-butyn-2-ol, $Pd(PPh_3)_4$, CuI, $(iPr)_2NH$; g) NaH, toluene; h) Fe, HOAc; i) H_2SO_4, $NaNO_2$, H_2O; j) $Cu(NO_3)_2$, Cu_2O; k) conc. NH_4OH, $(NH_4)_2Fe(SO_4)_2$, H_2O; l) NaN_3, H_2O; m) H_2SO_4, MeOH; n) sodium ascorbate, $CuSO_4$, *t*BuOH, H_2O; o) TFA, CH_2Cl_2; p) NaOH, THF, H_2O; q) 1-chloro-N,N,2-trimethylpropenylamine, CH_2Cl_2; r) CH_2Cl_2.

Table 1. Association constants [M^{-1}] of oligomers **1**, **2**, **3** and **4** for halide ions Cl^-, Br^- and I^- at ambient temperature.[a]

Anion	1	2	3	4
Cl^-	350	4900 (13) 250 (1.2)[b]	490 (38)[b]	540
Br^-	80	590 (3.2)	[c]	83
I^-	15	76	[c]	11

[a] All titrations were carried out in [D_5]pyridine unless otherwise specified. The association constants were calculated by the software WinEQNMR.[22a] All relative errors for the values are less than 10%. The values of K_2 are listed in parentheses. [b] In 20:80 (v/v) [D_6]DMSO/[D_5]Pyr. [c] Not determined.

spectra of **1** in [D_5]Pyr showed significant changes in the chemical shifts upon titration of chloride ions (Figure 1A and C). The triazole proton H_5 and amide proton H_9 largely downshifted from $\delta = 9.30$ and 11.44 ppm to 10.88 and 12.32 ppm ($\Delta\delta = 1.58$ and 0.88 ppm, respectively) upon addition of five equivalents $Bu_4N^+Cl^-$, as expected for the formation of strong hydrogen bonds between the binding motif and chloride ions. Similar downfield shifts were observed for the aryl protons H_4, H_6 and H_{10}. However, other protons such as H_1, H_3, H_7 and H_{12}, showed little change in chemical shift.

Titrations of **1** with chloride ions gave 1:1 binding stoichiometry, which was confirmed by a Job's plot. The best fit to the binding data yields an association constant of 350 M^{-1}, slightly smaller than that of **4**. It is presumably due to the steric hindrance of the extra phenyl-triazole group.[23] The titrations with bromide and iodide ions showed similar patterns to those observed in the case of chloride ions (Figure S28-35), and give an atom-radius-dependent sequence of K values ($Cl^- > Br^- > I^-$) as a result of electrostatic nature of hydrogen-bonding interactions (Table 1).

To address the formation of a helical conformation of **1** induced by halide ions (Figure 1B), we performed NOESY experiments. In the absence of halides, NOE correlations were observed between triazole protons H_5 and H_{13} and four adjacent protons at the consecutive phenyl rings. The similar NOE correlations also apply to proton H_9 (Figure 2A). The NOE data indicate oligomer **1** prevailed as a random-coiled conformation in solution. However, the NOE correlations displayed totally different patterns in the presence of halides, for example, of chlorides, triazole proton H_5 only exhibits strong NOE correlation with H_4 and H_6 which are supposed to be located at the inner cavity (Figure 1B). Similarly, the amide proton H_9 also shows significant contact with H_6 and H_{10}. Besides, the triazole proton H_{13} has a

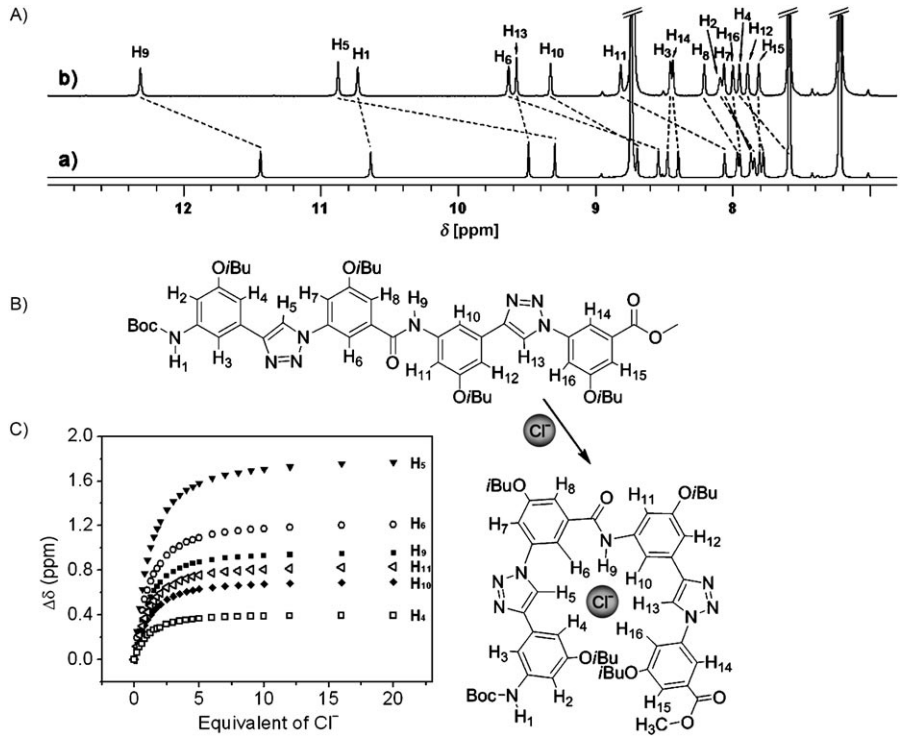


Figure 1. A) Partial ^{1}H NMR spectra changes of **1** upon addition of chloride ions: a) **1**, b) **1** + 5 equiv Cl^-. B) Representation of the folding of **1** with the help of chloride ions. C) Changes in chemical shift for protons of **1** at variable concentrations of chloride ions. All measurements were carried out in [D_5]Pyr at ambient temperature; [**1**] = 5 mM.

strong correlation with H_{10} rather than H_{12} (Figure 2B). These results present unequivocal evidence that **1** folded into a stable helical conformation upon complexation with chloride ions. Additionally, it is interesting to note that H_5 has a stronger contact with H_4 than H_3, indicating the BocNH group keeps away from the interior cavity due to its strong steric hindrance.

With these data at hand, we next explore the folding properties of longer oligomer **2**, which are expected to fold into helical conformation with two turns, in principle, in the presence of halide ions. The NMR titrations of **2** with chloride and bromide ions displayed totally different binding behaviors from those of **1**. That is, the chemical shifts of amide protons initially upshift upon titration of chloride ions up to 1.6 equivalence and then downshift while chloride ions beyond 1.6 equivalence (Figure 3A and B). The inversion on the chemical shift is indicative of two equilibria involved in which oligomer **2** presumably first folded into a helical conformation in the assistance of one chloride ion, and then the resulting foldamer is able to bind another chloride ion (Figure 3C). The similar inversions on the chemical shifts were observed in an anion-macrocycle system by Hamilton.[22b,c] In details, in the first process, the proton H_g upshift from $\delta = 11.41$ to 10.91 ppm with a large $\Delta\delta = -0.5$ ppm (Figure 3B). The upfield shifts of amide protons are ascribed to the ring-current effects arising from π-stacking within intramolecular aggregate. However, in the second process, all protons of amide and triazole shift downfield dramatically, partly due to the formation of hydrogen bindings between foldamers with the second Cl^-, and partly due to the decrease of the π-stacking effect which results from the increase of the helical pitch (see below). As expected, the binding isotherms of the amide protons fit well to a 1:2 complex model to yield the association constants for each step being the values of K_1 at $4.9\times10^3\,M^{-1}$ and K_2 at $13\,M^{-1}$ (Figure S38) suggesting that the folding process is not cooperative, which is sharply different from a cooperative process induced by cations in *meta*-phenylacetylene oligomer as described by Moore et al.[16b] Although K_2 is far lower than K_1, the findings give an obvious proof for the presence of the electrostatic repulsion between two chloride anions binding in helical cavity.

The titrations of **2** with bromide ions lead to a similar but weaker inversion on chemical shift in comparison with that of chloride ions, indicating **2** also form 1:2 complexes in the presence of bromide with association constants K_1 at $590\,M^{-1}$ and K_2 at $3.2\,M^{-1}$ (Figures S43–S45). However, the titrations of **2** with iodide ions show a homologous binding behavior as that of **1** in which all amide protons keep upshift upon addition of iodide ions due to the largest size and the lowest charge density of iodide (Figures S46–48). The fitting of binding profile yields a K value to be $76\,M^{-1}$ in a 1:1 binding stoichiometry that was confirmed by the Job's Plot.

NOESY measurements provide additional information about the conformation of **2** upon interaction with chloride ions. Expectedly, **2** exits in Pyr as a random-coiled conformation in the absence of halide ions. However, oligomer **2** is supposed to host one chloride ion in the helical cavity in the presence of 1.6 equivalent chlorides. At such a condition, the NOE cross-peaks (H_b–H_c, H_c–H_d, H_d–H_e, H_e–H_f, H_f–H_g, H_g–H_h) as shown in Figure 4 are strongly indicative of the existence of a helical conformation of **2** while complexing with one chloride ion (1:1 complexes). Besides, the NOE correlations can also be observed between the protons located at the adjacent helical turns, such as H_b–H_f and H_d–H_h, providing another direct evidence for the folding.[24] To further address the conformation of oligomer **2** binding two chloride ions (1:2 complexes), we repeated the NOESY measurements of **2** in the presence of 20 equivalents chloride ions. Under such conditions, the NOE correlations of H_b–H_c, H_c–H_d, H_d–H_e, H_e–H_f, H_f–H_g and H_g–H_h were still

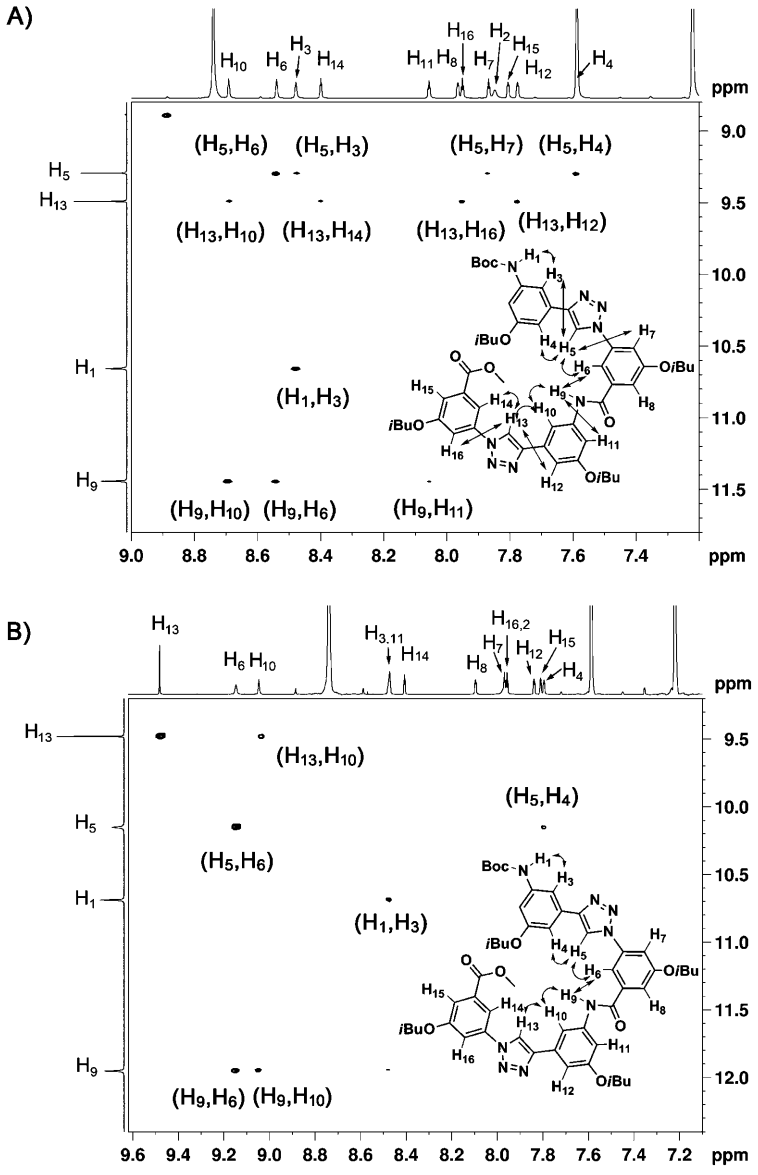


Figure 2. Partial ^{1}H–^{1}H NOESY spectra (600 MHz, [D_5]Pyr, 298 K) of **1** in the absence of chloride ions (A) and in the presence of 1.2 equivalent chloride ions (B). [**1**] = 5 mM.

observed (Figure S58), providing a possibility that **2** still exists in a helical conformation while complexing two chloride ions. However, the result of fitting analysis to the titration curve shows that, in the presence of 20 equivalents chloride ions, the 1:2 complexes only take up 50 rather than 100% (Figure S39). Therefore, the observed NOE correlations cannot guarantee **2** to adopt a helical conformation upon complexing two chlorides because these NOE correlations may also come from the 1:1 complexes. In order to extract detailed information from the NOE experiments, quantitative NOE calculation was conducted on **2** in the presence of 1.6 and 20 equivalents chloride ions using the intensity ratio method.[25,26] The molecular correlation times of **2** in the presence of 1.6 and 20 equivalents Cl^- were calculated to be 6.1×10^{-11} and $1.47\times10^{-10}\,s^{-1}$, respectively, which subsequently yield a ratio of the average hydromechanical radius of **2** in the presence of 20 equivalents Cl^- to that in the presence of 1.6 equivalent Cl^- to be 1.34.[26] These results suggest the foldamer **2** has to extend its helical pitch to certain extent so as to release the electrostatic repulsion originating from the two chloride accommodated within the cavity. Unfortunately, we did not obtain the X-ray structure of **2** upon binding two chlorides, so the detailed conformation of 1:2 complexes is unknown. Therefore, we speculated **2** might adopt a loose helical or an S-shape conformation, even a dynamic equilibrium between the helical and the S-shape conformation, to hold two chloride ions.

The findings presented above demonstrate that oligomer **2** is able to host two chloride or bromide ions. But K_2 is too small in comparison with K_1 in both cases. For example, K_2 is 377 times lower than K_1 in the case of chloride ions. We anticipated that binding constants could be enhanced while the length of oligomer was increased and the enhancement would be more favorable for K_2. To test our hypothesis, the longer oligomer **3**, which theoretically bears three helical turns, was designed and synthesized. The binding behaviors were first investigated by ^{1}H NMR in [D_5]Pyr. Unexpectedly, **3** shows slight aggregation in [D_5]Pyr (Figure S6). To circumvent this problem, NMR titrations of **3** were carried out in 20:80 (v/v) [D_6]DMSO/[D_5]Pyr at ambient temperature. The variations of chemical shifts of **3** upon titration of chloride ions also demonstrate an inversion (Figure 5 and S59) similar to that of **2** in pure pyridine. That is, all of the amide protons except BocNH undergo an upshift up to 5 equivalents chloride ions, and then shift downfield beyond 5 equivalents chloride ions. The overall titration data once again fits well to a 1:2 binding model and the association constants were determined to be $490\,M^{-1}$ for K_1 and $38\,M^{-1}$ for K_2. For comparison, NMR titration experiments of **2** with chloride ions were repeated under the condition of 20:80 (v/v) [D_6]DMSO/[D_5]Pyr. The fitting analysis of the titration

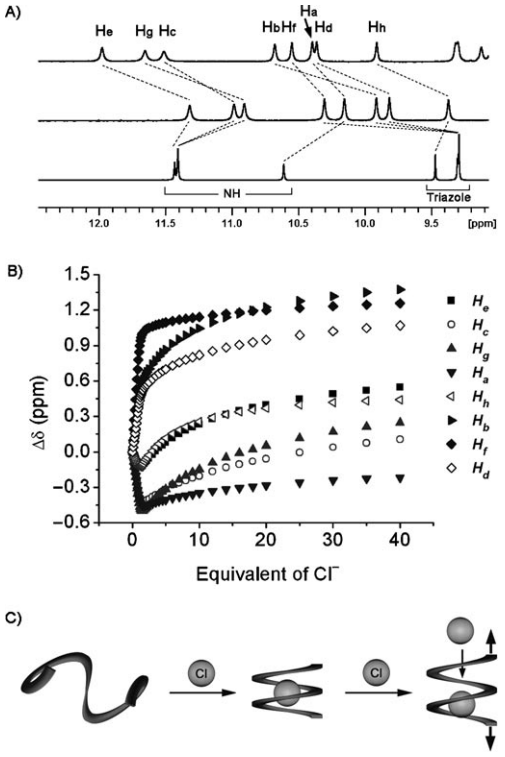


Figure 3. A) Partial ^{1}H NMR spectra changes of **2** in [D_5]Pyr upon addition of chloride ions: a) **2**, b) **2** + 1.6 equiv Cl^-, c) **2** + 40 equiv Cl^-. B) Changes in the amide and triazole ^{1}H chemical shift of **2** with increasing chloride ions at ambient temperature. The data were curve-fitted to a 1:2 binding equilibrium model.[26] [**2**] = 5 mM. C) Schematic representation of the complexation process of **2** with chloride ions, involving oligomer **2** folded into a helical conformation upon complex with chloride and the resulting foldamer further binds another chloride with folded but dynamic structure.

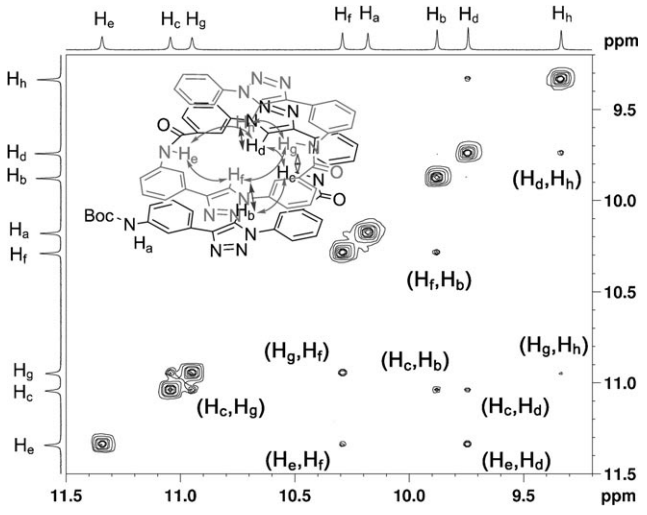


Figure 4. Partial ^{1}H–^{1}H NOESY spectra (600 MHz, [D_5]Pyr, 298 K) of **2** (5 mM) in the presence of 1.6 equiv chloride ions.

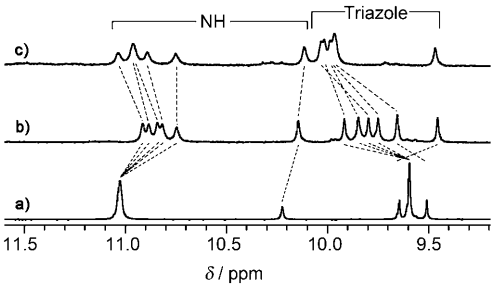


Figure 5. Partial changes of ^{1}H NMR of **3** in 20:80 (v/v) [D_6]DMSO/[D_5]Pyr upon addition of chloride ions: a) **3**, b) **3** + 5 equiv Cl^-, c) **3** + 40 equiv Cl^-. Measurements were taken at ambient temperature; [**3**] = 2 mM.

curves of **2** yields the values of K_1 at 250 M^{-1} and K_2 at only 1.2 M^{-1} (Figures S40–S42), which are much smaller than those in pure pyridine (Table 1). This shrinkage of the binding constants originates from the overwhelming competition of DMSO. On the other hand, we realized that the binding constants of **3** are greater than those of **2** in the mixed solvents supporting our hypothesis that the elongation on the length of oligomers consequently lead to the enhancement of binding constants at least in the present case, presumably because of the presence of more available hydrogen binding receptors for chloride ions. Additionally, it is worthy of note that the ratio of K_1/K_2 for **3** to be 12.9 is 16 folded lower than that of **2** to be 208. This means that increasing the chain length of oligomer is more favourable for K_2. An attempt to interpret the conformation of oligomer **3** in the presence of halide ions from NOESY experiments is unprofitable because of extensive overlaps of protons.

Conclusion

In the past decades, although foldamer-based molecular recognition has received extensive attention, the interaction between foldamers and the halide ions have not been investigated in great details due to the lack of foldamer which could complex halide ions in multiple binding models. In this paper, we prepared a series of halide-induced oligo(phenyl-1,2,3-triazole-amide)s foldamers, the binding model and affinity of which are dependent on the chain length and media. The short oligomer **1** shows a 1:1 binding stoichiometry to the chloride, bromide and iodide ions. However, the longer oligomers **2** and **3** were found to bind two chloride or bromide ions. Quantitative NOE calculation results suggest that, to accommodate the second halide ions, the foldamers have to increase their helical pitch to release the electrostatic repulsion between the halide ions bind to the foldamers. Increasing the chain length of the oligomer can improve its binding affinity for the chloride ions, especially for the second one. We expect that these findings may help us to design foldamers with a stable tube-like structure to bind multiple halide ions in their cavity, thus serving as an artificial halide transmembrane channels.[27]

Acknowledgements

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